ORGANIC LETTERS

2011
Vol. 13, No. 4
812–815

Redox Isomerization via Azomethine Ylide Intermediates: *N*-Alkyl Indoles from Indolines and Aldehydes

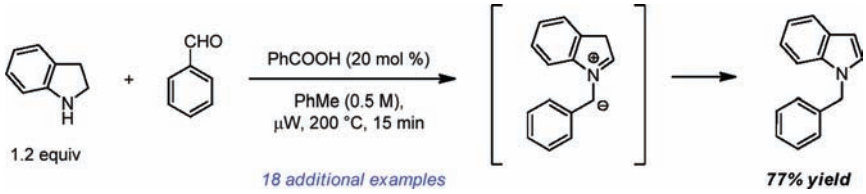
Indubhusan Deb, Deepankar Das, and Daniel Seidel*

Department of Chemistry and Chemical Biology, Rutgers, The State University of New Jersey, Piscataway, New Jersey 08854, United States

seidel@rutchem.rutgers.edu

Received December 25, 2010

ABSTRACT

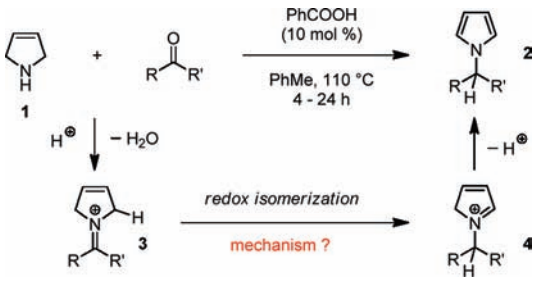


Indolines react with aromatic and heteroaromatic aldehydes to yield *N*-alkyl indoles in a benzoic acid catalyzed redox isomerization reaction. Azomethine ylides are intermediates in this process which was established by intramolecular [3 + 2] trapping experiments.

The ubiquity of the indole nucleus in natural products and medicinal agents continues to inspire the development of new synthetic approaches to this heterocyclic framework.[1,2] Here we report a redox neutral method for the formation of *N*-alkyl indoles from indolines and aldehydes.

In a recent publication, Tunge et al. described the intriguing formation of *N*-alkyl pyrroles **2** via the reaction of 3-pyrroline (**1**) with aldehydes or ketones in the presence of an acid catalyst (Scheme 1).[3] As proposed by these authors, this reaction proceeds via a redox isomerization process in which **3** and **4** are likely intermediates in the sequence leading up to the formation of pyrroles.

Scheme 1. Tunge's Redox Neutral Pyrrole Formation



In the course of our studies aimed at developing redox neutral amine functionalizations,[4,5] we became interested in the mechanism of this reaction and its possible application

(1) For selected reviews on indole chemistry, see: (a) Gribble, G. W. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1045. (b) Cacchi, S.; Fabrizi, G. *Chem. Rev.* **2005**, *105*, 2873. (c) Humphrey, G. R.; Kuethe, J. T. *Chem. Rev.* **2006**, *106*, 2875. (d) Bandini, M.; Eichholzer, A. *Angew. Chem., Int. Ed.* **2009**, *48*, 9608. (e) Palmieri, A.; Petrini, M.; Shaikh, R. R. *Org. Biomol. Chem.* **2010**, *8*, 1259.

(2) For the importance of indoles in the context of medicinal chemistry, see for example: (a) Alves, F. R. D.; Barreiro, E. J.; Fraga, C. A. M. *Mini-Rev. Med. Chem.* **2009**, *9*, 782. (b) Welsch, M. E.; Snyder, S. A.; Stockwell, B. R. *Curr. Opin. Chem. Biol.* **2010**, *14*, 347. (c) Kochanowska-Karamyan, A. J.; Hamann, M. T. *Chem. Rev.* **2010**, *110*, 4489.

