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Synthesis of Indolines, Indoles, and Benzopyrrolizidinones from Simple Aryl Azides

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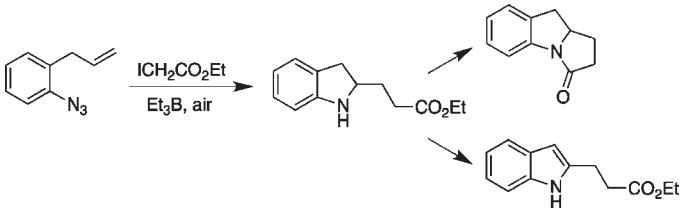
ABSTRACT



A simple approach to prepare indolines and benzopyrrolizidinones from *ortho*-azidoallylbenzenes via a tandem radical addition/cyclization is described. The use of triethylborane to initiate and sustain the process provides the best results. Indolines are easily converted into the corresponding indoles by oxidation with manganese dioxide.

Indoline and indole derivatives are ubiquitous in nature as well as in compounds of pharmaceutical interest.[1] Their preparation and functionalization are widely recognized as a privileged field of investigation.[2] Benzopyrrolizidines represent an important subclass of this family of heterocycles, encompassing for instance the mitomycin alkaloids.[3] In the past 30 years, radical chemistry has become a powerful tool for organic synthesis.[4] Of particular interest, C−N bonds have been shown to be readily formed when organic azides were used as radical traps.[5] In 1994, Kim et al. reported efficient radical cyclizations onto aliphatic azides to prepare *N*-heterocycles using tributyltin or tris(trimethylsilyl)silyl radicals and haloalkyl azides.[6] A related strategy was applied by Murphy et al. to the synthesis of the tetracyclic core of *Aspidosperma* and *Vinca* alkaloids involving iodoaryl azides as key intermediates.[7] Radical cyclizations involving aromatic azides are much less documented.[8] Spagnolo et al. reported the formation of indoles by addition of sulfanyl or silyl radicals onto (*o*-azidophenyl)acetylenes to generate vinyl radicals which undergo intramolecular 5-*exo* cyclization.[9] Here, we report a cascade reaction onto *o*-azidoallylbenzenes involving a radical addition to the terminal double bond followed by a cyclization onto the azido group in the absence of a H-donor reagent (Scheme 1).

Indoline Synthesis. In a preliminary experiment, the conversion of 2-allylaniline **3a** to indoline **2a** was attempted by

(1) For selected reviews, see: (a) Saxton, J. E. *Nat. Prod. Rep.* **1997**, *14*, 559–590. (b) Kochanowska-Karamyan, A. J.; Hamann, M. T. *Chem. Rev.* **2010**, *110*, 4489–4497. (c) Ruiz-Sanchis, P.; Savina, S. A.; Albericio, F.; Álvarez, M. *Chem.—Eur. J.* **2011**, *17*, 1388–1408.

(2) For selected reviews, see: (a) Humphrey, G. R.; Kuethe, J. T. *Chem. Rev.* **2006**, *106*, 2875–2911. (b) Bandini, M.; Eichholzer, A. *Angew. Chem., Int. Ed.* **2009**, *48*, 9608–9644. (c) Anas, S.; Kagan, H. B. *Tetrahedron: Asymmetry* **2009**, *20*, 2193–2199. (d) Liu, D.; Zhao, G.; Xiang, L. *Eur. J. Org. Chem.* **2010**, 3975–3984.

(3) For a recent review on the chemistry and biology of mitomycins, see: Andrez, J.-C. *Beilstein J. Org. Chem.* **2009**, *5*, 33.

(4) (a) Renaud, P., Sibi, M. P., Eds. *Radicals in Organic Synthesis*; Wiley-VCH: Weinheim, 2001. (b) Chatgilialoglu, C; Studer, A., Eds. Synthetic Applications and Strategies. *Encyclopedia of Radicals in Chemistry, Biology and Materials*, Vol. 2; Wiley: Chichester, 2012.

(5) (a) Panchaud, P.; Chabaud, L.; Landais, Y.; Ollivier, C.; Renaud, P.; Zigmantas, S. *Chem.—Eur. J.* **2004**, *10*, 3606–3614. (b) Minozzi, M.; Nanni, D.; Spagnolo, P. *Chem.—Eur. J.* **2009**, *15*, 7830–7840.

(6) Kim, S.; Joe, G. H.; Do, J. Y. *J. Am. Chem. Soc.* **1994**, *116*, 5521–5522.

