ORGANIC LETTERS

2004
Vol. 6, No. 20
3477−3480

One-Pot Homolytic Aromatic Substitutions/HWE Olefinations under Microwave Conditions for the Formation of a Small Oxindole Library

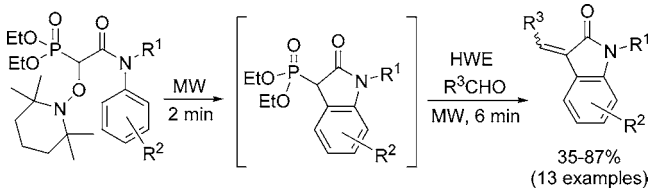
Antje Teichert,[†] Katja Jantos,[†] Klaus Harms,[†] and Armido Studer*[,†,‡]

Fachbereich Chemie, Philipps-Universität Marburg, 35032 Marburg, Germany. Organisch-Chemisches Institut, Westfälische Wilhelms-Universität Münster, Corrensstrasse 40, 48149 Münster, Germany

studer@uni-muenster.de

Received June 30, 2004

ABSTRACT

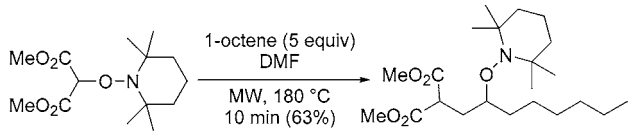


An efficient one-pot sequence comprising a homolytic aromatic substitution followed by an ionic Horner–Wadsworth–Emmons olefination for the preparation of a small library of α,β-unsaturated oxindoles is presented. Microwave-induced heating is used to conduct these reactions. The homolytic aromatic substitution is mediated by the persistent radical effect.

The indole core occurs in many natural products and pharmaceutically important compounds.[1] Indoles are designated as privileged structures in medicinal chemistry. Oxindoles belong to this important class of compounds and have therefore gained some interest during the past few years.[2]

Recently, we introduced the use of TEMPO-derived alkoxyamines (TEMPO = 2,2,6,6-tetramethylpiperidin-*N*-oxyl radical) as C-radical precursors for environmentally benign radical cyclization reactions.[3,4] These reactions are mediated by the so-called persistent radical effect (PRE).[5] We recently extended this concept to intermolecular alkoxyamine additions onto nonactivated olefins, so-called radical carboaminoxylation reactions.[6] Moreover, we have shown that these reactions can efficiently be conducted under microwave conditions.[7] An example is depicted in Scheme 1.

Scheme 1. Intermolecular Radical Carboaminoxylation of 1-Octene under Microwave Conditions



Herein, we present a new approach to substituted oxindoles using one-pot PRE-mediated intramolecular homolytic aro-

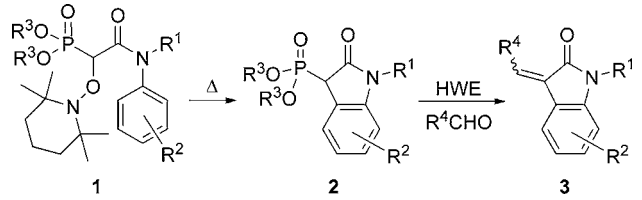
[†] Philipps-Universität Marburg.
[‡] Westfälische Wilhelms-Universität Münster.

(1) Bräse, S.; Gil, C.; Knepper, K. *Bioorg. Med. Chem.* **2002**, *10*, 2415. Horton, D. A.; Bourne, G. T.; Smythe, M. L. *Chem. Rev.* **2003**, *103*, 893.
(2) For an example see: Froestl, W. *Chimia* **2004**, *58*, 54.
(3) Studer, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 1108.
(4) For other applications of the PRE in synthesis, see: Allen, A. D.; Fenwick, M. F.; Henry-Riyad, H.; Tidwell, T. T. *J. Org. Chem.* **2001**, *66*, 5759. Leroi, C.; Fenet, B.; Couturier, J.-L.; Guerret, O.; Ciufolini, M. A. *Org. Lett.* **2003**, *5*, 1079. Alajarín, M.; Vidal, A.; Ortín, M.-M.; Bautista, D. *Synlett* **2004**, 991.
(5) Fischer, H. *Chem. Rev.* **2001**, *101*, 3581. Studer, A. *Chem. Eur. J.* **2001**, *7*, 1159. Studer, A. *Chem. Soc. Rev.* **2004**, *33*, 267.
(6) Wetter, C.; Jantos, K.; Woithe, K.; Studer, A. *Org. Lett.* **2003**, *5*, 2899.

