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Tetrahedron Letters 45 (2004) 8659–8662

Tetrahedron Letters

Straightforward access to 2-iminoisoindolines via three-component coupling of arynes, isocyanides and imines

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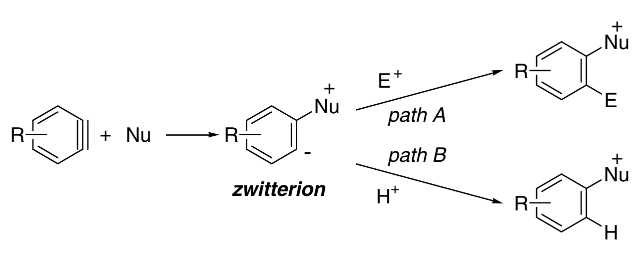
Received 11 August 2004; revised 17 September 2004; accepted 22 September 2004
Available online 8 October 2004

Abstract—A three-component coupling reaction of arynes, isocyanides and *N*-tosylaldimines has been developed to offer modest to high yields of diverse 2-iminoisoindolines in one step. Intermediacy of arynes in the coupling has been verified by the reaction of unsymmetrical arynes.

Electrophilic coupling reactions of arynes with nucleophiles have engaged considerable attention as potent synthetic approaches to substituted arenes, which would hardly be available by conventional methods.[1] Owing to marked electrophilicity of arynes, even neutral nucleophiles can be applied to the couplings. Although three-component couplings by trapping an initially formed zwitterion with a third component (electrophile) are much more beneficial from a synthetic standpoint (Scheme 1, path A), few examples have been available in the literature, because proton abstraction pathway predominates on the whole (path B).[2]

We have recently disclosed that the coupling reaction of arynes with isocyanides and aldehydes offered diverse benzo-annulated iminofurans straightforwardly, demonstrating that a suitable combination of nucleophiles and electrophiles allows arynes to undergo a three-component coupling selectively.[3,4] This coupling reaction would proceed through the zwitterion derived from an aryne and an isocyanide (vide infra), and thus, we envisaged that the zwitterion would be trapped by other electrophiles leading to a novel method for the synthesis of diverse benzo-annulated heterocyclic compounds. Herein we report a convenient and general synthesis of 2-iminoisoindolines via a three-component coupling using arynes, isocyanides and *N*-tosylaldimines.[5,6] The resulting heterocycles can be considered as nitrogen-analogues of 2-isoindolinones, for example, chlorthalidone and etomidoline, which have comprised an important group of therapeutic agents.[7]



Scheme 1.

First the reaction of benzyne, prepared in situ from 2-(trimethylsilyl)phenyl triflate (**1a**)[8] and a fluoride ion (KF/18-Crown-6), with 1,1,3,3-tetramethylbutyl isocyanide (*t*-OcNC, **2a**) and *N*-tosylbenzaldimine (**3a**) was conducted in THF at room temperature to afford 64% yield of the three-component coupling product, *N*-(3-phenyl-2-tosylisoindolinylidene)-*tert*-octylamine (**4a**) (Table 1, entry 1). An electron-rich (**3b**), electron-deficient (**3c**) or sterically hindered (**3d–f**) aldimine was also applicable to the reaction, giving the corresponding isoindoline (**4b–f**) in modest to good yields (entries 2–6). In addition, the reaction of an aldimine bearing a thienyl moiety (**3g**) took place smoothly to provide **4g** in 64% yield (entry 7). Similarly to the case of **2a**, *t*-butyl (**2b**), 1-adamantyl (**2c**), cyclohexyl (**2d**) or *n*-octyl isocyanide (**2e**) could also participate in the reaction to afford **4h–k**, although the yields

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Keywords: Arynes; Isocyanides; Multicomponent couplings; Nitrogen heterocycles.