(7) (a) Kizil, M.; Murphy, J. A. *J. Chem. Soc., Chem. Commun.* **1995**, 1409–1410. (b) Kizil, M.; Patro, B.; Callaghan, O.; Murphy, J. A.; Hursthouse, M. B.; Hibbs, D. *J. Org. Chem.* **1999**, *64*, 7856–7862. (c) Patro, B.; Murphy, J. A. *Org. Lett.* **2000**, *2*, 3599–3601. (d) Zhou, S.; Bommezijn, S.; Murphy, J. A. *Org. Lett.* **2002**, *4*, 443–445.

(8) Before publication of ref 9, only two papers were reported in the literature: (a) Benati, L.; Montevecchi, P. C.; Spagnolo, P. *Tetrahedron Lett.* **1978**, *19*, 815–818. (b) Benati, L.; Montevecchi, P. C. *J. Org. Chem.* **1981**, *46*, 4570–4573.

(9) Montevecchi, P. C.; Navacchia, M. L.; Spagnolo, P. *Eur. J. Org. Chem.* **1998**, 1219–1226.

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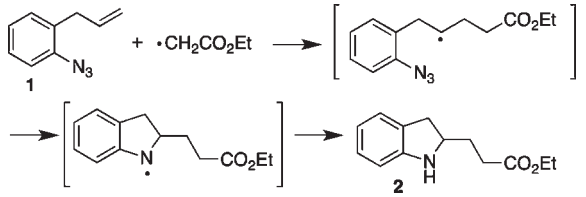
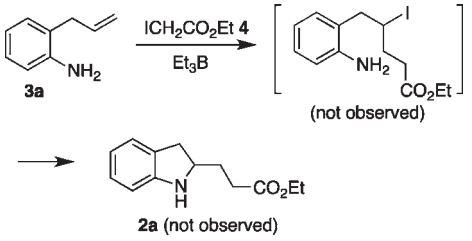
Scheme 1. Radical Cascade onto *ortho*-Azidoallylbenzenes



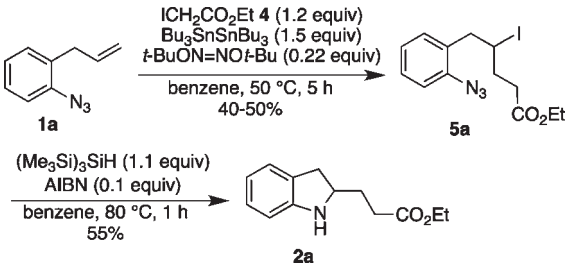
a two-step process consisting of the addition of ethyl iodoacetate **4** under iodine atom transfer conditions followed by an intramolecular nucleophilic substitution (Scheme 2).[10] However, the radical process did not take place since *N*-alkylation of the aniline by the highly reactive iodoacetate rapidly took place affording a mixture of *N*-alkylated products. This simple approach was therefore abandoned in favor of a radical cascade approach starting from 2-allyl-1-azidobenzene.

Scheme 2. Preliminary Experiment onto 2-Allylaniline



Several substituted 2-allyl-1-azidobenzenes **1** were readily prepared according to literature procedures from commercially available anilines via either a sequence involving *N*-alkylation, aza-Claisen rearrangement, and mild conversion into aryl azides or a two-step procedure using Stille coupling.[11] The tandem radical addition/cyclization was then investigated using the model reaction between **1a** and ethyl iodoacetate **4** as a radical precursor. The reaction temperature was critical for this transformation since *ortho*-azidoallylbenzene derivatives are known to undergo intramolecular cycloaddition at temperatures above 80 °C.[9,12] In an initial attempt, the use of hexabutylditin as a chain transfer reagent was tested (Scheme 3).[13] This reaction afforded exclusively the product of iodine atom transfer **5a** without cyclization. Treatment of the iodide **5a** with $(Me_3Si)_3SiH$ and AIBN as an initiator afforded the desired 2-substituted indoline **2a** in moderate yield (Scheme 3).[6] Attempts to optimize the cyclization reaction by varying the initiator and by using Bu_3SnH failed to afford a higher yield.