10.1021/ol048759t CCC: $27.50
Published on Web 09/02/2004

matic substitutions[8,9] followed by ionic Horner−Wadsworth−Emmons (HWE)-type olefination reactions. The reaction sequence is depicted in Scheme 2. HWE-type TEMPO

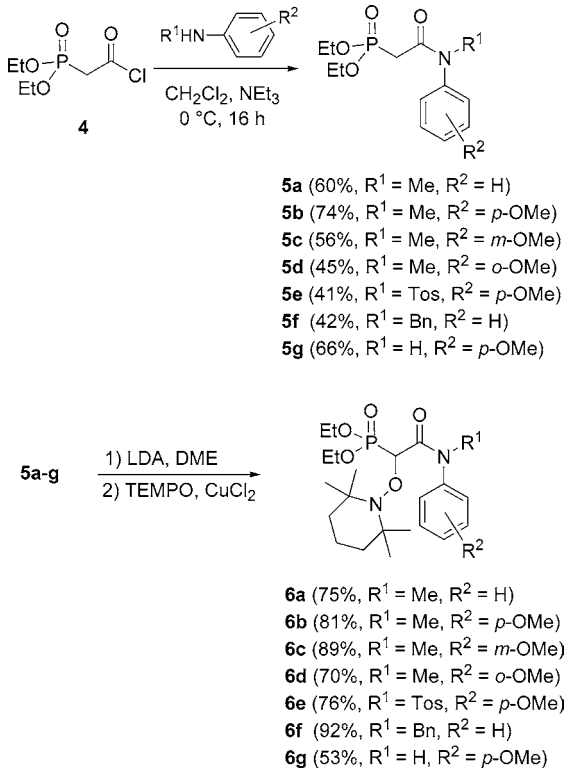
Scheme 2. Homolytic Aromatic Substitution/HWE Olefination



derivatives **1** should undergo homolytic aromatic substitution upon simple heating to provide oxindoles of type **2**, which are ready to be used in olefination reactions to eventually afford α,*β*-unsaturated oxindoles of type **3**.

Phosphonates **5a**−**g** were prepared from readily available acid chloride **4** and the corresponding aniline derivatives[10] (Scheme 3). Deprotonation of the phosphonates **5a**−**g** with

Scheme 3. Preparation of Phosphonates **6a**−**g**



lithium diisopropyl amide (LDA) in dimethoxyethane (DME) followed by Cu(II)-oxidation in the presence of TEMPO gave the alkoxyamines **6a**−**g** in moderate to excellent yields. Alkoxyamine **6d** was obtained as a 1:1 mixture of diastereoisomers.[11]

Before attempting the above sketched one-pot process, the intramolecular homolytic aromatic substitution was studied using alkoxyamine **6a**. The reaction was conducted using classical heating in a sealed tube at 135 °C. We were pleased to observe that the Horner-type radical[12] formed via C−O bond homolysis of alkoxamine **6a** undergoing the desired homolytic aromatic substitution process. Unfortunately, in THF (25%), in $ClCH_2CH_2Cl$ (32%), and in DMF (18%) unsatisfactory low yields of oxindole **7** were obtained (0.02 M). However, we found that microwave-induced heating in DMF (0.01 M) for 2 min at 180 °C provided **7** in 81%.[13] It is important to note that there are only a few reports in the literature on microwave-induced free radical chemistry.[7,14]

We next tried to run the HWE reaction of **7** in DMF under microwave conditions. The reaction was optimized using benzaldehyde as the electrophile. The base and the reaction time were systematically varied. The best results were obtained with KO*t*-Bu as a base at 180 °C for 6 min (92%). To our delight, we found that the homolytic aromatic substitution and the ionic HWE reaction can be conducted in a one-pot process. After extensive optimization the following protocol was obtained: (1) microwave-induced heating of **6a** in DMF (0.03 M) for 2 min at 180 °C and (2) addition of benzaldehyde (10 equiv) and KO*t*-Bu (1.2 equiv) and renewed microwave heating at 180 °C for 6 min. The α,*β*-unsaturated oxindole **8a** was isolated in 75% yield as a mixture of isomers (*trans*:*cis* = 3.4:1, Table 1, run 1).[15] Under the optimized conditions (less than 12 min is necessary to prepare the oxindoles) various aromatic aldehydes (10−20 equiv) were used for the one-pot radical/ionic process. The results are summarized in Table 1.

para-Substituted aldehydes reacted with moderate to excellent yields with low selectivities favoring the *trans*-isomer (→ **8b**−**f**, 38−87%, runs 2−6). The isomers were readily separated by chromatography. Slightly higher selec-

(7) Wetter, C.; Studer, A. *Chem. Commun.* **2004**, 174.

