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RESEARCH ARTICLE

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# Effect of the tether length upon Truce-Smiles rearrangement reactions

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**Abstract**

This report examines the effect of substrate design upon the Truce-Smiles rearrangement, an intramolecular nucleophilic aromatic substitution reaction. The length of the molecular spacer that tethers the carbanion nucleophile to the substituted benzene ring was found to have a strong influence on the ability of the substrate to undergo the reaction successfully. Our experimental results show highest yield of desired aryl migration product for substrates designed with a 3-atom tether, which proceed through a 5-membered spirocyclic intermediate. The results are interpreted in comparison with a survey of Truce-Smiles rearrangements described in the literature and found to be consistent. Computational studies support the observed reactivity trend and suggest an explanation of a favorable combination of ring strain and electrostatic repulsion leading to optimal reactivity of the substrate designed with a 3-atom tether. Comparison of our results with trends for related ring-closing reactions illustrate the unique electrostatic features of the system studied herein.

**KEYWORDS**

aromatic substitution, cyclization, nucleophilic substitution, rearrangement, synthetic methods

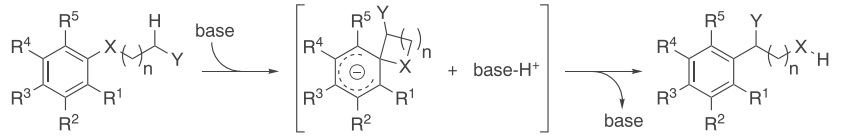
## 1 | INTRODUCTION

The Truce-Smiles rearrangement is a relatively unknown and unexploited intramolecular nucleophilic aromatic substitution reaction (Scheme 1). The reaction has great synthetic potential due to its ability to efficiently form a $sp^2$-$sp^3$ carbon-carbon bond at the expense of an easily installed carbon-heteroatom bond, while simultaneously revealing a heteroatom-containing functional group. There is some discrepancy between the modern definition[1] of the Truce-Smiles rearrangement and the definition originally introduced by Truce,[2] with respect to mechanism and substrate structure. The reaction is now recognized as a carbanion variation of the Smiles rearrangement, and it is accepted that it should therefore normally proceed through a $S_NAr$ mechanism.[1]

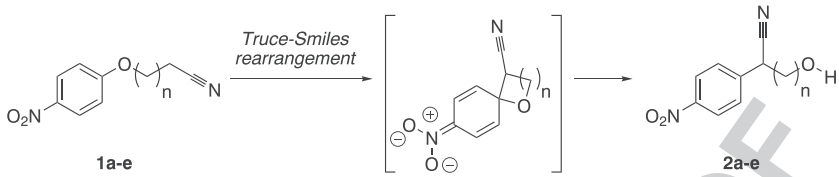
A review of the literature indicates that the substrate scope of the Truce-Smiles rearrangement is versatile, and not entirely defined.[3] There has been renewed interest in further defining this reaction and transforming it into a synthetically reliable method.[4] Our previous paper reported results supporting the $S_NAr$ mechanism for this reaction and specified the substrate scope with respect to electron-withdrawing substituents on the phenyl ring.[4d] Herein, we examine the variable of the molecular spacer that links the carbanion nucleophile to the aryl ring. Due to the spirocyclic nature of the intermediate, wherein the size of the transient ring is determined by the length of the spacer, this variable would be predicted to have great influence on the reaction.

## 2 | RESULTS AND DISCUSSION

The experimental substrates **1a-e** (Scheme 2) were designed based upon a molecular structure that has been found to readily undergo the proposed aryl migration reaction.[4d] The inclusion of a strongly electron-withdrawing nitro substituent at the 4-position of the phenyl ring provides requisite




**SCHEME 1** General reaction for the Truce-Smiles rearrangement



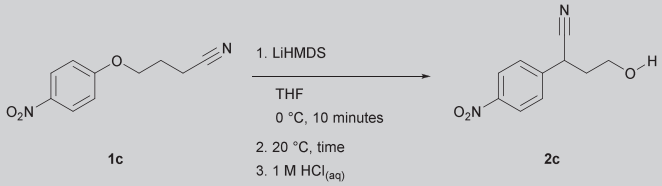

**SCHEME 2** Substrates and products examined in this study

stabilization of the delocalized hexadienyl anion σ-adduct, known as a Meisenheimer adduct. The substrates incorporate a nitrile functional group to lend stabilization to the proposed α-carbanion,[5] such that the nucleophile can be generated using standard bases in an organic solvent. The ether linkage provides an easily installed tether between the intended α-cyano carbanion nucleophile and the aryl ring *ipso*-carbon electrophile. Compounds **1a**, **1c**,[4d] **1d**, and **1e** were prepared using the standard Williamson ether synthesis method using 4-nitrophenol and the corresponding ω-haloalkylnitrile. Compound **1b** was prepared using the alternate strategy of conjugate addition of 4-nitrophenol to acrylonitrile because attempted synthesis using 3-bromopropanenitrile resulted exclusively in elimination products.

Conditions to promote Truce-Smiles rearrangement of substrates **1a-e** were investigated using compound **1c** as a model substrate. We have previously shown that **1c** is an excellent substrate for this aryl migration reaction.[4d] Inspired by the success of related aryl migration reactions using organolithium reagents,[6] we returned to further investigate our previous experiments[4d] involving the addition of lithium bis(trimethylsilyl)amide (LiHMDS) as a base to a 50 mM solution of **1c** in anhydrous tetrahydrofuran (THF) cooled at 0°C under inert atmosphere followed by passive warming to 20°C for 4 hours. The reaction is quenched through the addition of dilute aqueous acid. It became apparent that our previous efforts with these conditions had failed to optimize the reaction conditions with respect to equivalents of LiHMDS (Table 1, entries 1-5) and that we had naively used a substoichiometric amount of base.[4d] The optimal stoichiometry was found to be 2.5 equivalents of LiHMDS relative to substrate **1c** (Table 1, entry 4). An optimal conversion and isolated yield of 87% **2c** was achieved by increasing the reaction time to 20 hours (Table 1, entry 6).