Scheme 3. Initial Cascade Reaction Attempt



The use of triethylborane was investigated next. In the presence of oxygen, Et_3B efficiently produces ethyl radicals that initiate radical chain processes, even at low temperature.[14] Moreover, it can also act as a chain transfer reagent since it undergoes homolytic substitution with aminyl radicals[15] (such an intermediate aminyl radical is expected in our proposed cascade; see Scheme 1). Based on the tin-free conditions developed in our group for the radical carboazidation,[16] we first tried to prepare indoline **2a** from azide **1a** and iodide **4** in the presence of an excess of Et_3B in $EtOH/H_2O$. Under these conditions, only the iodine atom transfer product **5a** was obtained (Table 1, entry 1). With an open to air system the radical cascade was still unsuccessful in $EtOH/H_2O$. However, indoline **2a** was obtained in 63% yield along with a small amount of the corresponding indole **6a** when benzene and 4 equiv of Et_3B were used (entry 2). Increasing the amount of borane did not give a higher yield, and using less than 4 equiv resulted in the incomplete conversion of **5a** to **2a**. Indeed, **5a** was always formed after addition of the first equivalent of Et_3B, and its complete conversion to the cyclized product occurred only after further addition 3 equiv of Et_3B. Working with a slight excess of aryl azide (ratio 1.5:1) afforded **2a** in 88% yield contaminated by 9% of **6a** (entry 3). The influence of the ratios of starting materials on the yield is explained by minor side reactions involving the azide.[17] A rapid screening of solvents (Table 1, entries 4–7) showed a significant reduction of the formation of **6a** when the reaction was carried out in

(10) For Et_3B-induced halogen atom transfer reactions, see: (a) Yorimitsu, H.; Nakamura, T.; Shinokubo, H.; Oshima, K.; Omoto, K.; Fujimoto, H. *J. Am. Chem. Soc.* **2000**, *122*, 11041–11047. (b) Yorimitsu, H.; Shinokubo, H.; Matsubara, S.; Oshima, K.; Omoto, K.; Fujimoto, H. *J. Org. Chem.* **2001**, *66*, 7776–7785.

(11) For detailled preparation of azides **1**, see Supporting Information.

(12) Smith, P. A. S.; Chou, S. P. *J. Org. Chem.* **1981**, *46*, 3970–3977.

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(14) Darmency, V.; Renaud, P. *Top. Curr. Chem.* **2006**, *263*, 71–106.

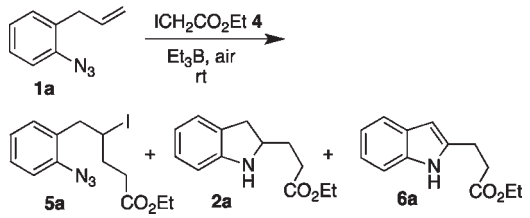
(15) For selected examples, see: (a) Bertrand, M. P.; Feray, L.; Nouguier, R.; Stella, L. *Synlett* **1998**, 780–782. (b) Miyabe, H.; Ueda, M.; Naito, T. *J. Org. Chem.* **2000**, *65*, 5043–5047. (c) Ueda, M.; Miyabe, H.; Miyata, O.; Naito, T. *Tetrahedron* **2009**, *65*, 1321–1326. (d) Valpuesta, M.; Muñoz, C.; Díaz, A.; Torres, G.; Suau, R. *Eur. J. Org. Chem.* **2010**, 1934–1942.

(16) Panchaud, P.; Renaud, P. *J. Org. Chem.* **2004**, *69*, 3205–3207.

(17) Trace amounts of 2-propylindoline resulting from the addition of an ethyl radical to the double bond of **1a** followed by cyclization were observed. By running the reaction in the absence of iodide **4**, 2-propylindoline could be isolated in 5–10% yield. Products resulting from an intramolecular dipolar cycloaddition of the azidoalkene **1a** could not be identified, but this process could also be responsible for a partial decomposition of **1a**.

good H-donor solvents such as toluene (entry 4) or Et_2O (entry 7).

Table 1. Optimization of the Et_3B-Mediated Cascade Reaction Converting Azidoalkene **1a** into Indoline **2a**