(8) Leroi, C.; Bertin, D.; Dufils, P.-E.; Gigmes, D.; Marque, S.; Tordo, P.; Couturier, J.-L.; Guerret, O.; Ciufolini, M. A. *Org. Lett.* **2003**, *5*, 4943.

(9) For a review on homolytic aromatic substitutions, see: Studer, A.; Bossart, M. In *Radicals in Organic Synthesis*; Renaud, P., Sibi, M. P., Eds.; Wiley-VCH: Weinheim, 2001; Vol. 2, p 62.

(10) Prepared according to: Barluenga, J.; Bayón, A. M.; Asensio, G. *Chem. Commun.* **1983**, 1109.

(11) Axial chirality in radical chemistry: Curran, D. P.; Liu, W.; Chen, C. H.-T. *J. Am. Chem. Soc.* **1999**, *121*, 11012.

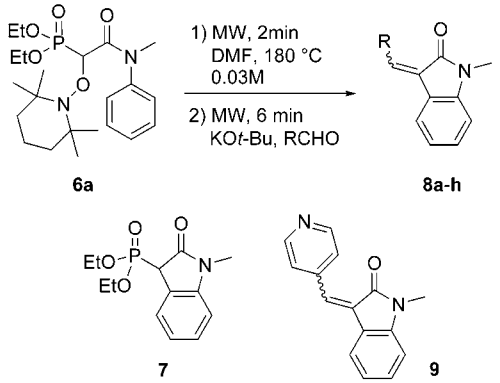
(12) Cholleton, N.; Gauthier-Gillaizeau, I.; Six, Y.; Zard, S. Z. *Chem. Commun.* **2000**, 535.

(13) The microwave experiments were conducted using professional laboratory microwave equipment. A MLS-Ethos 1600 Mikrowellen System (Milestone) was used for the present studies. The reactions were run in 40 mL MLS high-pressure reaction vessels (up to 15 bar) that contain pressure control valves. An advanced temperature control system from MLS allowing direct contactless temperature monitoring was used. The microwave power is continuously and dynamically adjusted to follow the defined temperature profile. Temperature profile for the homolytic aromatic substitution: from 25 to 100 °C in 10 s; from 100 to 150 °C in 10 s; from 150 to 180 °C in 10 s; then keep the temperature at 180 °C for 2 min.

(14) Bose, A. K.; Manhas, M. S.; Ghosh, M.; Shah, M.; Raju, V. S.; Bari, S. S.; Newaz. S. N.; Banik, B. K.; Chaudhary, A. G.; Barakat, K. J. *J. Org. Chem.* **1991**, *56*, 6968. Olofsson, K.; Kim, S.-Y.; Larhed, M.; Curran, D. P.; Hallberg, A. *J. Org. Chem.* **1999**, *64*, 4539. Lamberto, M.; Corbett, D. F.; Kilburn, J. D. *Tetrahedron Lett.* **2003**, *44*, 1347. Ericcson, C.; Engman, L. *J. Org. Chem.* **2004**, *69*, 5143.

(15) The same selectivity was obtained upon running the HWE reaction at 100 °C. At room temperature HWE reaction did not work as controlled by TLC. The HWE reaction in THF at 100 °C occurred with lower selectivity (*trans*:*cis* = 1.9:1).

Table 1. One-Pot Homolytic Aromatic Substitution/HWE Olefination Using Alkoxyamine **6a**



6a **8a-h** **7** **9**

run	R	equiv	oxindole	ratio (*trans*:*cis*)	yield (%)
1	Ph	1.0	**8a**	3.4:1	75
2	4-CF_3-Ph	1.0	**8b**	1.9:1	87
3	4-NO_2-Ph	1.0	**8c**	1.4:1	44
4	4-Br-Ph	1.5	**8d**	2.4:1	38
5	4-Me-Ph	1.5	**8e**	2.3:1	43[a]
6	4-MeO-Ph	2.0	**8f**	1.9:1	52
7	2-Br−Ph	1.5	**8g**	3.6:1	58[b]
8	2-Me-Ph	1.5	**8h**	6.0:1	38

[a] Conducted at 0.02 M. [b] Conducted at 0.04 M.