These newly optimized conditions of addition of 2.5 equivalents of LiHMDS to a 50 mM solution of aryl ether substrate in anhydrous THF cooled at 0°C under inert atmosphere followed by passive warming to 20°C for 20 hours were tried with each of the other substrates **1a**, **1b**, **1d**, and

**TABLE 1** Optimization of Truce-Smiles rearrangement of substrate **1c** using LiHMDS as a base in tetrahydrofuran




| Entry | Equivalents | Time, h | Ratio of 1c:2c[a] | % yield 2 |
|---|---|---|---|---|
| 1 | 1.0 | 4 | 95:<5 | - |
| 2 | 1.5 | 4 | 48:52 | 43 |
| 3 | 2.0 | 4 | 46:54 | n.d. |
| 4 | 2.5 | 4 | 14:86 | 80 |
| 5 | 3.0 | 4 | 11:89 | n.d. |
| 6 | 2.5 | 20 | <5:95 | 87 |

[a]determined by $^1$H NMR spectrum integrations of crude reaction mixtures

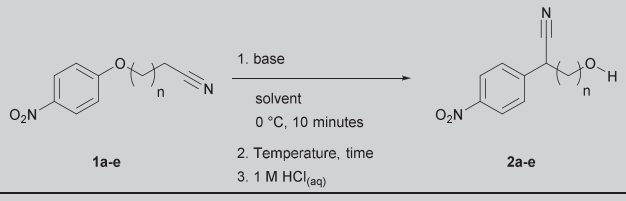
**1e**, yet failed to yield the rearranged products. Further, the rearrangement of these substrates was attempted using similar reaction conditions except for increasing temperatures to 40°C and 60°C. Increased temperature failed to yield products **2a**, **2b**, or **2e** (Table 2, entries 1, 3, and 9) but did however afford rearrangement product **2d** in 48% yield (Table 2, entry 7) at 40°C. The crude reaction mixtures of **1a** and **1e** were composed of recovered substrate. The crude reaction mixture of **1b** initially only yielded 4-nitrophenol; however, careful evaporation of the reaction mixture revealed acrylonitrile as a second product, suggesting elimination (assumedly by an E1cB mechanism) as the preferred reaction path of the α-cyano carbanion formed in situ (Scheme 3).

We have previously determined optimized reaction conditions for the rearrangement of substrate **1c**, using sodium hydride as a base.[4d] These conditions were established to be addition of 1.5 equivalents of sodium hydride to a 50 mM solution of **1c** in anhydrous *N*,*N*-dimethylformamide (DMF) at 0°C under inert atmosphere followed by passive warming to 20°C over 4 hours.[4d] We applied these prior established optimized conditions to attempt the rearrangement of **1a**, **1b**, **1d**, and **1e** when the newly optimized LiHMDS in THF conditions failed to achieve rearrangement. These NaH/DMF conditions failed to yield the rearranged products. We have previously shown that increasing the reaction temperature decreases reaction time for substrate **1c**;[4d] therefore, the rearrangement of substrates **1a**, **1b**, **1d**, and **1e** were attempted using reaction temperatures of 40°C and 60°C and at increasing lengths of time up to 20 hours. Increasing reaction temperature and/or time failed to yield product **2a**, **2b**, or **2e** (Table 2, summarized as entries 2, 4, and 10). The crude reaction mixtures of **1a** and **1e** were composed of recovered substrate. The crude reaction mixture of **1b** again showed elimination products acrylonitrile and 4-nitrophenol. The rearranged product **2d** was isolated from reaction mixtures for **1d**, showing the greatest yield, 51%, when the reaction was conducted at 60°C for 20 hours (Table 2, entry 8). The remainder of the reaction mixture constituted hydrolysis product 4-nitrophenol and recovered **1d**.

These experiments therefore illustrated highest Truce-Smiles rearrangement reactivity for substrate **1c**, which proceeds through a 5-membered ring spirocyclic Meisenheimer intermediate, and lower reactivity for substrate **1d**, which proceeds through a 6-membered ring intermediate. No apparent reactivity was observed for substrates **1a** and **1e**, which proceed through 3-membered ring, and 7-membered ring intermediates, respectively. The ability to assess the reactivity of substrate **1b** via Truce-Smiles rearrangement was confounded by the competing reactivity of the substrate via the E1cB elimination mechanism and therefore cannot be determined by these experiments.

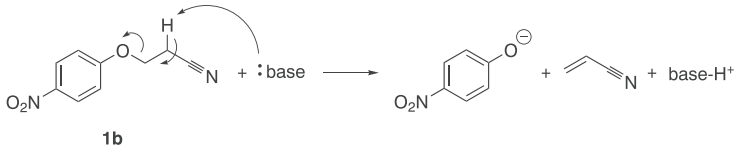
A review of the literature reveals putative Truce-Smiles rearrangements that have proceeded through 3-, 4-, 5-, and 6-membered ring spirocyclic intermediates. Although there have been no reported systematic studies of the effect of the spacer structure, the incomplete data from this literature survey reveal that substrates providing a 5-membered ring intermediate constitute the largest portion of the successful