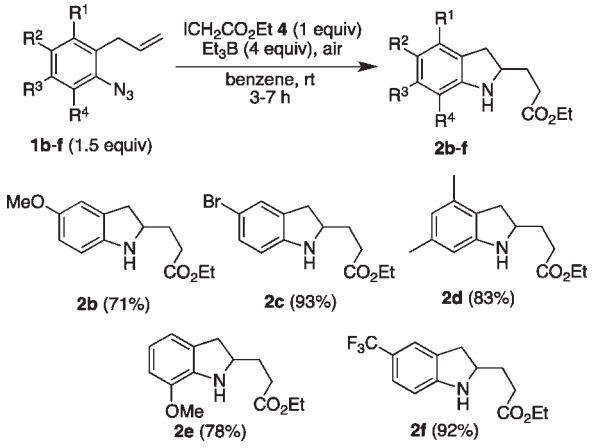


entry	**1a**/**4** (equiv)	Et_3B (equiv)[a]	solvent	product (yield)[b]	ratio **2a**/**6a**[c]
1	1/2	5	EtOH/H_2O 2.3:1	**5a** (52%)	–
2[d]	1/1	4	benzene	**2a** (63%)[e]	97:3
3[d]	1.5/1	4	benzene	**2a** (88%)[e]	91:9
4[d]	1.5/1	4	toluene	**2a** (82%)[e]	96:4
5[d]	1.5/1	4	CH_2Cl_2	**2a** (82%)[e]	92:8
6[d]	1.5/1	5	*t*-BuOH	**2a** (62%)[e]	94:6
7[d]	1.5/1	5	Et_2O	**2a** (40%)[e]	99:1

[a] 2 M solution of Et_3B in EtOH used (entry 1) or 1 M in hexane (entries 2–7). [b] Isolated yield based on the limiting reagent. [c] Determined by ^1H NMR on the purified mixture. [d] Open to air reaction. [e] Combined yield of **2a** and **6a**.

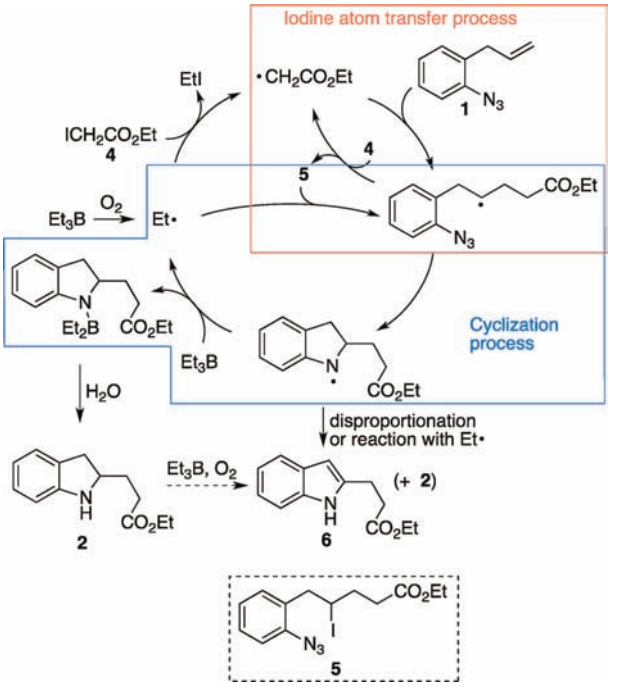
2-Allyl-1-azidobenzenes **1b**–**f** were then submitted to the radical cascade according to the optimized procedure (Scheme 4). As expected, indolines **2** were obtained in good yields when a slight excess (1.5 equiv) of the azidoalkene **1** was used. Aryl azides bearing an electron-donating group gave lower yields than those bearing an electron-withdrawing group. Traces of the corresponding indoles (< 12%) were detected in all examples excepted when azide **1f** was used. Unsurprisingly, indole formation is apparently favored by electron-donating substituents and disfavored by electron-withdrawing substituents.[18]

Scheme 4. Radical Cascade with Azidoalkenes **1b**–**f**



A plausible mechanism for our radical cascade is outlined in Scheme 5. Experimentally, we observed that the intermediate iodine atom transfer product **5** accumulates in the mixture during the first part of the reaction. Its formation is optimal when 1 equiv of Et_3B and a small quantity of oxygen (< 10 mol %) are used. The 5-*exo* cyclization starts only when most of the ethyl iodoacetate **4** is consumed. To achieve an efficient cyclization, an excess of Et_3B and oxygen is required. The chain is propagated by reaction of the aminyl radical with triethylborane. Hydrolysis of the aminoborane during the reaction (open flask) or during the workup procedure affords the indoline **2**. As previously reported, Et_3B is proposed to act as a radical initiator and a chain propagator.[15] Formation of indole **6** presumably occurs by disproportionation of the aminyl radical or by H-atom abstraction involving an ethyl radical.[19] Indole **6** may also be generated from **2** since our open to air conditions should favor the presence of radical species (oxygen-centered radicals for instance) able to perform such oxidative side reactions. This hypothesis is supported by a control experiment furnishing a small quantity of indole **6a** when **2a** and triethylborane were mixed together in benzene, in a flask open to air without ethyl iodoacetate. Solvents able to undergo competitive H-atom abstraction, like toluene or Et_2O, protect the indoline against such oxidations.

