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Remote Aryl Cyanation via Isocyanide−Cyanide Rearrangement on Tosylmethyl Isocyanide Derivatives

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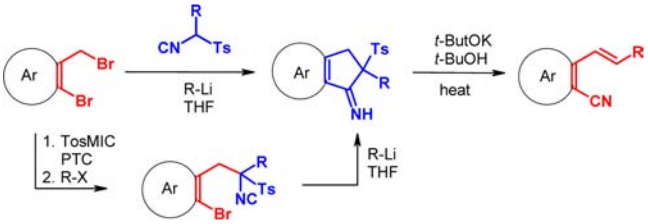
ABSTRACT



The reaction of alkyl tosylmethyl isocyanides and 2-bromobenzyl bromides in the presence of *t*-BuLi gives rise to a cascade reaction to give unexpected 2-substituted 2,3-dihydro-1*H*-indenimines which, upon treatment with *t*-BuOK, rearrange to 2-vinylbenzonitriles in high overall yields. This simple procedure represents a new approach to the synthesis of aromatic nitriles via isocyanide−cyanide interconversion.

Aromatic nitriles are commonly found in pharmaceuticals, agrochemicals, dyes, and natural products.[1] Moreover, the nitrile group serves as an intermediate for a multitude of transformations into other important functional groups, such as aldehydes, ketones, amines, acids, and heterocycles, a fact that makes cyano compounds important building blocks. Cyano groups have commonly been introduced through the Sandmeyer[2] or Rosenmund−von Braun[3] reactions in protocols that require stoichiometric amounts of Cu or high temperatures, which may not be compatible with densely functionalized substrates. More recently, these methods have been replaced either by transition-metal-catalyzed cyanation of aryl halides with metal cyanides or by the electrophilic cyanation of aryl nucleophiles, with the former method being the most widely studied.[4] However, this attractive method has two main drawbacks: the facile deactivation of the Pd-, Ni-, and Cu-based catalysts by excess cyanide, a phenomenon that has been widely recognized since the original work by Takagi's group in the 1970s,[5] and the toxicity often associated with nucleophilic cyanation sources.[6] As a result, the development of new methods is of continuing academic interest.[7]

Tosylmethyl isocyanide (TosMIC)[8] is a densely functionalized building block with three groups that can engage in a multitude of reactions: the isocyano function can undergo α-addition reactions, and the acidic α-carbon atom and the sulfonyl group in the α-position can also act as a leaving group or further enhance the acidity of the α-carbon. Although the remarkable properties of this isocyanide facilitate a wide range of transformations, its most important application has been in the synthesis of five-membered heterocycles.[9]

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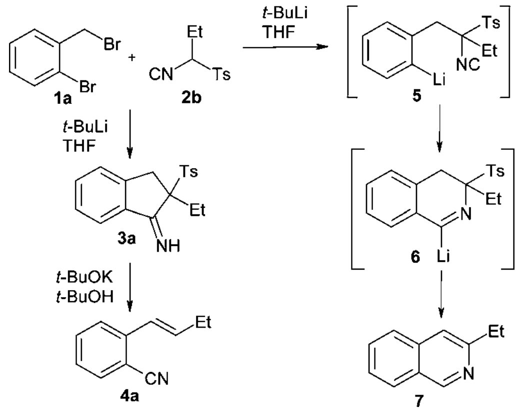
In the course of our research aimed at expanding TosMIC chemistry to the preparation of six-membered heterocycles,[10] we explored a new method for the synthesis of isoquinolines through the reaction of α-alkyl TosMIC derivatives and 2-bromobenzyl bromides, as shown in Scheme 1.

Scheme 1. Expected (**7**) and Obtained (**3a**) Products from the Reaction of **1a** and **2b**



In this study we initially tested the one-pot reaction between 2-bromobenzyl bromide (**1a**) and ethyltosylmethyl isocyanide (**2b**)[8] in the presence of 2.0 equiv of *t*-BuLi. The aim was to remove the α-proton of **2b** and displace the aryl halogen in **1a** to produce the heterocyclization reaction. However, the expected 3-ethylisoquinoline (**7**) was not formed and the unprecedented 2,3-dihydro-1*H*-indenimine **3a** was the main isolated product. Moreover, the attempted elimination of *p*-toluenesulfinic acid from **3a** under basic conditions also resulted in the formation of the unexpected 2-vinylbenzonitrile **4a**, with the best yield coming from heating **3a** under reflux in the presence of 1 equiv of *t*-BuOK in *t*-BuOH (Scheme 1).