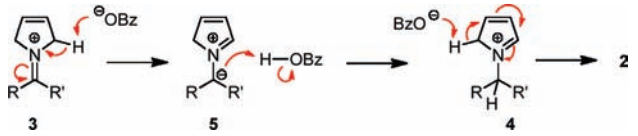
(3) Pahadi, N. K.; Paley, M.; Jana, R.; Waetzig, S. R.; Tunge, J. A. *J. Am. Chem. Soc.* **2009**, *131*, 16626.

(4) (a) Zhang, C.; De, C. K.; Mal, R.; Seidel, D. *J. Am. Chem. Soc.* **2008**, *130*, 416. (b) Murarka, S.; Zhang, C.; Konieczynska, M. D.; Seidel, D. *Org. Lett.* **2009**, *11*, 129. (c) Zhang, C.; Murarka, S.; Seidel, D. *J. Org. Chem.* **2009**, *74*, 419. (d) Murarka, S.; Deb, I.; Zhang, C.; Seidel, D. *J. Am. Chem. Soc.* **2009**, *131*, 13226. (e) Zhang, C.; Seidel, D. *J. Am. Chem. Soc.* **2010**, *132*, 1798. (f) Deb, I.; Seidel, D. *Tetrahedron Lett.* **2010**, *51*, 2945. (g) Zhang, C.; Das, D.; Seidel, D. *Chem. Sci.* **2011**, *2*, Advance Article DOI: 10.1039/C0SC00432D.

10.1021/ol1031359
Published on Web 01/19/2011

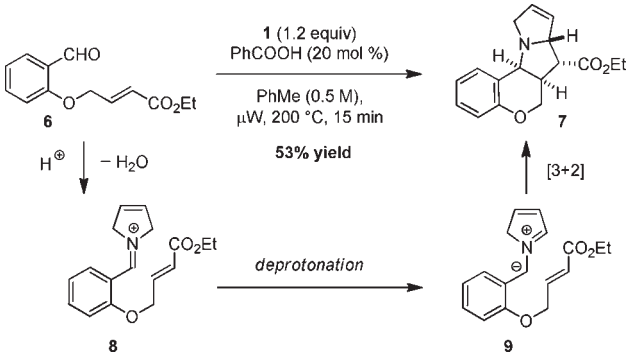
to other processes. The most direct pathway leading from **3** to **4** would involve a 1,3-hydride shift.[6] However, orbital symmetry considerations dictate that, in the case of a migrating hydrogen, a 1,3-hydride shift would have to occur antarafacially and thus represents an essentially geometry-forbidden pathway.[7] In addition, given the relatively mild reaction conditions, a 1,3-hydride shift seems to be unlikely to account for this transformation.

Scheme 2. Proposed Mechanism for Redox Isomerization



In considering alternative mechanisms, we proposed the reaction sequence as outlined in Scheme 2. Deprotonation of iminium ion **3** is envisioned to give rise to the formation of azomethine ylide **5**.[8,9] Reprotonation of this dipolar intermediate results in the new iminium ion **4**. Subsequent proton loss leads to aromatization and formation of pyrrole **2**. As an alternative to benzoate, which is depicted as the proposed base in this process, deprotonation could also be promoted by unmodified 3-pyrroline.

Scheme 3. Evidence for Azomethine Ylide Intermediates



In order to establish the intermediacy of azomethine ylides such as **5**, we opted to investigate the reaction of 3-pyrroline (**1**) with aldehyde **6** (Scheme 3). The latter reaction partner possesses a pendant dipolarophile and has previously been used in intramolecular [3 + 2] cycloadditions.[10,11] Indeed, a reaction of **1** and **6**, conducted in the presence of catalytic amounts of benzoic acid under microwave irradiation, led to the rapid formation of **7** in 53% yield.[12] The expected [3 + 2] cycloaddition product **7** was obtained in the form of a single diastereomer. This strongly suggests the intermediacy of azomethine ylides in this redox neutral reaction cascade.