tivities were obtained with the *ortho*-substituted aldehydes (→ **8g**,**h**, up to 6:1, runs 7 and 8). Reaction of 4-pyridinecarboxaldehyde with **6a** provided oxindole **9** in 48% yield (*trans*:*cis* = 2.3:1). The relative configuration of the oxindoles was assigned on the basis of X-ray analysis of *cis*-**8b** and *trans*-**8c** (Figure 1).[16] Furthermore, we found that during chromatography on silia gel the *cis*-isomer was always eluted faster than its *trans*-congener. In addition, the vinylic proton of the *trans*-isomer always appears at slightly lower field in the ^{1}H NMR spectrum than the corresponding signal of the *cis*-isomer.

We then tested whether the one-pot sequence works also with substituted anilides. These studies were performed with benzaldehyde as electrophile in the HWE step using the optimized protocol. Reaction with the *p*-MeO-substituted anilide **6b** afforded the oxindole **10** in 65% yield (*trans*:*cis* = 3.1:1, Figure 2). A lower yield was obtained for the *o*-MeO-derivative **6d** (→ **11**, 42%, *trans*:*cis* = 2.6:1). Surprisingly, for the *m*-MeO-compound **6c**, the sterically more hindered isomer **12a** was formed as the major compound in 51% yield (*cis*:*trans* = 5.0:1). Interestingly, for regioisomer **12b** only the *cis*-isomer was isolated (36%). The assignment of the regioisomers is based on the reduction of **12a** (Pd/C, MeOH, H_2) to **13a** for which an X-ray structure was obtained (Figure 3).[17] In analogy the regioisomeric oxindole **12b** was reduced to **13b**.

(16) The data for the structure of *cis*-**8b** and *trans*-**8c** have been deposited with the Cambridge Crystallographic Data Center as supplementary publications no. CCDC 241647 (*cis*-**8b**) and CCDC 241648 (*trans*-**8c**).

(17) The data for the structure of **13a** have been deposited with the Cambridge Crystallographic Data Center as supplementary publication no. CCDC 241649.

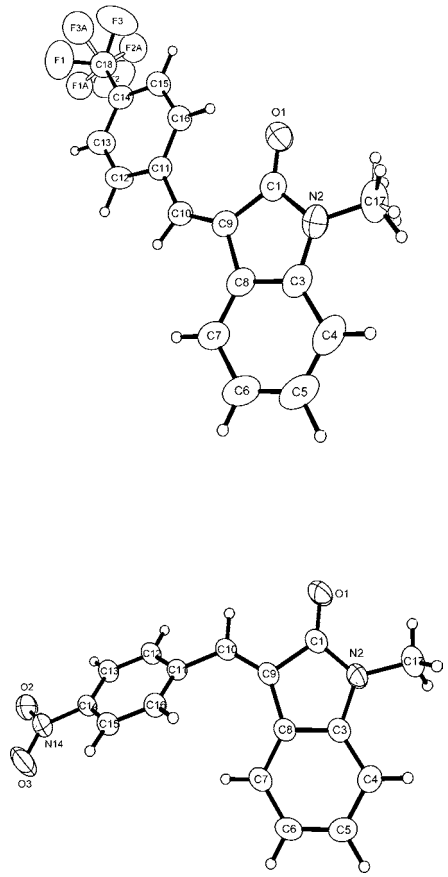
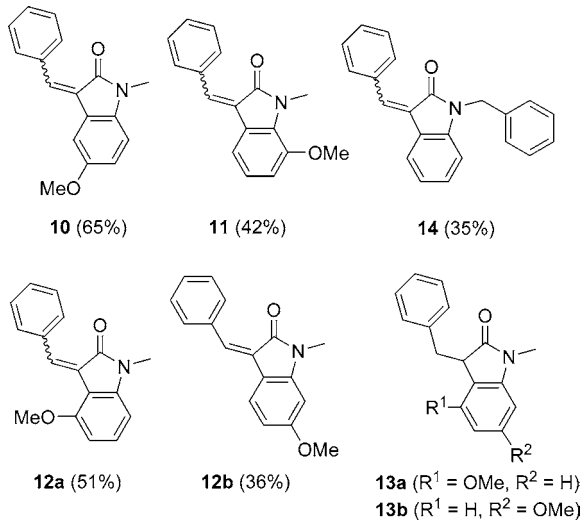


Figure 1. X-ray structure of cis-*8b* (above) and *trans*-**8c** (below).

