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Alkoxyamine-Mediated Radical Synthesis of Indolinones and Indolines

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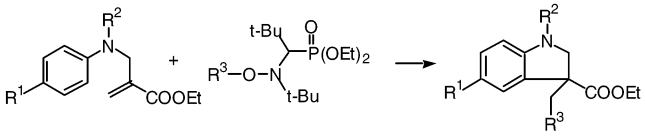
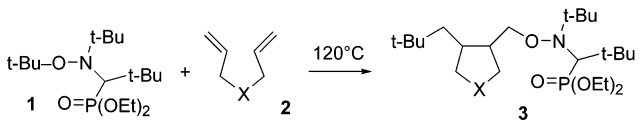
ABSTRACT



Thermolysis of α-alkoxyamino propionanilides produces indolinones, whereas thermal reaction of *N*-allylaniline derivatives with various Tordo-type alkoxyamines results in formation of indolines in the radical regime.

We have recently described a new radical cyclization process that relies on the reaction of the Tordo alkoxyamine, **1**, with a 1,6-diene, **2**, leading to products **3** (Scheme 1).[1] An even more recent paper by Studer expands the scope of his earlier, seminal studies to a like mode of reactivity with TEMPO-derived alkoxyamines.[2]

Scheme 1. Alkoxyamine-Mediated Radical Cyclization



Such alkoxyamine-based techniques suppress any need for halogenated substrates and Sn/Si hydrides to promote C−C bond formation in the radical regime, providing a relatively environmentally benign alternative to traditional radical methodology. Furthermore, the chain termination step involves the capture of a carbon radical by a nitroxyl radical, thereby introducing useful oxygenated functionality, instead of simply reducing the radical intermediate through H-atom transfer from a metal hydride.

In an effort to extend this chemistry to the heterocyclic domain, we have focused on the synthesis of indole derivatives. Indeed, considerable activity has been recorded in the area of indole synthesis through radical processes.[3]

In this paper, we disclose the alkoxyamine-mediated assembly of indolinones and indolines through cyclization of aniline derivatives **4** (Scheme 2).

The process that we envisioned involves the attack of a radical species onto a benzenoid π system (cf. **6** and **7**). This general type of reaction is well documented,[3e−h] but in our case, such an event would have to occur in the presence of a free nitroxyl radical. A priori, it was not clear whether the

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(1) Leroi, C.; Fenet, B.; Couturier, J. L.; Guerret, O.; Ciufolini, M. A. *Org. Lett.* **2003**, *5*, 1079.
(2) Wetter, C.; Jantos, K.; Woithe, K.; Studer, A. *Org. Lett.* **2003**, *5*, 2899.

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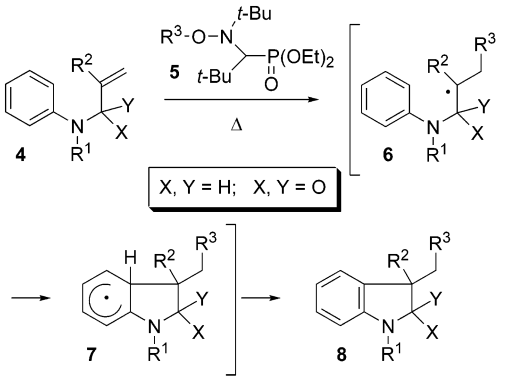
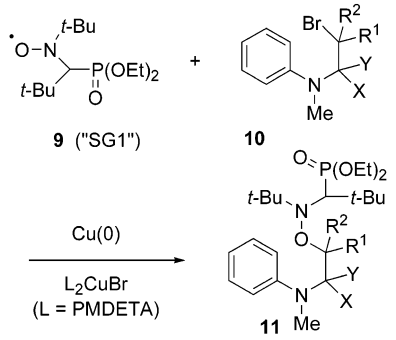
Scheme 2. Alkoxyamine-Mediated Avenue to Indole Derivatives



reversible trapping of **6** by the nitroxyl radical would be beneficial (or even critical) to the success of the reaction or whether complications might arise as a result of this trapping. Consequently, the feasibility of the transformation of Scheme 2 was initially explored through a study of the thermal cyclization of *preformed* intermediates **11**.[4] These were prepared by a coupling reaction between the stable free nitroxyl radical **9** ("SG1") and an alkyl radical generated in situ through Cu(I)-mediated reduction of an appropriate alkyl bromide **10** (Scheme 3).

