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An isonitrile–alkyne cascade to di-substituted indoles

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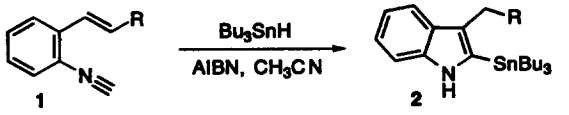
Abstract

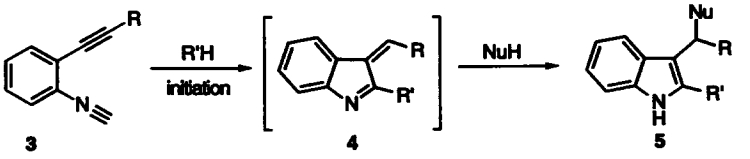
Intramolecular tin and sulfur mediated free-radical cyclizations between an aryl isonitrile and a pendant TMS-substituted alkyne give 2,3-disubstituted indoles from 5-*exo*-dig cyclization and nucleophilic trapping of the resulting indolenine intermediate. © 1999 Elsevier Science Ltd. All rights reserved.

In spite of the fact that Fischer first described their synthesis some 115 years ago,[1] the generation of indoles continues to be an area of active research. Undoubtedly, their presence in a number of bioactive molecules plays a role in the current level of activity. Of the various methods to substituted indole ring systems, Fukayama's isonitrile–alkene free-radical coupling reactions are among the most efficient (Eq. 1).[2]



(1)

Our interest in the synthesis of indole containing natural products directed our attention to the analogous alkyne–isonitrile free-radical reactions.[3] As depicted in Scheme 1, if isonitrile **3** proceeded through a mechanism similar to Fukayama's,[2] the radical cyclization would result in **4**. Indolenine **4** is reminiscent of the intermediate from the fragmentation of gramine and should therefore be susceptible to attack by nucleophiles.[4,5] From our perspective, the development of a cascade of this nature would allow us to access a number of highly functionalized indoles from very simple precursors. Described herein are our preliminary experiments which demonstrate the successful execution of this strategy.



Scheme 1.

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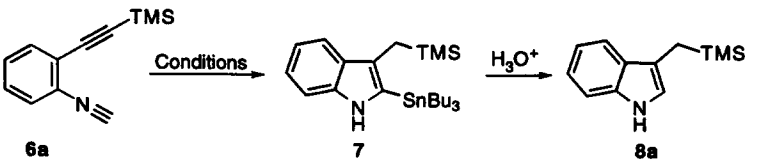
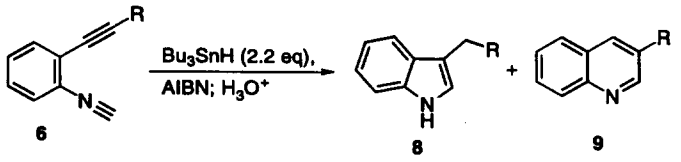
Table 1



6a 7 8a

Entry	Conditions	Yield
1	Bu_3SnH (2.2 eq), AIBN (10%), PhH (CH_3CN), 80°C	82%
2	Bu_3SnH (2.2 eq), PhH, 80°C	12%
3	Bu_3SnH (2.2 eq), $MgBr_2 \cdot Et_2O$ (10%), PhH, 80°C	34%

Table 2



6 8 9

isonitrile	R	8:9	Yield
6a	TMS	1:0	82%
6b	Bu	1:5.3	63%
6c	H	0:1	18%
6d	Ph	2.2:1	41%
6e	CH_2OBn	2:1	11%

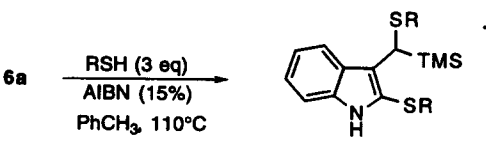
With the aforementioned goals in mind, a variety of substituted alkynyl–isonitriles were synthesized[6,15,16] and subjected to Fukayama's radical cyclization conditions. To our delight, when TMS capped alkyne **6a** was treated with 2 equivalents of Bu_3SnH and 10% AIBN in either benzene or acetonitrile we were able to isolate indole **8a** in 82% yield after acidic workup (Table 1).[7] Interestingly, both the thermally induced and Lewis acid catalyzed reactions also provided disubstituted indole **8a**, albeit in lower yields (Table 1, entries 2 and 3).