Next we sought to apply this method to a related process, namely the formation of *N*-alkyl indoles from indolines and aldehydes. This approach would provide an efficient alternative to the *N*-alkylation of preformed indoles which sometimes suffers from issues of regioselectivity.[13] Although iminium ions derived from aldehydes and indoline might be expected to be somewhat less acidic than species such as **3**, these reactions proceeded efficiently when conducted under microwave irradiation. As outlined in Figure 1, indoline readily underwent reactions with a range of electronically diverse benzaldehydes.[14] The use of only 1.2 equiv of indoline proved sufficient to achieve

(5) For other selected examples of redox neutral amine functionalizations, see: (a) Ten Broeke, J.; Douglas, A. W.; Grabowski, E. J. J. *J. Org. Chem.* **1976**, *41*, 3159. (b) Verboom, W.; Reinhoudt, D. N.; Visser, R.; Harkema, S. *J. Org. Chem.* **1984**, *49*, 269. (c) De Boeck, B.; Jiang, S.; Janousek, Z.; Viehe, H. G. *Tetrahedron* **1994**, *50*, 7075. (d) Pastine, S. J.; McQuaid, K. M.; Sames, D. *J. Am. Chem. Soc.* **2005**, *127*, 12180. (e) Tobisu, M.; Chatani, N. *Angew. Chem., Int. Ed.* **2006**, *45*, 1683. (f) Matyus, P.; Elias, O.; Tapolcsanyi, P.; Polonka-Balint, A.; Halasz-Dajka, B. *Synthesis* **2006**, 2625. (g) Indumathi, S.; Kumar, R. R.; Perumal, S. *Tetrahedron* **2007**, *63*, 1411. (h) Ryabukhin, S. V.; Plaskon, A. S.; Volochnyuk, D. M.; Shivanyuk, A. N.; Tolmachev, A. A. *Synthesis* **2007**, 2872. (i) Ryabukhin, S. V.; Plaskon, A. S.; Volochnyuk, D. M.; Shivanyuk, A. N.; Tolmachev, A. A. *J. Org. Chem.* **2007**, *72*, 7417. (j) Belskaia, N. P.; Deryabina, T. G.; Koksharov, A. V.; Kodess, M. I.; Dehaen, W.; Lebedev, A. T.; Bakulev, V. A. *Tetrahedron Lett.* **2007**, *48*, 9128. (k) Oda, M.; Fukuchi, Y.; Ito, S.; Thanh, N. C.; Kuroda, S. *Tetrahedron Lett.* **2007**, *48*, 9159. (l) Zheng, L.; Yang, F.; Dang, Q.; Bai, X. *Org. Lett.* **2008**, *10*, 889. (m) Che, X.; Zheng, L.; Dang, Q.; Bai, X. *Synlett* **2008**, 2373. (n) Polonka-Balint, A.; Saraceno, C.; Ludányi, K.; Bényei, A.; Matyus, P. *Synlett* **2008**, 2846. (o) Barluenga, J.; Fananas-Mastral, M.; Aznar, F.; Valdes, C. *Angew. Chem., Int. Ed.* **2008**, *47*, 6594. (p) Mori, K.; Ohshima, Y.; Ehara, K.; Akiyama, T. *Chem. Lett.* **2009**, *38*, 524. (q) Ruble, J. C.; Hurd, A. R.; Johnson, T. A.; Sherry, D. A.; Barbachyn, M. R.; Toogood, P. L.; Bundy, G. L.; Graber, D. R.; Kamilar, G. M. *J. Am. Chem. Soc.* **2009**, *131*, 3991. (r) Cui, L.; Peng, Y.; Zhang, L. *J. Am. Chem. Soc.* **2009**, *131*, 8394. (s) Vadola, P. A.; Sames, D. *J. Am. Chem. Soc.* **2009**, *131*, 16525. (t) Lo, V. K.-Y.; Zhou, C.-Y.; Wong, M.-K.; Che, C.-M. *Chem. Commun.* **2010**, *46*, 213. (u) Kuang, J.; Ma, S. *J. Am. Chem. Soc.* **2010**, *132*, 1786. (v) Cui, L.; Ye, L.; Zhang, L. *Chem. Commun.* **2010**, *46*, 3351. (w) Kang, Y. K.; Kim, S. M.; Kim, D. Y. *J. Am. Chem. Soc.* **2010**, *132*, 11847. (x) Dunkel, P.; Turos, G.; Benyei, A.; Ludanyi, K.; Matyus, P. *Tetrahedron* **2010**, *66*, 2331. (y) Zhou, G.; Zhang, J. *Chem. Commun.* **2010**, *46*, 6593.