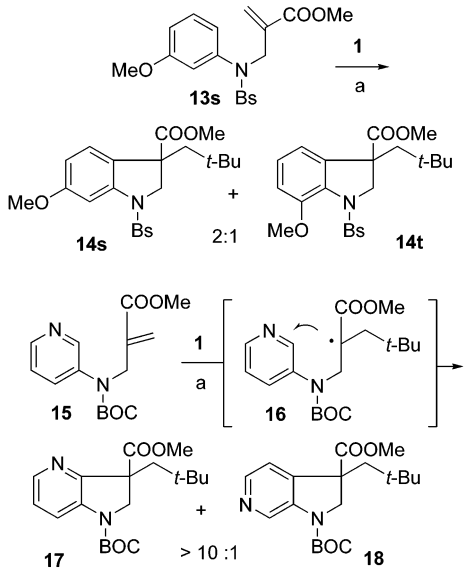
Scheme 3. Preparation of Alkoxyamines **11**[a]



[a] PMDETA = *N*,*N*,*N*′,*N*″,*N*′-pentamethyldiethylenetriamine.

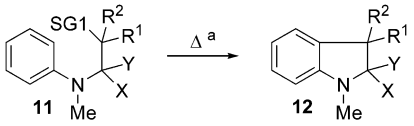
When a solution of **11** in PhCl or *t*-BuOH was heated at 80−120 °C for 12 h, complete consumption of the starting material was observed leading directly to compounds **12**. No products arising from trapping of the presumed radical intermediate **7** by SG1 were detected in the reaction mixture. Evidently, either **7** suffers H-atom transfer to the nitroxyl radical or the product of its recombination with SG1 undergoes facile elimination to the ultimate **12**. Some examples of this transformation are provided in Table 1.

Scheme 4. Indolines from Unsymmetrically Substituted Anilines



[a] Conditions: 120 °C, 0.5 M in *t*-BuOH, 20 h. Chromatographed Yields: 15% for **14s**, 8% for **14t**, 30% for **17**. Bs = brosyl (4-bromobenzenesulfonyl).

Table 1. Indolinone and Indoline Synthesis by Thermolysis of Compounds **11**



entry	R^1	R^2	X, Y	*T* (°C)	yield[b]
a	Me	H	O	120	68
b	Me	Me	O	80	63
c	COOMe	H	H, H	120	75

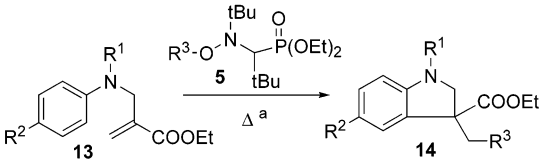
[a] Reactions were carried out as a 0.025 M solution in PhCl for entry **a** and in *t*-BuOH for entries **b** and **c**. [b] Chromatographed.

The more challenging bimolecular mode of reactivity was initially investigated with intermediates **4** wherein R^2 = X = Y = H or R^2 = H; X, Y = O. Disappointingly, both types of substrate failed to yield indolinones or indolines upon thermal reaction with alkoxyamine **1**. By contrast, compounds **4** in which R^2 = COOMe and X,Y = H proved to be competent substrates. Presumably, the presence of the ester function facilitates the addition of the radical produced by the initial dissociation of the alkoxyamine to the olefinic

(3) Cf. (a) Fukuyama, T.; Chen, X.; Peng, G. *J. Am. Chem. Soc.* **1994**, *116*, 3127. (b) Tokuyama, H.; Yamashita, T.; Reding, M. T.; Kaburagi, Y.; Fukuyama, T. *J. Am. Chem. Soc.* **1999**, *121*, 3791. (c) Reding, M. T.; Fukuyama, T. *Org. Lett.* **1999**, *1*, 973. (d) Yokoshima, S.; Ueda, T.; Kobayashi, S.; Sato, A.; Kuboyama, T.; Tokuyama, H.; Fukuyama, T. *J. Am. Chem. Soc.* **2002**, *124*, 2137. (e) Boivin, J.; Yousfi, M.; Zard, S. Z. *Tetrahedron Lett.* **1994**, *35*, 9553. (f) Axon, J.; Boiteau, L.; Boivin, J.; Forbes, J. E.; Zard, S. Z. *Tetrahedron Lett.* **1994**, *35*, 1719. (g) Ly, T. M.; Quiclet-Sire, B.; Sortais, B.; Zard, S. Z. *Tetrahedron Lett.* **1999**, *40*, 2533. (h) Quiclet-Sire, B.; Sortais, B. S.; Zard, S. Z. *J. Chem. Soc., Chem. Commun*. **2002**, 1692. (i) Rainier, J. D.; Kennedy, A. R.; Chase, E. *Tetrahedron Lett*. **1999**, *40*, 6325. (j) Rainier, J. D.; Kennedy, A. R. *J. Org. Chem.* **2000**, *65*, 6213.