**TABLE 2** Truce-Smiles rearrangement of alkanenitrile 4-nitrophenyl ether substrates




| Entry | 1 | n | Solvent | Base | Equivalents | Temperature, °C | Time, h | % yield 2 |
|---|---|---|---|---|---|---|---|---|
| 1 | **a** | 0 | THF | LiHMDS | 2.5 | 60 | 20 | - |
| 2 | **a** | 0 | DMF | NaH | 1.5 | 60 | 20 | - |
| 3 | **b** | 1 | THF | LiHMDS | 2.5 | 60 | 20 | - |
| 4 | **b** | 1 | DMF | NaH | 1.5 | 60 | 20 | - |
| 5 | **c** | 2 | THF | LiHMDS | 2.5 | 20 | 20 | 87 |
| 6 | **c** | 2 | DMF | NaH | 1.5 | 20 | 4 | 86 |
| 7 | **d** | 3 | THF | LiHMDS | 2.5 | 40 | 20 | 48 |
| 8 | **d** | 3 | DMF | NaH | 1.5 | 60 | 20 | 51 |
| 9 | **e** | 4 | THF | LiHMDS | 2.5 | 60 | 20 | - |
| 10 | **e** | 4 | DMF | NaH | 1.5 | 60 | 20 | - |

Abbreviations: DMF, dimethylformamide; THF, tetrahydrofuran.




**SCHEME 3** Proposed elimination mechanism for substrate **1b**

rearrangement reactions. This is consistent with the reactivity trend that we have revealed in the experiments reported here.

Examples of Truce-Smiles rearrangements occurring through the formation of 3-membered ring spirocyclic Meisenheimer intermediates (Figure 1).are rare.[7] It could be argued that the ring contractions observed as part of the domino Ugi-Smiles/Truce-Smiles reactions reported by El Kaïm et al are specially favored by stable conformations accessible to the bicylic substrate, formed in situ, that are not easily accessed by typical acylic substrates.[7a] The intermediacy of an ionic benzyllithium species, in keeping with the intramolecular $S_NAr$ mechanism of the Truce-Smiles rearrangement, is favored by Dudley's research group for their reported 1,2-aryl migration of 2-benzyloxypyridines; however, they also concede that a radical mechanism, in keeping with the [1,2]-Wittig reaction, cannot be entirely ruled out.[7b]

Arguments for the involvement of 4-membered ring spirocyclic Meisenheimer intermediates are more compelling than those for 3-membered ring spirocyclic Meisenheimer intermediates; however, examples of Truce-Smiles rearrangements occurring through the formation of 4-membered ring spirocyclic Meisenheimer intermediates are also relatively uncommon[8] in comparison to examples occurring through the formation of 5-membered ring spirocyclic Meisenheimer intermediates, which are most common in the literature. These include the reactions reported by Dohmori and colleagues[9] and the research groups of Truce,[10] Drozd,[11] Hirota,[12, 4a] Snape,[4c] and Wood,[4d] but also many isolated,[13] seemingly adventitious, reactions reported. The so-called[14] "Clayden rearrangement" 1,4-aryl migration reaction[6,15] could be viewed as proceeding through an intermediate highly related to a 5-membered spirocyclic Meisenheimer intermediate.

The relative stability of 6-membered saturated carbocyclic rings supports the existence of 6-membered ring spirocyclic Meisenheimer intermediates such as would be invoked for explaining the rearrangement of substrate **1d** in this report. However, examples of Truce-Smiles rearrangements occurring through the formation of 6-membered ring spirocyclic Meisenheimer intermediates are relatively uncommon.[16, 4b] Generally, the structural linker connecting the electrophilic aryl ring to the nucleophilic carbanion center in the examples tend to be more unsaturated than in substrates that favor smaller ring spirocyclic Meisenheimer intermediates, perhaps suggesting that the fewer degrees of rotational freedom of the atoms in the linker permits the formation of these less common, larger intermediate rings. To our knowledge, there are no reported examples of Truce-Smiles rearrangement reactions that have been proposed to proceed through a spirocyclic Meisenheimer intermediate with greater than 6 atoms in one ring.

The influence of various structural design features of substrate molecules upon intramolecular rate enhancement has not been extensively studied for $S_NAr$ reactions, in comparison to certain other reaction mechanisms. The addition step of the $S_NAr$ reaction mechanism could be classified as an *exo-trig* process by extension of Baldwin's Rules for ring-forming reactions,[17] which would therefore predict no disfavored ring sizes for the various substrates studied here. Bimolecular nucleophilic substitution ($S_N2$) is an example of a mechanism for which the effect of ring size in ring-closing reactions that has been examined in relatively greater detail, likely due to its prevalent implication in many enzyme-catalyzed reaction mechanisms. The term "effective molarity" has been used for several decades to make comparisons between intramolecular and intermolecular chemical processes, and it is a useful parameter for evaluating the effect of substrate structural variables upon an intramolecular reaction.[18] Effective molarity is a quantitative parameter defined as the ratio of the rate of a given intramolecular reaction and its corresponding intermolecular analog following an identical mechanism ($k_{intra}/k_{inter}$). Factors that influence the extremely wide range (<1 to $>10^{10}$) of observed effective molarities for $S_N2$ ring-closing reactions have been shown to include reaction type (particularly the nature of the nucleophile), solvent, and ring size.[18] Comparison of the reaction rate data for various different $S_N2$ ring-closing reactions,[18] such as the formation of cycloalkanes and lactones, have given the same trend for the ease of ring formation: 5 > 3 > 6 > 7 ≈ 4, which is similar to the trend observed in our study of the Truce-Smiles rearrangement, despite the differences between the $S_N2$ and the $S_NAr$ reaction

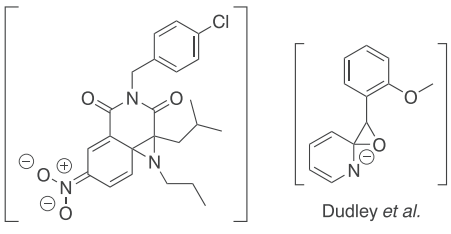



**FIGURE 1** Putative 3-membered ring spirocyclic Meisenheimer intermediates from literature[7]

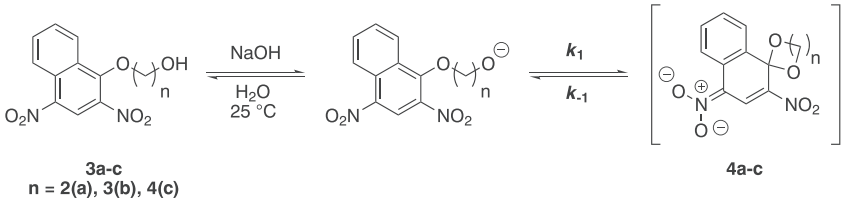
mechanisms. One major discrepancy is our lack of any observed reactivity for the substrate, which proceeds through a 3-membered ring spirocyclic intermediate.