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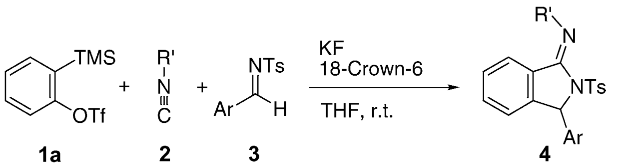
doi:10.1016/j.tetlet.2004.09.144

Table 1. Three-component coupling of benzyne, isocyanides and *N*-tosylaldimines[a]



Entry	R′	Ar	Time (h)	Yield (%)[b]	Product
1	*t*-Oc (**2a**)	Ph (**3a**)	5	64	**4a**
2		4-MeOC$_6$H$_4$ (**3b**)	9	61	**4b**
3		4-CF$_3$C$_6$H$_4$ (**3c**)	24	44	**4c**
4		2,4-Me$_2$C$_6$H$_3$ (**3d**)	18	66	**4d**
5		Mesityl (**3e**)	24	68	**4e**
6		1-Naphthyl (**3f**)	19	59	**4f**
7		2-Thienyl (**3g**)	16	64	**4g**
8	*t*-Bu (**2b**)	Ph (**3a**)	19	55	**4h**
9	1-Ad (**2c**)	Ph (**3a**)	24	35	**4i**
10	Cy (**2d**)	Ph (**3a**)	6	23	**4j**
11	*n*-Oc (**2e**)	Ph (**3a**)	22	46	**4k**

[a] The reaction was carried out in THF (2mL) at room temperature using **1** (0.60mmol), **2** (0.30mmol), **3** (0.60mmol), KF (1.2mmol) and 18-Crown-6 (1.2mmol).

[b] Isolated yield based on an isocyanide.

were relatively low (entries 8–11). As shown in Figure 1, configuration of the imine unit of the product has been determined to be (*E*) by an X-ray diffraction study of **4b**.[9]

We next investigated the three-component coupling of substituted arynes (Scheme 2). Thus, 4,5-disubstituted aryne (from **1b–d**) reacted efficiently with **2a** and **3b**, affording the corresponding product (**4l–n**) in 78%, 75% or 68% yield, whereas the reaction of 2,3-naphthalyne (from **1e**) resulted in a low yield. Such a sterically congested aryne as 3,6-dimethylbenzyne (from **1f**) or 3,6-dimethoxybenzyne (from **1g**) could also be applied to the reaction, leading to the formation of the respective isoindoline (**4p** or **4q**) in 71% or 43% yield.

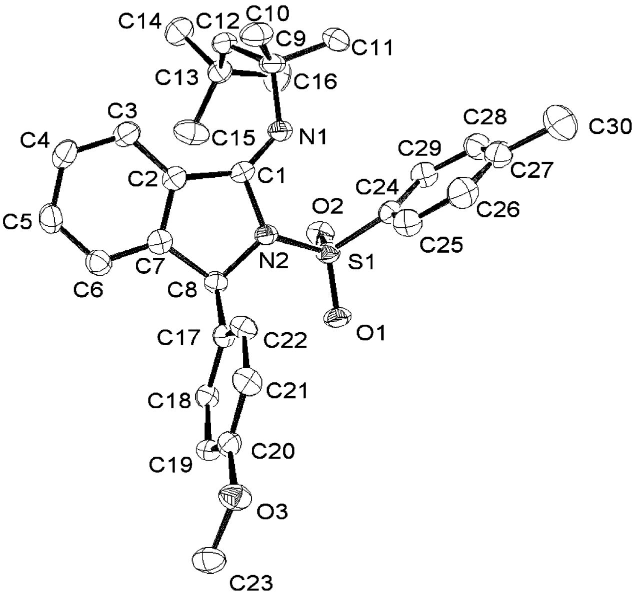
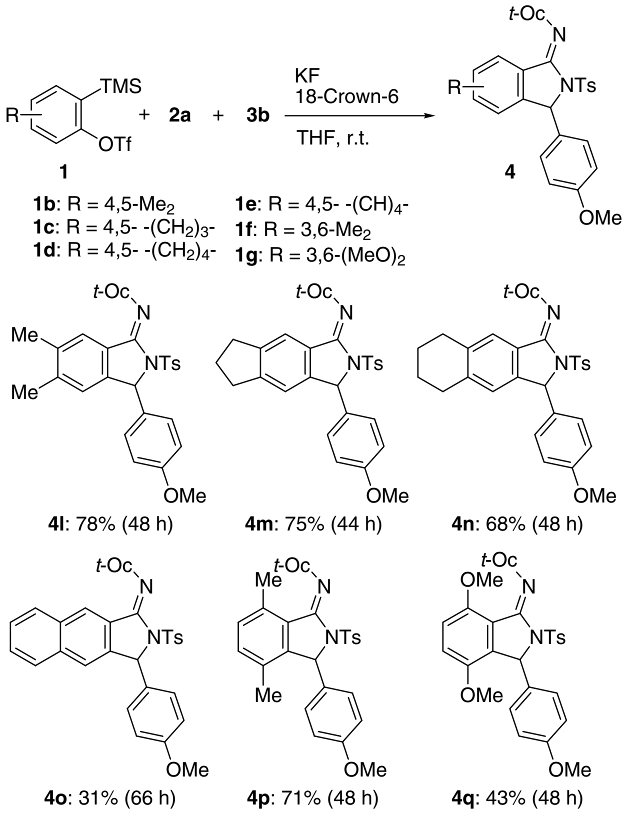