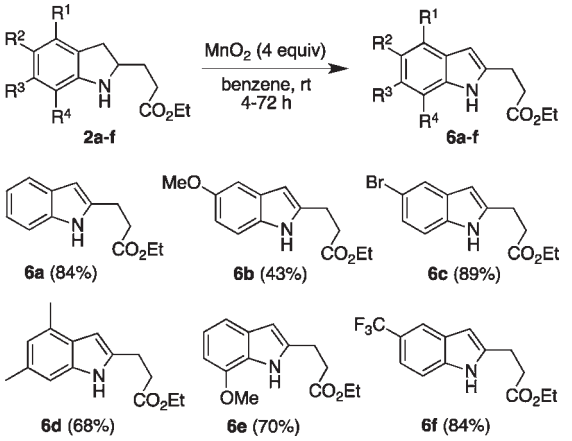
Scheme 5. Proposed Mechanism



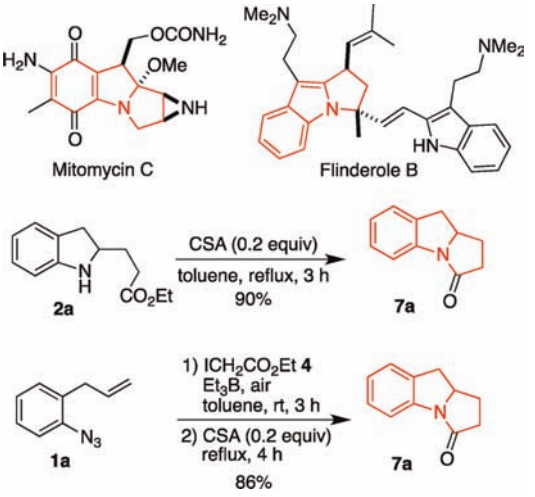
(18) Amounts of indoles **6** are reported in the Supporting Information.

(19) A similar disproportionation event was observed by Zard et al. during a radical cascade: Biechy, A.; Zard, S. Z. *Org. Lett.* **2009**, *11*, 2800–2803.

Scheme 6. Oxidation into Indoles



Scheme 7. Benzopyrrolizidinone Synthesis



Indole Synthesis. The formation of indole side products during our radical cascade prompted us to investigate conditions for the oxidation of our indolines. Manganese dioxide was reported in the literature to be suitable for the oxidation of indolines to indoles.[20] After optimization of the reaction conditions, **2a** was efficiently converted into **6a** in 84% yield (Scheme 6). Other indoles were also prepared in good to high yields, except **6b** which decomposed partly under our oxidation conditions. Attempts to prepare indoles from azides **1** via a one-pot procedure involving the radical cascade and the MnO_2 oxidation resulted in complex mixtures of products.

Benzopyrrolizidinone Synthesis. Benzopyrrolizidines constitute the core structure of several natural products such as mitomycins,[3,21] a class of very potent antibiotic and antitumor alkaloids, or flinderoles,[22] which possess selective antimalarial activity. Interestingly, the indoline **2a** furnished the tricyclic lactam **7a** in 90% yield by simple treatment with camphorsulfonic acid (CSA) in refluxing toluene (Scheme 7).[23] The same benzopyrrolizidinone **7a** was prepared in a one-pot sequence from **1a** in 86% yield. This method compares favorably with previous approaches.[24]

In conclusion, we have developed a mild and efficient procedure to selectively prepare indolines and indoles via a radical cascade starting from 2-allyl-1-azidobenzene derivatives using tin-free conditions. The 2-substituted indolines prepared by this process are readily transformed by lactamization into benzopyrrolizidinones, the core of several alkaloids.

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Supporting Information Available. Experimental procedures, full characterization of new products, and copies of NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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(21) For a recent example of work related to mitomycins, see: Trost, B. M.; O'Boyle, B. M.; Torres, W.; Ameriks, M. K. *Chem.—Eur. J.* **2011**, *17*, 7890–7903.

(22) (a) Dethe, D. H.; Erande, R. D.; Ranjan, A. *J. Am. Chem. Soc.* **2011**, *133*, 2864–2867. (b) Zeldin, R. M.; Toste, F. D. *Chem. Sci.* **2011**, *2*, 1706–1709.

(23) Danishefsky, S. J.; Regan, J.; Doehner, R. *J. Org. Chem.* **1981**, *46*, 5255–5261.

(24) Danishefsky, S. J.; Doehner, R. *Tetrahedron Lett.* **1977**, *35*, 3029–3030.

The authors declare no competing financial interest.