It has been proposed that the strong dependency of $S_N2$ ring-closing reaction rates upon the size of the ring can be attributed to factors influencing 2 major aspects of the reaction: ring strain and the probability of the electrophile and nucleophile reacting.[19] Factors that influence ring strain include those that put constraints on molecular geometries in a cyclic structure including steric strain, torsional strain, and angle strain. Factors that influence the probability of the nucleophile and electrophile reacting include those that affect the proximity and orientation of the 2 functional groups, including the increasing distance between the 2 with increasing chain length, conformational flexibility in the molecular spacer that links the 2, and the *gem*-dialkyl effect. These 2 sets of factors are independent of each other yet result in the observed typical trend of the 5-membered ring being the easiest to form as a result of a compromise between the trend in the proximity of nucleophile and electrophile typically decreasing with increasing ring size for conformationally flexible systems comprised mostly of atoms with tetrahedral geometries and the ring strain that would correspondingly see a minimum value at the 6-membered ring.

The increased stability of, and therefore ease of forming, 5-membered ring spirocyclic intermediates over 6- and 7-membered is a trend that has been observed for the Smiles rearrangement, which is believed to follow a $S_NAr$ mechanism in analogy to the Truce-Smiles rearrangement.[20] These studies showed that, for the Smiles rearrangement system shown in Scheme 4, spectrophotometrically determined rate constants for the formation of the spirocyclic Meisenheimer intermediates **4a-c** showed large decreases on increasing the ring size from 5 to 6 or 7 members, while the deprotonation step and the rate of the spirocyclic ring opening were largely unaffected. The authors applied the previously seen arguments of proximity and ring strain by hypothesizing that increasing ring size was resulting in increasingly more negative activation entropies due to the increased rotational freedom of the larger rings and that this was combining with the trend in ring strain, assuming that this spirocyclic ketal ring series followed the observed trend for cycloalkanes[21] with a minimum at the 6-membered ring, to produce a trend where the 5-membered spirocyclic intermediate **4a** showed the greatest reaction rate for ring closure. It was also argued that steric strain caused by interaction of the spacer atoms with ortho-substituents of the aryl ring destabilizes 6- and 7-membered spirocyclic intermediates relative to 5-membered.[20] This last factor is one that could be predicted to exert a strong influence especially on spirocyclic ring systems[22] formed as the Meisenheimer intermediates in intramolecular $S_NAr$ reactions due to the sterically congested quaternary spirocenter.

An extension of these conclusions from the Smiles rearrangement studies to the reaction system that is the focus of our study is complicated by the numerous differences between the 2 systems studied. However, the observed trend in reactivity is consistent between these fundamentally related reactions. One particularly complicating factor to the extension of Bernasconi and Crampton's hypotheses is the presence of nitro substituents in the ortho-positions flanking the electrophilic site of reaction on the aryl ring in every substrate (**3a-c**) studied. Therefore, the argument that steric strain between spacer atoms and ortho-substituents is tainted by electronic effects since distortion of the nitro groups' orientations will also result in destabilization of the intermediate due to less efficient overlap of orbitals in the delocalized cyclohexadienyl anion system.

Since the unique aspects of the Truce-Smiles reaction system that we have studied herein complicate the comparison of our results with similar results in the literature, we have performed a computational study of the reaction pathway of the α-cyano carbanions derived from substrates **1a-e** in their conversion to the corresponding spirocyclic Meisenheimer intermediates, to elucidate the origins of the observed trend in reactivity. The existence of the Meisenheimer intermediate as a stable species has been established from our previous $^1$H NMR spectroscopy experiments showing the in situ formation of the intermediate in DMSO-$d_6$ with NaH.[4d] To further understand the influence of the spacer group length, we located the transition state structures that produce the spirocyclic intermediates from the α-cyano carbanions by a $S_NAr$ mechanism as well as the transition state structures that lead to the production of the rearranged aryl migration product of the Truce-Smiles rearrangement. There has been one previous report of a computational study into the potential energy surface of a Truce-Smiles rearrangement reaction pathway.[8d] Unfortunately, the dissimilarity between the structures of the intermediates involved in the previously studied reaction and the computational methods used with those used in this study preclude comparison of the results.