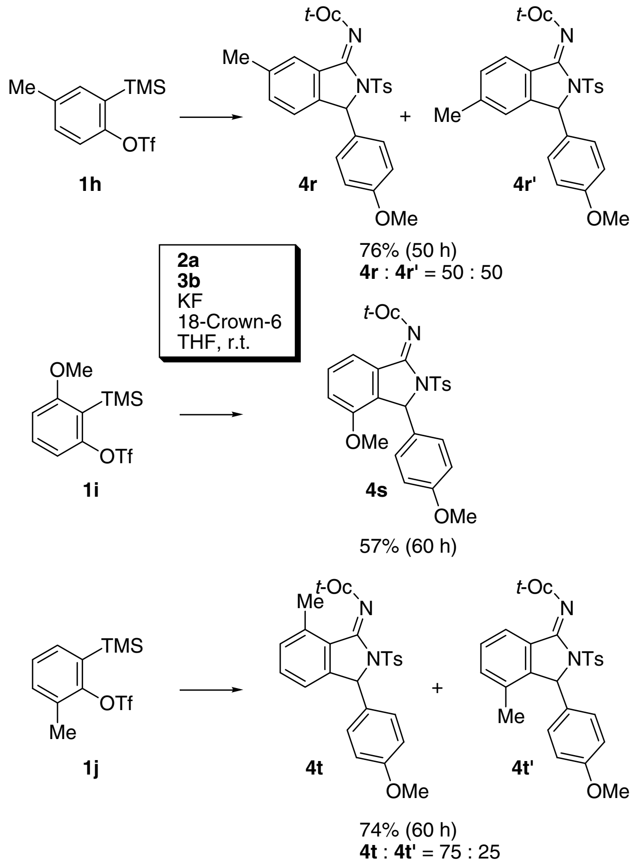
Figure 1.



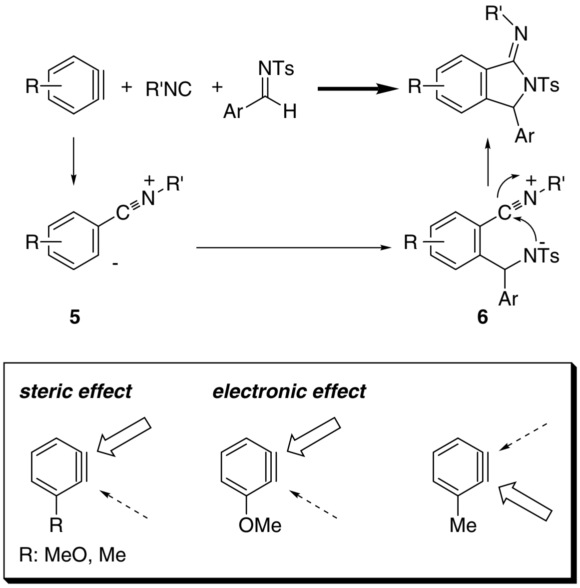
Scheme 2.

Furthermore, the three-component coupling of unsymmetrical arynes was carried out in order to clarify the regioselectivities (Scheme 3). When 4-methylbenzyne (from **1h**) was treated with **2a** and **3b**, an equal amount of regioisomers (**4r** and **4r′**) was produced in 76% yield, implying that the three-component coupling actually proceeds through an aryne intermediate. The reaction of 3-methoxybenzyne (from **1i**) gave **4s** exclusively, where the imino moiety was introduced into the *meta* position of the methoxy group. It should be noted that the reaction of 3-methylbenzyne (from **1j**) took place with the opposite regioselectivity to offer **4t** and **4t′** in 75:25 ratio.[10]