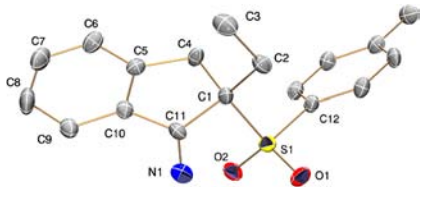
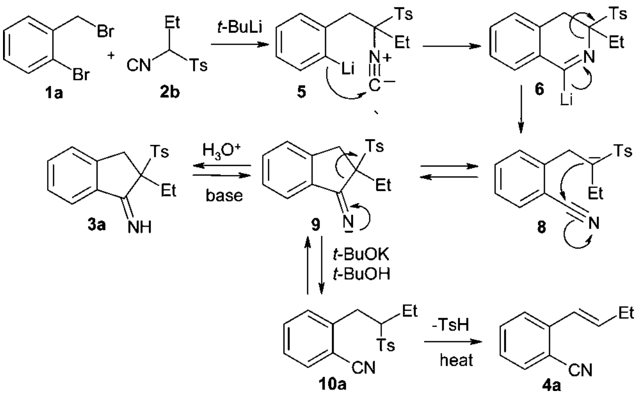


Figure 1. X-ray crystal structure of **3a**.

The structure of **3a** was unambiguously established by X-ray crystallography (Figure 1), and a plausible mechanistic hypothesis for its formation is shown in Scheme 2. The intermediate **5** would afford the expected anionic bicyclic intermediate **6**, which would undergo a ring-opening process to form the anionic intermediate **8**. Finally, intramolecular attack of this anion on the cyano group would lead to a five-membered ring formation. Treatment of the isolated imino compound **3a** with *t*-BuOK in *t*-BuOH could afford the vinyl arylnitrile derivative **4a** through a ring-opening process followed by loss of *p*-toluenesulfinic acid.

Scheme 2. Tentative Mechanism for the Formation of **3a** and **4a**



This overall process could represent a novel approach for the synthesis of a variety of aromatic nitriles through an unprecedented isocyanide–cyanide rearrangement in a heterocyclization process. Our initial efforts focused on the study of the transformation of **1a** to **4a** in a ‘one pot’ process. However, under different conditions—including a change of solvent and lithium base, the use of a large excess of lithium base, and an increase in temperature—the only isolable compound was **3a** and evidence for the formation of **4a** was not found. Only when the reaction of **1a** and **2b** was conducted in the same way as before, followed by the sequential addition of different amounts of *t*-BuOH to the reaction at −78 °C and then heating the mixture, was **4a** isolated, albeit in only 20% yield. We therefore focused our efforts on a search for the best conditions for each reaction separately and then applied the optimized conditions to explore the scope of this reaction for the synthesis of aromatic vinyl nitriles. The results show that the best yield of **3a** was obtained with *t*-BuLi in THF at −78 °C. The best conditions to produce the **3a** → **4a** rearrangement involved heating **3a** under reflux in the presence of *t*-BuOK/*t*-BuOH.

Under optimized conditions dibromo derivative **1a** reacted with different α-alkyl TosMIC derivatives[7,11] to give 2,3-dihydro-1*H*-indenimines **3a**–**d** with yields shown in Table 1 (entries 1–4). Other commercially available 2-bromobenzyl bromides such as **1b,c** also reacted with **2b** to afford moderate yields of the corresponding imines **3e,f** (Table 1, entries 5 and 6). However, the attempted reactions of other bromomethyl aryl bromides such as **1d**, bromomethyl naphthyl bromides such as **1e**, or bromomethyl heteroaryl bromides such as **1f,g** failed or gave very low yields of the corresponding 2,3-dihydro-1*H*-indenimines **3**.

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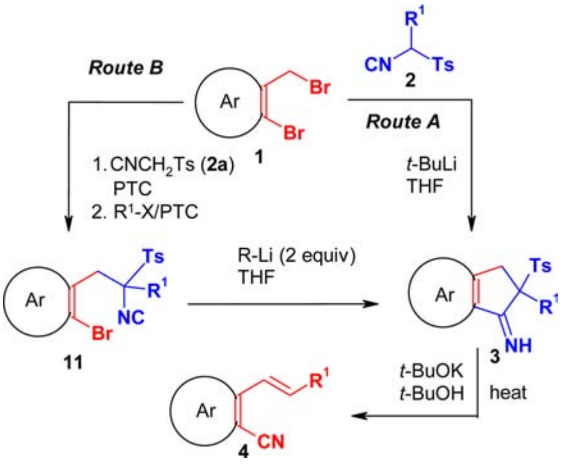
Scheme 3. Alternative Routes for the Synthesis of **3** and the Synthesis of Aryl and Heteroarylnitriles **4**