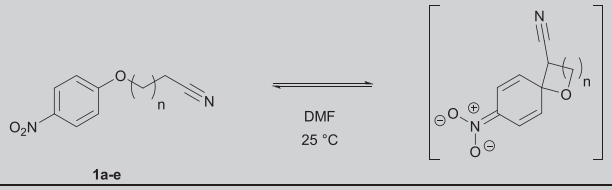

**SCHEME 4** Smiles rearrangement reactions studied by Crampton and Bernasconi[20]

For our computational study, stationary points (minima and saddle points) on the determined at the ωB97X-D/6-31 + G(d,p) level of theory,[23] with solvation in DMF simulated using the SMD solvent model.[24] The connection of each transition state structure to its corresponding minima (reactant and product) was determined by an intrinsic reaction coordinate calculation, and each stationary point was verified by harmonic frequency analysis. Energies were corrected for zero-point and thermodynamic effects at 298 K.[25] The influence of ion pairing was not investigated. The Truce-Smiles rearrangement of substrates **1a-e** is a stereogenic reaction; however, the products are enantiomeric and so calculation of the 2 reaction scenarios would be redundant. For each substrate the pathways to the formation of 2 conformational isomeric spirocyclic intermediates, referred to here as conformer A and conformer B, were calculated individually. Each of these pairs of 2 conformers can be viewed as differing by the orientation of the cyano group (ranging between an axial or equatorial orientation at the extreme) on the conformationally flexible cycloalkane ring of the spirocyclic intermediate. The results obtained from these calculations are summarized in Table 3, with a representative potential energy surface for the reaction of **1c** to yield **2c** shown in Figure 2. The transition state for the formation of the C–C bond during the Truce-Smiles rearrangement of substrate **1c** when the cyano group is oriented in an equatorial position (conformer A) was found to have $\Delta G^{\ddagger} = 30.8$ kJ·mol$^{-1}$, which was the lowest for any of the substrates studied here. The calculated activation energies for the conversion of the α-cyano carbanions derived from substrates **1a-e** to their corresponding spirocyclic cyclohexadienyl anion intermediate via the $S_NAr$ pathway correspond to relative rates giving a trend in reactivity of **1c** >> **1d** ≈ **1a** > **1e** >> **1b** (ie, 5 >> 6 ≈ 3 > 7 >> 4) at 25°C. Although we observed no reactivity for substrate **1a**, the trend is still generally in qualitative agreement with the reactivity observed experimentally, bearing in mind that measuring the rearrangement reactivity of **1b** was potentially obscured by the competing elimination reaction shown in Scheme 3.

The calculated potential energy surface shown in Figure 2 provides an illustration of the experimentally observed stability of the Meisenheimer intermediate derived from substrate **1c**,[4d] in that this structure is a thermodynamic minimum. The calculated potential energy surface also provides support for the observed high conversion of the Meisenheimer intermediate by the forward direction to break the C–O bond preferentially (isolated yield of 87%), this reaction having a lower $\Delta G^{\ddagger}$ barrier than the reverse, unproductive, C–C bond breaking reaction.

The trend in free energies of reaction, $\Delta G$, follows that of the free energies of activation, $\Delta G^{\ddagger}$ (Table 3). Due to the

**TABLE 3** Calculated thermodynamic and kinetic parameters for α-cyano carbanions derived from substrates **1a-e** to their corresponding spirocyclic cyclohexadienyl anion Meisenheimer intermediate via the $S_NAr$ pathway




1a-e

| Reactant | n | Conformer | $\Delta G$, kJ·mol$^{-1}$ | $\Delta G^{\ddagger}$, kJ·mol$^{-1}$ | $\Delta H^{\ddagger}$, kJ·mol$^{-1}$ | $\Delta S^{\ddagger}$, J·mol$^{-1}$·T$^{-1}$ | Relative Rate at $T$= 25°C |
|---|---|---|---|---|---|---|---|
| **1a** | 0 | A | +10 | 54 | +49 | −16 | $9 \times 10^{-5}$ |
| | | B | +11 | 54 | +48 | −20 | $8 \times 10^{-5}$ |
| **1b** | 1 | A[a] | +34 | 83 | +80 | −10 | $9 \times 10^{-10}$ |
| | | B[b] | +34 | 83 | +80 | −10 | $8 \times 10^{-10}$ |
| **1c** | 2 | A[c] | −51 | 31 | +28 | −10 | 1 |
| | | B[d] | −44 | 34 | +29 | −18 | 0.2 |
| **1d** | 3 | A[a] | −36 | 59 | +47 | −39 | $1 \times 10^{-5}$ |
| | | B[b] | −32 | 54 | +44 | −35 | $7 \times 10^{-5}$ |
| **1e** | 4 | A[a] | −37 | 61 | +48 | −46 | $5 \times 10^{-6}$ |
| | | B[b] | −31 | 58 | +47 | −37 | $2 \times 10^{-5}$ |

[a]Cyano group occupies pseudo-equatorial position.

[b]Cyano group occupies pseudo-axial position.

[c]Cyano group occupies equatorial position.

[d]Cyano group occupies axial position.

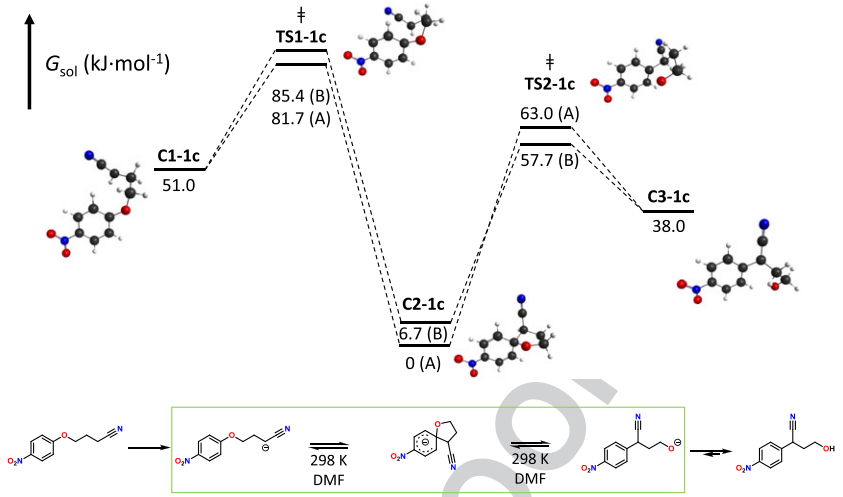



**FIGURE 2** Calculated potential energy surface for the reaction of the α-cyano carbanion derived from **1c** via the Truce-Smiles rearrangement with 2 possible Meisenheimer intermediate conformers: (A) cyano group equatorial and (B) cyano group axial