(4) This mode of reactivity constitutes a variant of the original Studer cycloisomerization of alkoxyamines: see ref 2 and literature cited therein.

Table 2. Indoline Synthesis by Alkoxyamine-Induced Radical Cyclization



entry	R^1	R^2	R^3	T (°C)	yield [b]
a	Me	H	*t*-Bu	120	54
b	Me	MeO	"	"	47
c	BOC	H	"	"	53
d	BOC	MeO	"	"	59
e	Bs	H	"	"	46
f	Bs	MeO	"	"	35
g	Me	H		"	61
h	BOC	H	"	"	63
i	BOC	MeO	"	"	54
j	Bs	H	"	"	42
k	Bs	MeO	"	"	31
l	Me	H		70	47
m	Me	MeO	"	"	38
n	BOC	H	"	"	45
o	BOC	MeO	"	"	48
p	Bs	H	"	"	62
q	Bs	MeO	"	"	54
r	BOC	NO_2	"	"	58

[a] All reactions were carried out as a 0.5 M solution in *t*-BuOH. [b] Chromatographed. [c] Bs = brosyl (4-bromobenzenesulfonyl).

π system.[5] Representative examples with three Tordo-type alkoxyamines[6] are provided in Table 2.

The experiments summarized in Table 2 were carried out with substrates in which the aryl group is either unsubstituted or symmetrically (para) substituted. Results of a brief study of indoline formation from unsymmetrically substituted anilines are presented in Scheme 3. Reaction of *meta*-anisidine derivative **13s** with alkoxyamine **1** led to a mixture of regioisomers in which the major component was the para-type cyclization product **14s**. However, the product ratio was a weak 2:1.[7] On the other hand, pyridine derivative **15** reacted with *tert*-butyl SG1 to furnish indoline **17** in 30% unoptimized yield. Compound **17** accounted for more than 90% of the product mixture: regioisomer **18** was estimated (^{1}H NMR) to represent less than 10% of the total product (i.e., $<$3% chemical yield) and was not fully characterized. The observed selectivity for attack of the presumed radical intermediate **16** at C-2 of the pyridine nucleus is consistent with precedent, notably with the work of Minisci on the radical alkylation of electron-deficient nitrogen heterocycles.[8]

In summary, Tordo alkoxyamines, originally developed as control agents in radical polymerization reactions,[9] appear to be valuable intermediates for the synthesis of indole derivatives in the radical mode. Additional synthetic applications of alkoxyamines are under study and will be described in due course.

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Supporting Information Available: Detailed descriptions of experimental procedures and full characterization data for the compounds described herein. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0358049

(5) For a thorough discussion, see: Fischer, H.; Radom, L. *Angew. Chem., Int. Ed.* **2001**, *40*, 1340. An amide carbonyl may not provide sufficient activation of the olefinic π system, explaining the failure of compounds **4** (X, Y = O) to cyclize.

(6) Alkoxyamines **5** where R^3 = $CH_3CHCOOMe$ or $(CH_3)_2CHCOOH$ were prepared by the method detailed in Scheme 3. The *tert*-butyl analogue was obtained by reaction of 2 equiv of free SG1 with commercial *tert*-butylmagnesium chloride (55−60% yield).

(7) Yield of this reaction was not optimized due to the weak isomer ratio observed.

(8) Cf., e.g.: Minisci, F.; Vismara, E.; Fontana, F. *Heterocycles* **1989**, *28*, 489.

(9) Review: Hawker, C. J.; Bosman, A. W.; Hart, E. *Chem. Rev.* **2001**. *101*, 3661.