(6) A 1,3-hydride shift has been proposed to occur in a thermal, uncatalyzed reaction between 3-pyrroline and cyclohexanone to yield *N*-cyclohexylpyrrole: Cook, A. G.; Switek, K. A.; Cutler, K. A.; Witt, A. N. *Lett. Org. Chem.* **2004**, *1*, 1.

(7) (a) Woodward, R. B.; Hoffman, R. *J. Am. Chem. Soc.* **1965**, *78*, 2511. (b) Berson, J. A. *Acc. Chem. Res.* **1968**, *1*, 152.

(8) Deprotonation of iminium ions is an established concept for the generation of azomethine ylides. For examples, see: (a) Huisgen, R.; Grashey, R.; Steingruber, E. *Tetrahedron Lett.* **1963**, 1441. (b) Toth, G.; Frank, J.; Bende, Z.; Weber, L.; Simon, K. *J. Chem. Soc., Perkin Trans. 1* **1983**, 1961. (c) Ardill, H.; Grigg, R.; Sridharan, V.; Surendrakumar, S.; Thianpatanagul, S.; Kanajun, S. *J. Chem. Soc., Chem. Commun.* **1986**, 602. (d) Kanemasa, S.; Takenaka, S.; Watanabe, H.; Tsuge, O. *J. Org. Chem.* **1989**, *54*, 420. (e) Ardill, H.; Fontaine, X. L. R.; Grigg, R.; Henderson, D.; Montgomery, J.; Sridharan, V.; Surendrakumar, S. *Tetrahedron* **1990**, *46*, 6449. (f) Grigg, R.; Sridharan, V.; Thornton-Pett, M.; Wang, J.; Xu, J.; Zhang, J. *Tetrahedron* **2002**, *58*, 2627.

(9) See also: Kadas, I.; Szanto, G.; Toke, L.; Simon, A.; Toth, G. *J. Heterocycl. Chem.* **2007**, *44*, 1373 and references cited therein.

(10) See for instance ref 8e.

(11) For a review on intramolecular azomethine ylide cycloadditions, see: Coldham, I.; Hufton, R. *Chem. Rev.* **2005**, *105*, 2765.

(12) Conventional thermal conditions were also evaluated briefly. However, we found the use of microwave irradiation to be superior in terms of overall efficiency. Consequently, microwave acceleration was used as the method of choice throughout this study.

(13) For an example of efficient indole *N*-alkylation, see: Hayat, S.; Attaur, R.; Choudhary, M. I.; Khan, K. M.; Schumann, W.; Bayer, E. *Tetrahedron* **2001**, *57*, 9951 and references cited therein.

(14) During the preparation of this manuscript, Sun, Pan and coworkers reported the formation of *N*-alkyl indoles under very similar but reflux conditions, using 2 equiv of indoline. These authors proposed the intervention of a 1,3-hydride shift: Mao, H.; Xu, R.; Wan, J.; Jiang, Z.; Sun, C.; Pan, Y. *Chem.—Eur. J.* **2010**, *16*, 13352.