relative simplicity in which the Meisenheimer adduct is formed from the carbanion (ie, the formation of a single C–C bond), the transition state structures resemble the structure of the α-cyano carbanion intermediates quite closely. Therefore, we believe that trends observed in both energies regarding spacer length, n, are due to the same phenomena and will be discussed as such. The apparently anomalous increase in $\Delta G$ and $\Delta G^{\ddagger}$ upon increasing the spacer length from $n = 0$ to $n = 1$ is due to the exceptional stability of **1b**. Unlike **1a** and **1c**-**1e**, **1b** can decompose by transfer of the negative charge to the O and formation of a CC double bond, as indicated by Scheme 3. The increased stability of the carbanion by negative hyperconjugation[26] attained through resonance with the pseudo-eliminated structure (supported by increased C–O and decreased C–C bond lengths, decreased C–O bond order,[27] and LMO analysis[28] [see Supporting Information]) lowers its energy with respect to the transition structure and intermediate compared to the reactants of other spacer lengths.

The $\Delta G$ values for **1c** are lower than those for **1a** and **1b**, and this is explained by the decrease in ring strain of the intermediate as the size of the ring is increased. However, upon going from a 5-membered ring (**1c**) to a 6-membered ring (**1d**), a system with arguably less or the same amount of strain, $\Delta G$ increases. The overall trend (**1a**-**1e**) in $\Delta G$ and $\Delta G^{\ddagger}$ is reproduced when considering only enthalpies or internal energies with no thermal correction, which means entropy does not play a significant role. The increase in $\Delta G$ from **1c** to **1d** is explained by considering the relative stability of the spirocyclic intermediates. Compared to the 5-membered ring intermediate of **1c**, there may be less strain in the 6-membered ring of the **1d** intermediate, but there is also more electrostatic repulsion between the oxygen (O) and the cyano-substituted carbon ($C_{CN}$), adjacent to the spirocarbon ($C_{spiro}$), and the *para*-nitrophenyl group where the negative charge resides. Interaction energies between fragments of molecules were obtained for gas phase ωB97X-D/6-31 + G(d,p) structures using the localized molecular orbital energy decomposition analysis (LMO-EDA)[29] by Su and Li. The increase in electrostatic repulsion is due to the larger $C_{CN}$–$C_{spiro}$–O bond angle in the **1d** intermediate of 108.4°, compared to 101.4° in the **1c** intermediate, which puts these groups in closer proximity to each other. Therefore, the optimal spacer length of $n = 2$, which corresponds to a 5-membered ring, is a result of a balance between ring strain and electrostatic repulsion between the 2 rings.

## 3 | CONCLUSION

This study has filled its intended goal of continuing our systematic survey of the substrate scope of the Truce-Smiles rearrangement. The length of the molecular tether connecting the carbanion nucleophile to the electrophilic aromatic ring determines the size of one ring in the spirocyclic Meisenheimer intermediates of the Truce-Smiles rearrangement. Literature reports of successful rearrangement reactions imply a trend that substrates bearing a tether that results in a 5-membered ring spirocyclic intermediate are favored substrates. Our experimental results support this trend showing highest yields for product **2c**, which we have previously shown to proceed through the proposed $S_NAr$ spirocyclic Meisenheimer intermediate incorporating a 5-membered ring,[4d] and for product **2d**, which is proposed to proceed through a 6-membered ring intermediate, by analogy. The reactivity of substrate **1b** via the Truce-Smiles rearrangement could not be measured due to a competing elimination reaction. Computational studies derived a series of calculated relative reaction rates for the formation of spirocyclic Meisenheimer intermediates from substrates **1a**-**e** that also support the trend implied by the literature, predicting an optimal reaction rate for substrate **1c** and decreasing as the variable ring in the proposed spirocyclic Meisenheimer intermediate becomes either larger or smaller

than a 5-membered ring. Examination of the structures of the calculated transition states derived from substrates **1a-e** suggest that the factors of ring strain, as measured by enthalpy of activation, and electrostatic repulsion between the 2 rings of the Meisenheimer adduct, combine to produce the observed trend in reactivity. Steric interactions between the ortho-substituents of the aromatic ring and atoms in the tether, which has been proposed for related Smiles rearrangement ring-size reactivity trends, do not seem to exert a strong influence upon the reactivity of substrates **1a-e** in the Truce-Smiles rearrangement studied here.

## 4 | EXPERIMENTAL

### General methods

All glassware used for Truce-Smile rearrangement reactions was flame-dried under a vacuum and reactions were run under an inert atmosphere of nitrogen. All reagents and solvents were commercial grade. All organic layers collected from extractions were dried using anhydrous $MgSO_4$. Thin layer chromatography (TLC) was performed using aluminum-backed silica gel plates (250 μm), and flash column chromatography used 230-400 mesh silica. Compounds were visualized using UV light (λ = 254 nm) and either phosphomolybdic acid or vanillin solutions. Melting points were determined using a capillary melting point apparatus and are reported uncorrected. FTIR spectra were recorded of samples as a thin film on a KBr plate (transmission). NMR spectra were acquired on a 400 MHz instrument. Chemical shifts are reported relative to tetramethylsilane as an internal standard set to δ 0.00 ppm for $^1H$ and relative to the $CDCl_3$ solvent residual as an internal standard set to δ 77.16 ppm for $^{13}C$. Multiplicities are reported as apparent (app), broad (br), singlet (s), doublet (d), triplet (t), quartet (q) and combinations thereof, or multiplet (m). HRMS data are obtained by electrospray (ESI) using an ion trap.