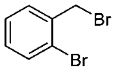
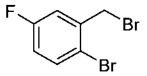
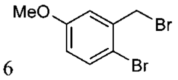
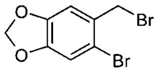
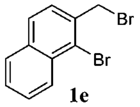
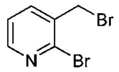
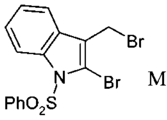
We realized that the problem concerned the S_N2 reaction between the deprotonated TosMIC derivative and the corresponding dibromides, and we therefore explored the S_N2 reaction under different conditions. It was found that phase-transfer catalysis conditions gave better yields than homogeneous conditions.[7,12] Thus, after testing different reaction conditions, we found that TosMIC reagent **2a** (R^1 = H) was able to react sequentially with two different alkyl halides in a single two-phase medium [CH_2Cl_2/NaOH (40%)] in the presence of tetrabutylammonium iodide (TBAI) as the catalyst. The first addition of 1 equiv of the 2-bromobenzyl bromide (**1**) over TosMIC (**2a**) and a second addition of a simple alkyl halide gave isonitriles **11** in high yields (Scheme 3 and Table 1, entries 7–11).

Compounds **3b** and **3f** were also prepared by route B in an attempt to improve the yields obtained by route A (Table 1, entries 2 and 6), but a significant improvement could not be achieved.

Treatment of these isonitriles with 2 equiv of *t*-BuLi in THF yielded the corresponding 2,3-dihydro-1*H*-indenimines **3g**–**k** in moderate yields (Table 1, entries 7–11). It is worth noting that the attempted reaction with **11l** failed to give the corresponding 2,3-dihydro-1*H*-indenimine. Complex mixtures were obtained, and the best yield of **3m** was achieved by treatment of **11m** with *n*-BuLi in THF (Table 1, entry 13).

Treatment of isolated 2,3-dihydro-1*H*-indenimines **3** with 1 equiv of *t*-BuOK in *t*-BuOH gave the desired *E*-vinylnitriles as the sole reaction product, in high yields in most cases (Table 1). The formation of the *E* isomer was unambiguously established for compound **4b** by comparison of the spectroscopic data with those reported in the literature.[13] The reaction of **1a** and **2d** (Table 1, entry 3) gave a 2:1 mixture of two benzonitriles[14] due to the presence of two different benzylic moieties on the presumed intermediate precursor (**10c**). Similar behavior was also found in the preparation of **4i**, which was accompanied by the formation of the corresponding 6-[(2*E*)-3-phenyl-2-propen-1-yl]-1,3-benzodioxone-5-carbonitrile as the major compound (2:3 ratio, entry 9). In an analogous way, the reaction of starting materials **1a** and **2e** (R^1 = allyl, entry 4) furnished the fully conjugated 2-[(1*E*, 3*E*)-1,3-butadienyl]benzonitrile as the only product. The reaction

Table 1. TosMIC Derivatives **11**, 2,3-Dihydro-1*H*-indenimines **3**, and Aryl Nitriles **4**

entry	1	R^1	yield (%) **11**	yield (%) **3**	yield (%) **4**
1	 **1a**	Et (**2b**)	--	66 (**3a**)[a]	83 (**4a**)
2		Me (**2c**)	--	40 (**3b**)[a]	80 (**4b**)
3		Bn (**2d**)	--	73 (**3c**)[a]	82 (**4c**)[c]
4		Allyl (**2e**)	--	45 (**3d**)[a]	80 (**4d**)
5	 **1b**	Et (**2b**)	--	46 (**3e**)[a]	60 (**4e**)
6	 **1c**	Et (**2b**)	--	40 (**3f**)[a]	83 (**4f**)
7	 **1d**	Et (**2b**)	80 (**11g**)	60 (**3g**)[b]	93(**4g**)
8		Me (**2c**)	96 (**11h**)	60 (**3h**)[b]	90 (**4h**)
9		Bn (**2d**)	75 (**11i**)	65 (**3i**)[b]	80 (**4i**)
10	 **1e**	Et (**2b**)	83 (**11j**)	62 (**3j**)[b]	82 (**4j**)
11		Bn (**2d**)	70 (**11k**)	65 (**3k**)[b]	80 (**4k**)[d]
12	 **1f**	Et (**2b**)	31 (**11l**)	0 (**3l**)[b]	--
13	 **1g**	Me (**2c**)	75 (**11m**)	44 (**3m**)[b,e]	83 (**4m**)[f]

[a] Isolated yield by route A. [b] Isolated yields from **11** (route B). [c] Isolated yield of a 2:1 mixture of 2-[(2*E*)-3-phenyl-2-propen-1-yl]-benzonitrile and [(1*E*)-3-phenyl-1-propen-1-yl]benzonitrile. [d] Isolated yield of a 3:2 mixture of 6-[(2*E*)-3-phenyl-2-propen-1-yl]-1,3-benzodioxone-5-carbonitrile and 6-[(1*E*)-3-phenyl-1-propen-1-yl]-1,3-benzodioxone-5-carbonitrile. [e] Reaction was carried out in the presence of *n*-BuLi in THF. [f] Elimination of TsH is accompanied by deprotection of the indole.