The three-component coupling would be commenced by a nucleophilic addition of an isocyanide to an aryne, as depicted in Scheme 4.[11] Subsequent nucleophilic attack of the resulting zwitterion (**5**) to an aldimine gives **6**, which then undergoes intramolecular cyclization to provide the product. The observed regioselectivities in the reaction of 3-substituted arynes can be construed in terms of steric and electronic effects.[1a] Because of steric repulsion between a substituent (MeO or Me) at 3-position in the aryne and an incoming isocyanide, the nucleophilic addition of the isocyanide to the *meta* position of the substituent would be sterically favoured in each case. Moreover, an electron-withdrawing effect of the methoxy group also prefers the nucleophilic addition with the same regioselectivity, resulting in the sole formation



Scheme 3.



Scheme 4.

of **4s**. In contrast, the steric effect would vie with an electron-donating effect of the methyl group, which induces the nucleophilic addition to the *ortho* position, and a mixture of **4t** and **4t**′ is produced.[12,13] In the case of 4-methylbenzyne, steric and electronic differences around the triple bond would be so slight that an equal addition to the both ends takes place.

In conclusion, we have disclosed that diverse 2-iminoisoindolines can be synthesized straightforwardly based upon the novel three-component coupling of arynes, isocyanides and *N*-tosylaldimines. Further studies on a multicomponent coupling of arynes utilizing another combination of nucleophiles and electrophiles are in progress.

General procedure: To a THF solution (2.0mL) of KF (0.070g, 1.20mmol), 18-Crown-6 (0.32g, 1.20mmol), **2** (0.30mmol) and **3** (0.60mmol) was added **1** (0.60mmol), and the resulting mixture was stirred at room temperature. After the time specified in Table 1, Scheme 2 or 3, the mixture was diluted with ethyl acetate, filtered through a Celite plug and concentrated. Silica gel column chromatography (17% ethyl acetate/hexane as an eluent) followed by gel permeation chromatography (benzene as an eluent) gave the corresponding product.

Acknowledgements

We thank Central Glass Co. Ltd for a generous gift of trifluoromethanesulfonic anhydride. We also thank Mr. Yoshiaki Nakao and Professor Tamejiro Hiyama (Kyoto University) for HRMS measurements.

References and notes

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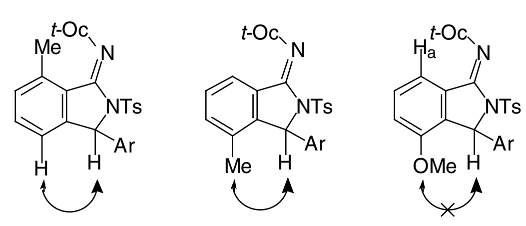
9. Crystallographic data for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 247264. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].
10. The structure of **4t** and **4t′** was determined by NOE in ^{1}H NMR as shown below. On the other hand, irradiation of the methine proton of **4s** did not enhance the MeO moiety. However, the absence of NOE between the methine proton and H_a as well as the general regioselectivity in the electrophilic coupling of 3-methoxybenzyne should support the assignment of the stereochemistry of **4s**.



4t: 3.5% **4t'**: 1.7% **4s**

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12. The three-component coupling of 3-methylbenzyne, **2a** and 4-methoxybenzaldehyde proceeded faster (0 °C, 8 h) than the reaction using **3b** with a perfect regioselectivity to give the single product, which holds the imine moiety at the *meta* position of the methyl group (Ref. 3). The different regioselectivities can be explained by the reversibility in the nucleophilic addition of **2a** to 3-methylbenzyne. The zwitterion bearing the anionic moiety at the *meta* position of the methyl group would be thermodynamically stable among two possible zwitterions owing to the electron-donating character of the methyl group. In contrast, formation of another zwitterion should be kinetically favoured because of less steric repulsion between the methyl group and **2a**. Therefore, imine **3b** of lower reactivity gave **4t** predominantly, since kinetically generated zwitterion should isomerize to thermodynamically stable one prior to the reaction with the imine. For the reversibility in the addition of nucleophiles to arynes, see Ref. 1a.
13. The electronic effects of the substituents (methoxy or methyl) would depend considerably upon their inductive effects compared with their resonance effects, since the triple bond of the arynes is orthogonal to the ring π-system. Thus, the methoxy group would exert electron-withdrawing effect, whereas opposite electronic effect would be induced by the methyl group.