### 4.1 | Preparation of alkanenitrile 4-nitrophenoxy ether substrates 1a, b, d, e

#### 4.1.1 | General procedure A

To a round-bottom flask fitted with a reflux condenser was added 4-nitrophenol (1.53 g, 11 mmol, 1.1 equiv), anhydrous potassium carbonate (1.38 g, 10 mmol, 1.0 equiv.), ω-haloalkanenitrile (10 mmol), and acetone (30 mL). The reaction mixture was heated with stirring to the boiling point of acetone using a heating block, and reflux was maintained for 20 hours. The solution was concentrated, diluted with ethyl acetate (50 mL), washed with 1 M $HCl_{(aq)}$ (30 mL), and washed with 1 M $NaOH_{(aq)}$ (2 × 30 mL). The organic layer from the extraction was dried, filtered, and concentrated.

#### 4.1.2 | 2-(4-Nitrophenoxy)acetonitrile (1a)

General procedure A: The product was prepared from chloroacetonitrile (0.63 mL). Flash column chromatography (30% ethyl acetate, 70% hexanes) yielded the product as a light yellow crystalline solid (1.26 g, 71%). CAS: 33901-46-1; mp 70-73°C (lit.[30] 73-75°C); TLC $R_f$ = 0.34 (30% ethyl acetate, 70% hexanes); IR (KBr, thin film) $\bar{\nu}_{max}$ = 3090, 2941, 2831, 2258, 1601, 1507, 1331, 1216, 850 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) δ = 8.29 (d, $J$ = 6.9 Hz, 2H), 7.09 (d, $J$ = 6.9 Hz, 2H), 4.88 (s, 2H) ppm (consistent with lit.[30]); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ = 161.0 (arom. C1), 143.5 (arom. C4), 126.3 (arom. C3, C5), 115.1 (arom. C2, C6), 114.1 (C≡N), 53.7 ($OCH_2$) ppm; LRMS (ESI) *m/z* (relative intensity) = 201.0 (100%); HRMS (ESI) *m/z*: $[M + Na]^+$ calcd for $C_8H_6N_2O_3$: 201.0271, found: 201.0266.

#### 4.1.3 | 3-(4-Nitrophenoxy)propanenitrile (1b)

The product was prepared using a procedure modified from literature.[31] To a round-bottom flask fitted with a reflux condenser was added 4-nitrophenol (1.38 g, 10 mmol), acrylonitrile (66 mL, 1.0 mol, 100 equiv.), anhydrous potassium carbonate (0.069 g, 0.5 mmol, 0.05 equiv.), and *tert*-butanol (0.10 mL, 1.0 mmol, 0.1 equiv.). The reaction mixture was heated with stirring to the boiling point of acrylonitrile using a heating block, and reflux was maintained for 8 hours. Anhydrous potassium carbonate was added (0.069 g, 0.5 mmol, 0.05 equiv.). Reflux was maintained for 28 hours. Phosphoric acid (85 wt% in $H_2O$, 0.09 mL, 0.8 mmol, 0.08 equiv.) was added and the mixture stirred for 0.5 hours. The mixture was concentrated, diluted with toluene (100 mL), washed with 1 M $HCl_{(aq)}$ (30 mL), and washed with 1 M $NaOH_{(aq)}$ (2 × 30 mL). The organic layer from the extraction was dried, filtered, and concentrated. Flash column chromatography (40% ethyl acetate, 60% hexanes) yielded the product as a light yellow crystalline solid (0.29 g, 17%). CAS: 69333-42-2; mp 61-63°C (lit.[32] 78-79°C, lit.[33] 53.1°C); TLC $R_f$ = 0.50 (40% ethyl acetate, 60% hexanes); IR (KBr, thin film) $\bar{\nu}_{max}$ = 3089, 2941, 2838, 2258, 1599, 1509, 1343, 1264, 852 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) δ = 8.24 (d, $J$ = 7.0 Hz, 2H), 7.00 (d, $J$ = 7.0 Hz, 2H), 4.30 (t, $J$ = 6.3 Hz, 2H), 2.91 (t, $J$ = 6.3 Hz, 2H) ppm (consistent with lit.[32]); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ = 162.6 (arom. C1), 142.4 (arom. C4), 126.1 (arom. C3, C5), 116.7 (C≡N), 114.7 (arom. C2, C6), 63.3 ($OCH_2$), 18.6 ($CH_2CN$) ppm (consistent with lit.[32]); LRMS (ESI) *m/z* (relative intensity) = 215.0 (100%); HRMS (ESI) *m/z*: $[M + Na]^+$ calcd for $C_9H_8N_2O_3$: 215.0427, found: 215.0426.

#### 4.1.4 | 5-(4-Nitrophenoxy)pentanenitrile (1d)

General procedure A: The product was prepared from 5-bromovaleronitrile (1.2 mL). Flash column chromatography (30% ethyl acetate, 70% hexanes) yielded the product as a light yellow crystalline solid (2.09 g, 95%). CAS: 104296-36-8; mp 31-33°C (lit.[34] 35-36°C); TLC $R_f$ = 0.34 (30% ethyl acetate, 70% hexanes); IR (KBr, thin film) $\bar{\nu}_{max}$ = 3114, 2974, 2834, 2258, 1509, 1409, 1321, 853 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) δ = 8.21 (d, *J* = 7.1 Hz, 2H), 6.95 (d, *J* = 7.1 Hz, 2H), 4.11 (t, *J* = 5.8 Hz, 2H), 2.47 (t, *J* = 6.9 Hz, 2H), 2.05-1.98 (m, 2H), 1.94-1.87 (m, 2H) ppm; $^{13}C$ NMR (100 MHz, $CDCl_3$) δ = 163.7 (arom. C1), 141.4 (arom. C4), 125.8 (arom. C3, C5), 119.4 (C ≡ N), 114.4 (arom. C2, C6), 67.6 ($OCH_2$), 27.9 ($OCH_2CH_2$), 22.2 ($CH_2CN$), 16.9 ($CH_2CH_2CN$) ppm; LRMS (ESI) *m/z* (relative intensity) = 244.1 (100%); HRMS (ESI) *m/z*: $[M + Na]^+$ calcd for $C_{11}H_{12}N_2O_3$: 243.0740, found: 243.0731.