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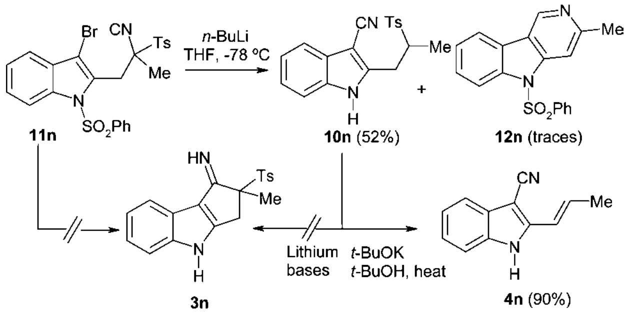
(13) Peyroux, E.; Berthiol, F.; Doucet, H.; Santelli, M. *Eur. J. Org. Chem.* **2004**, 1075.

(14) Both benzonitriles were established by comparison of spectroscopic data with those reported in the literature: (a) Lyaskovskyy, V.; Fröhlich, R.; Würthwein, E.-U. *Chem.—Eur. J.* **2007**, *13*, 3113. (b) Sharma, R.; Bulger, P. G.; McNevin, M.; Dormer, P. G.; Ball, R. G.; Streckfuss, E.; Cuff, J. F.; Yin, J.; Chen, C.-Y. *Org. Lett.* **2009**, *11*, 3194.

Scheme 4. Isocyanide–Cyanide Rearrangement in **11n**



of tricyclic 2,3-dihydro-indenimine **3m**, obtained from *N*-protected 3-bromo-2-bromomethyl-indole (**1g**),[15] also gave the nitrile **4m** in high yield, although in this case total deprotection of the indole ring was observed (Table 1, entry 13).

Remarkable behavior was found in the attempted rearrangement of isonitrile derivative **11n**, which was obtained from TosMIC, *N*-protected 3-bromo-2-bromomethyl indole **1h**, and methyl iodide under PTC conditions. Treatment of **11n** with *n*-BuLi in THF resulted in the isolation of compound **10n** as the main reaction product, and evidence of the formation of the corresponding 2,3-dihydro-1*H*-indenimine **3n** was not observed (Scheme 4).

According to the mechanism in Scheme 2, this compound is probably formed by the rearrangement of the corresponding 2,3-dihydro-indenimine **3n** followed by indole deprotection, although it could also be viewed as a potential precursor of the tricyclic imine.

It is noteworthy that all our attempts to obtain **3n** from **10n** failed and our attempted cyclization of the *N*-phenylsulfonyl derivative of **10n** also failed. However, the reaction of **10n** under the conditions used for the rearrangement of 2,3-dihydro-indenimines **3** gave *E*-3-cyano-2-(1-propenyl)indole (**4n**) in excellent yield. Moreover, from the reaction mixtures obtained in the transformation of **11n** into **10n** small amounts of the 3-methyl-*N*-phenylsulfonyl-γ-carboline (**12n**) were isolated, thus supporting the initial heterocyclization step shown in Scheme 2. In light of this latter result a reinvestigation of the reaction mixtures formed in the reaction of **1h** and **2c** allowed the isolation and identification of **12n** as one of the minor components of the mixture (less than 5%).[16]

In summary, the reaction of bromobenzyl TosMIC derivatives in the presence of organolithium bases produces an unexpected cascade process that involves a six-membered ring heterocyclization reaction, followed by an isocyanide–cyanide rearrangement and subsequent iminic five-membered ring formation to give 2,3-dihydroindenimines, which are able to rearrange to aryl (or heteroaryl) cyano derivatives in *t*-BuOK/*t*-BuOH. The full process can be viewed as a novel remote cyanation reaction on halo arylic substrates to afford a variety of aromatic nitriles. Work is in progress to explore the potential of the reaction and to improve the synthesis of relevant bioactive and pharmacologically interesting compounds.

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Supporting Information Available. Experimental procedures, X-ray crystallographic analysis, and ^{1}H and ^{13}C NMR spectra for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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[15] Dhayalan, V.; Ramesh, N.; Mohanakrishnan, A. K. *Synth. Commun.* **2009**, *39*, 1241.

[16] Carboline **12n** was identified on the basis of its structural data and by comparison with reported 3-methyl-γ-carbolines: Molina, A.; Vaquero, J. J.; Garcia-Navio, J. L.; Alvarez-Builla, J.; de Pascual-Teresa, B.; Gago, F.; Rodrigo, M. M.; Ballesteros, M. *J. Org. Chem.* **1996**, *61*, 5587.

The authors declare no competing financial interest.