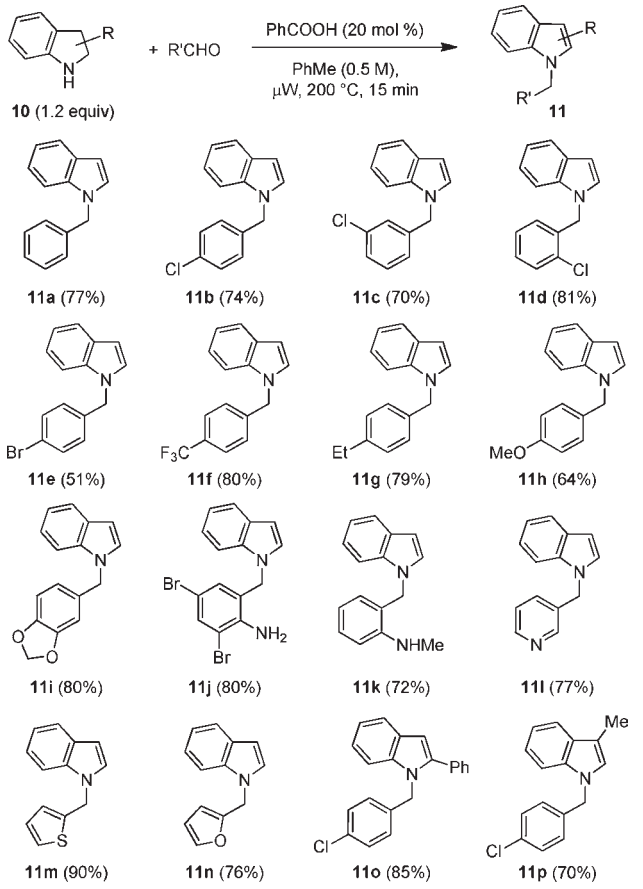


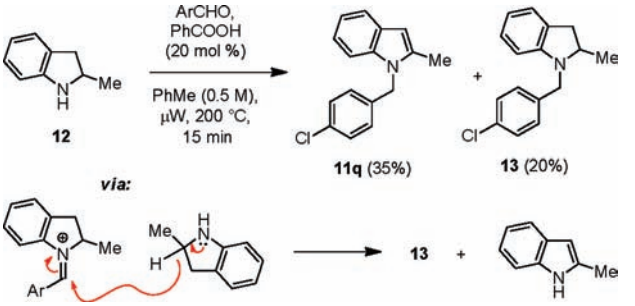
Figure 1. Synthesis of *N*-alkylated indoles.

full conversion of the aldehydes. Interestingly, reactions of indoline with aminobenzaldehydes also gave rise to *N*-alkylated indoles.[15] Thiophene, furan, and pyridine aldehydes led to the formation of alkylated indoles in good yields. Substituted indolines such as 2-phenylindoline and 3-methylindoline were also viable substrates in this redox isomerization. Enolizable aldehydes failed to yield indoles, presumably due to the facile formation of enamines.

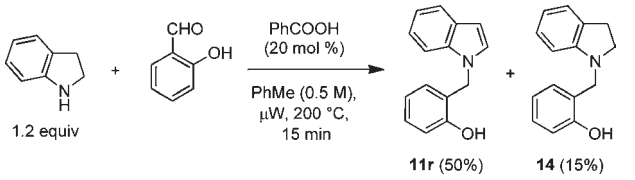
Interestingly, in a reaction between 2-methylindoline and *p*-chlorobenzaldehyde, in addition to the expected indole product **11q** which was isolated in 35% yield, we observed the formation of *N*-alkylated 2-methylindoline **13** in 20% yield (Scheme 4). An additional product of this reaction was identified as 2-methylindole. Given the observation of the latter, we propose that the formation of **13** is the result of an intermolecular hydride transfer as outlined in Scheme 4.[16]

A substantial amount of reduced product (**14**) was also observed in the reaction between indoline and salicylaldehyde (Scheme 5). While the *N*-alkyl indole **11r** was still the major product (50% yield), the corresponding *N*-alkylated indoline **14** was obtained in 15% isolated yield.[17] We attribute this observation to the presence of an acidic phenol proton. The latter makes it likely more challenging to regioselectively deprotonate the initially formed iminium ion to generate the required azomethine ylide intermediate. Consequently, the intermolecular reduction pathway as illustrated in Scheme 4 becomes more predominant than in reactions of indoline with other aldehydes lacking such an acidic functionality.[16]