In contrast to the results with **6a**, the attempted cyclization of alkynes **6b–e** resulted in mixtures of disubstituted indoles and/or quinolines in lower overall yields (Table 2). The TMS group is clearly playing a role in both directing the reaction toward the 5-*exo*-dig manifold and in enhancing the overall yield. Presumably, this is both due to the steric encumbrance associated with having the TMS and tributylstannyl groups adjacent to one another in the corresponding quinoline as well as to silicon's ability to stabilize α-radicals.[8]

Having demonstrated that **6a** could serve as a precursor to disubstituted indoles, we set out to trap the presumed indolenine intermediate with nucleophiles other than Bu_3SnH. Our initial attempts using nitrogen and oxygen nucleophiles in the presence of Bu_3SnH gave only reduced indole **8a** after acidic workup;[9] the reduction of **4** with Bu_3SnH appears to be more facile than the addition of the other nucleophile.[10,11] Recognizing that we might be able to utilize a thiol as both the source of the free radical in the initial cyclization as well as the nucleophile in the subsequent aromatization, we subjected **6a** to excess ethanethiol and AIBN.[12] To our immense satisfaction, the product was the bis-thiol adduct **10**, formed in 82% yield (Table 3).[13,14] The reaction appears to be amenable to the use of other thiols; in addition to **10**, we were also able to generate bis-thiol adducts **11** and **12** by subjecting isonitrile **6a** and AIBN to butanethiol and thiophenol, respectively. In contrast to the results with alkyl thiols and thiophenol, the use of benzyl mercaptan resulted in a complex mixture of products.

In summary, we have demonstrated that isonitriles having pendant TMS-substituted alkynes can serve as efficient precursors to 2,3-disubstituted indoles. In addition, we have shown that indolenines from isonitrile–alkyne free-radical cyclizations can be trapped with Bu_3SnH and thiols. Our current efforts are

Table 3



Indole	R	Yield
10	Et	82%
11	Bu	65%
12	Ph	49%
13	Bn	0%

focused on the optimization and utilization of this interesting process. We are also currently investigating the use of bis-thiols in the synthesis of substituted indoles.

Acknowledgements

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3. Intramolecular isonitrile–alkyne couplings have been utilized by the Curran group. See: (a) Curran, D. P.; Liu, H. *J. Am. Chem. Soc.* **1991**, *113*, 2127. (a) Curran, D. P.; Liu, H. *J. Am. Chem. Soc.* **1992**, *114*, 5863. (c) Curran, D. P.; Ko, S.-B.; Josien, H. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2683. (d) Josien, H.; Ko, S.-B.; Bom, D.; Curran, D. P. *Chem. Eur. J.* **1998**, *4*, 67.
4. For the use of gramine fragmentations in synthesis see: (a) Smith III, A. B.; Haseltine, J. N.; Visnick, M. *Tetrahedron* **1989**, *45*, 2431. (b) Remers, W. A.; Brown, R. K. In *Indoles*; Houlihan, W. J., Ed.; Heterocyclic compounds; Wiley-Interscience: New York, 1972; Part One, pp. 200–203.
5. Indolenine **4** is isoelectronic with enones; for the free-radical reduction of enones with Bu_3SnH see: Enholm, E. J.; Whitley, P. E. *Tetrahedron Lett.* **1996**, *37*, 559, and references contained within.
6. Isonitrile cyclization precursors were generated from 2-iodoformanilide via Sonagashira couplings with the appropriate alkyne[15] and dehydration.[16]
7. Non-acidic workup resulted in the formation of 2-stannylindole **7a**. Fukuyama has shown that 2-stannylindoles can serve as precursors to a variety of 2-substituted indoles via a subsequent coupling reaction.[2]
8. (a) Shi, C.; Zhang, Q.; Wang, K. K. *J. Org. Chem.* **1999**, *64*, 925. (b) Wilt, J. W.; Aznavoorian, P. M. *J. Org. Chem.* **1978**, *43*, 1285.
9. Thus far, we have used diethyl amine, aniline, benzyl amine, and methanol.
10. It is also possible that the reduced product is coming from a reversible amine (methanol) addition and irreversible indolenine reduction.[4]
11. It is not clear to us at the present time whether nucleophilic addition to **4** is occurring heterolytically[4] or homolytically.[5]
12. For the addition of thiol-radicals to isonitriles, see: Bachi, M. D.; Balanov, A.; Bar-Ner, N. *J. Org. Chem.* **1994**, *59*, 7752.
13. **10**: Pale yellow solid, mp 94–96°C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.04 (bd, *J*=8.0 Hz, 1H), 7.92 (bs, 1H), 7.26 (d, *J*=8.0 Hz, 1H), 7.17 (dt, *J*=7.5, 1.2 Hz, 1H), 7.05 (dt, *J*=8.0, 1.0 Hz, 1H), 3.97 (bs, 1H), 2.77 (m, 2H), 2.25 (m, 2H), 1.27 (t, *J*=7.4 Hz, 3H), 1.12 (t, *J*=7.4 Hz, 3H), 0.08 (s, 9H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 137.0, 126.7, 125.0, 122.8, 120.5, 118.9, 110.4, 31.0, 29.7, 25.9, 15.4, 14.3, −1.5; IR (CCl_4) 3472, 2961, 2920 cm^{-1}; MS (FAB$^+$) 323 (M$^+$), 294, 262; HRMS calcd for $C_{16}H_{25}NS_2Si$ (M$^+$): 323.1198; found: 323.1192.
14. We have utilized **10** in carbon–carbon bond forming reactions with nucleophiles; this work will be communicated shortly.
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16. Obrecht, R.; Hermann, R.; Ugi, I. *Synthesis* **1985**, *4*, 400.