#### 4.1.5 | 6-(4-Nitrophenoxy)hexanenitrile (1e)

General procedure A: The product was prepared from 6-bromohexanenitrile (1.3 mL). Flash column chromatography (30% ethyl acetate, 70% hexanes) yielded the product as a light yellow crystalline solid (2.04 g, 87%). CAS: 100135-38-4; mp 33-35°C (lit.[34] 38-39°C); TLC $R_f$ = 0.40 (30% ethyl acetate, 70% hexanes); IR (KBr, thin film) $\bar{\nu}_{max}$ = 3115, 3086, 2946, 2871, 2245, 1515, 1339, 1264, 1045 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) δ = 8.20 (d, *J* = 9.3 Hz, 2H), 6.94 (d, *J* = 9.3 Hz, 2H), 4.08 (t, *J* = 6.2 Hz, 2H), 2.41 (t, *J* = 6.9 Hz, 2H), 1.92-1.85 (m, 2H), 1.81-1.63 (m, 4H) ppm; $^{13}C$ NMR (100 MHz, $CDCl_3$) δ = 163.9 (arom. C1), 141.3 (arom. C4), 125.8 (arom. C3, C5), 119.5 (C≡N), 114.4 (arom. C2, C6), 68.2 ($OCH_2$), 28.1 ($OCH_2CH_2$), 25.1 ($CH_2CH_2CN$), 25.0 ($OCH_2CH_2CH_2$), 17.0 ($CH_2CN$) ppm; LRMS (ESI) *m/z* (relative intensity) = 257.1 (100%); HRMS (ESI) *m/z*: $[M + Na]^+$ calcd for $C_{12}H_{14}N_2O_3$: 257.0897, found: 257.0889.

#### 4.1.6 | Preparation of rearrangement products 2c, d

### 4.2 | General procedure B

To a round-bottom flask was added the rearrangement substrate (**1**) (1.0 mmol), and the flask was evacuated and backfilled with nitrogen 3 times. Anhydrous THF (20 mL) was added, and the solution was cooled with stirring using an ice water cooling bath. Lithium bis(trimethylsilyl)amide solution (1M in THF) (1.0 mL g, 1.0 mmol, 1.0 equiv.) was added, and low temperature was maintained for 10 minutes. The reaction mixture was removed from the cooling bath and brought to a temperature for an amount of time as described in Table 2. The solution was neutralized at room temperature with 1 M $HCl_{(aq)}$, diluted with ethyl acetate (30 mL), washed with 1 M $HCl_{(aq)}$ (15 mL), and washed with water (2 × 20 mL). The organic layer from the extraction was dried, filtered, and concentrated.

### 4.3 | General procedure C

To a round-bottom flask was added the rearrangement substrate (**1**) (1.0 mmol), and the flask was evacuated and backfilled with nitrogen three times. Anhydrous DMF (20 mL) was added, and the solution was cooled with stirring using an ice water cooling bath. Sodium hydride (60% dispersion in oil) (0.060 g, 1.5 mmol, 1.5 equiv.) was added, and low temperature was maintained for 10 minutes. The reaction mixture was removed from the cooling bath and brought to a temperature for an amount of time as described in Table 2. The solution was neutralized at room temperature with 1 M $HCl_{(aq)}$, diluted with ethyl acetate (30 mL), washed with 1 M $HCl_{(aq)}$ (15 mL), and washed with water (2 × 20 mL). The organic layer from the extraction was dried, filtered, and concentrated.

#### 4.3.1 | 4-Hydroxy-2-(4-nitrophenyl) butanenitrile (2c)

General procedure B: Flash column chromatography (40% ethyl acetate, 60% hexanes) yielded the product as a yellow oil (0.179 g, 87%). CAS: 1791439-23-0

#### 4.3.2 | 5-Hydroxy-2-(4-nitrophenyl) pentanenitrile (2d)

General procedure B: Flash column chromatography (50% ethyl acetate, 50% hexanes) yielded the product as a colourless oil (0.105 g, 48%). mp <25°C; TLC $R_f$ = 0.21 (50% ethyl acetate, 50% hexanes); IR (KBr, thin film) $\bar{\nu}_{max}$ = 3090, 2941, 2258, 1599, 1509, 1332, 1110, 850 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) δ = 8.27 (d, *J* = 8.7 Hz, 2H), 7.56 (d, *J* = 8.7 Hz, 2H), 4.05 (t, *J* = 7.5 Hz, 1H), 3.75-3.74 (m, 2H), 2.11-2.05 (m, 2H), 1.81-1.74 (m, 2H), 1.37 (br s, 1H) ppm; $^{13}C$ NMR (100 MHz, $CDCl_3$) δ = 147.9 (arom. C4), 143.0 (arom. C1), 128.5 (arom. C2, C6), 124.5 (arom. C3, C5), 119.6 (C ≡ N), 61.8 ($CH_2OH$), 37.2 ($CHCN$), 32.6 ($CH_2CH_2OH$), 29.7 ($CH_2CH_2CH_2OH$) ppm; LRMS (ESI) *m/z* (relative intensity) = 243.1 (100%); HRMS (ESI) *m/z*: $[M + Na]^+$ calcd for $C_{11}H_{12}N_2O_3$: 243.0740, found: 243.0744.

General procedure C: Flash column chromatography (50% ethyl acetate, 50% hexanes) yielded the product as a colourless oil (0.112 g, 51%).

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