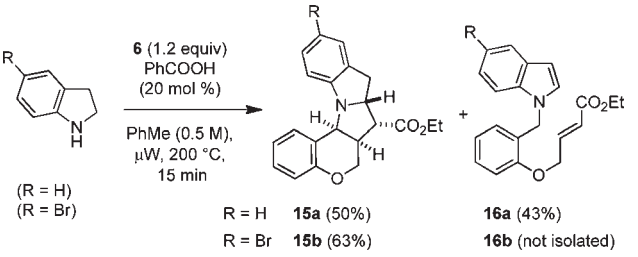
Scheme 4. Redox Isomerization vs Intermolecular Hydride Transfer



Scheme 5. Reaction of Indoline and Salicylaldehyde



Scheme 6. Intramolecular [3 + 2] vs Indole Formation



To establish the intermediacy of azomethine ylides in the formation of *N*-alkyl-indoles, we conducted a similar trapping experiment as discussed earlier in the case of

(15) In related cases where aromatization is not possible, we have previously observed the formation of aminals upon trapping of azomethine ylides. See refs 4a and 4g.

(16) In most reactions leading to the formation of products shown in Chart 1, small amounts of the corresponding *N*-alkyl indolines were also observed. These compounds were typically recovered in less than 3% yield.

(17) Interestingly, in a reaction of indoline and salicylaldehyde conducted under thermal conditions, Sun, Pan and co-workers observed the exclusive formation of the reduced product **14** (ref 14). They attributed this to a potential involvement of the phenolic OH group in an intramolecular hydrogen bonding interaction that was thought to interfere with the redox isomerization.

3-pyrroline (**1**). As outlined in Scheme 6, reaction of indoline with aldehyde **6** resulted in the formation of the expected cycloaddition product **15a** as a single diastereomer in 50% yield. In addition, the *N*-alkylated indole **16a** was obtained in 43% yield. These observations are again consistent with the proposed intermediacy of azomethine ylides.

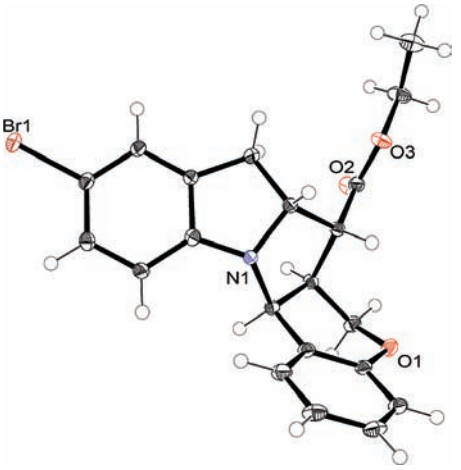


Figure 2. ORTEP view (50% probability thermal ellipsoids) of the molecular structure of **15b**.

A reaction of 5-bromoindoline with aldehyde **6** resulted in the formation of the crystalline cycloaddition product **15b** as a single diastereomer in 63% yield. The X-ray crystal structure of **15b** is shown in Figure 2. In this instance, none of the *N*-alkylated indole **16b** was isolated. Instead, a small amount (5%) of the corresponding *N*-alkylated indoline was recovered (product not shown).

In summary, we have reported a facile redox neutral method for the synthesis of *N*-alkylated indoles from indolines and aldehydes. Rather than proceeding through a deceptively apparent (but orbital-symmetry forbidden) 1,3-hydride shift mechanism, this reaction involves the intermediacy of azomethine ylides as established by intramolecular trapping experiments. This observation has implications for the future development of related transformations.

Acknowledgment. We thank the National Science Foundation for partial support of this research (Grant CHE-0911192). We thank Dr. Tom Emge (Rutgers University) for crystallographic analysis.

Supporting Information Available. Experimental procedures, characterization data, and X-ray crystal structure of **15b**. This material is available free of charge via the Internet at http://pubs.acs.org.