We could also show that the *N*-methyl group, which is difficult to remove, can be replaced by a benzyl group. Thus, one-pot reaction of **6f** afforded oxindole **14** in 35% yield



10 (65%) **11** (42%) **14** (35%)

12a (51%) **12b** (36%) **13a** (R^1 = OMe, R^2 = H) **13b** (R^1 = H, R^2 = OMe)

Figure 2. Variation of the arene core and substitution of the *N*-methyl group.

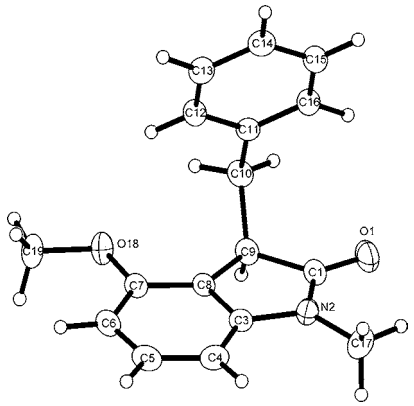


Figure 3. X-ray structure of **13a**.

(*trans*:*cis* = 4.2:1).[18] For the *N*-tosyl derivative **6e** and the secondary amide **6g** the desired oxindoles were not formed.

Because the TEMPO-phosphonates **6** are highly sterically hindered, direct HWE olefination on **6** should be very slow and two-component reactions should be feasible. Indeed, the heating of a DMF solution of **6a**, benzaldehyde, and KO*t*-Bu under microwave conditions at 180 °C for 17 min provided the desired oxindole **8a**. However, compared to the above-described protocol, a lower yield was obtained (32%). In analogy, **8b** was prepared in 30% yield.

The mechanistic picture of the nitroxide-mediated homolytic aromatic substitution is currently not clear. C-Radical addition onto the arene generates the corresponding cyclohexadienyl radical **15** (Figure 4). Trapping of **15** with TEMPO provides the dienes **16** and **17**. The formation of the tertiary diene **18** is unlikely for steric reasons. Because the C−O-alkoxyamine bond is very weak,[19] TEMPO trapping is reversible. Rearomatization can occur via H-transfer from the cyclohexadienyl radical **15** to TEMPO to eventually form the homolytic aromatic substitution product and TEMPOH.[20] Moreover, concerted ionic 1,2- (see **19**)[21] and 1,4-elimination (see **20**) of TEMPOH is also feasible. In addition, SET transfer from the cyclohexadienyl radical to TEMPO followed by deprotonation cannot be ruled out.

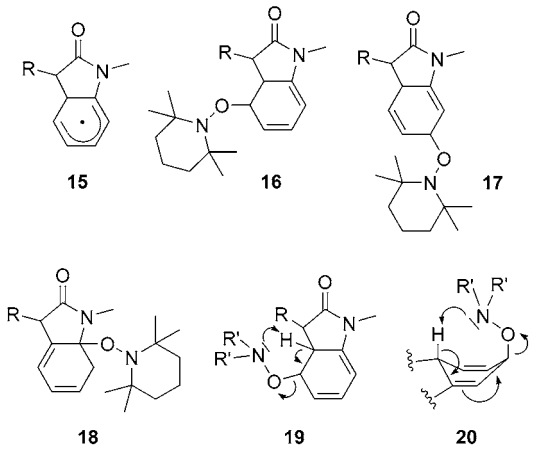


Figure 4. Intermediates of the homolytic aromatic substitution.

In conclusion, we have shown that PRE-mediated homolytic aromatic substitutions can be combined with Horner-type olefinations. These one-pot reactions can efficiently be performed under microwave conditions. Biologically interesting compounds can be prepared in a short time. It is obvious that Horner-type alkoxyamines can also be used for radical carboaminoxylation/olefination reactions. Studies are currently underway and will be reported in due course.

Acknowledgment. We thank the Deutsche Forschungsgemeinschaft (STU 280/4-1) and the Fonds der Chemischen Industrie for support. Kian Molawi, Jason Spruell and Christoph Knoop are acknowledged for proofreading. LONZA AG is acknowledged for a generous gift of solvents.

Supporting Information Available: Experimental procedures, analytical data of all new compounds, and crystallographic data in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

OL048759T

(18) In a separate experiment, the reaction was stopped after the homolytic aromatic substitution. The product was obtained in 68% yield. Compared to the *N*-methyl compound **6a** the *N*-benzyl congener affords a lower yield in the homolytic aromatic substitution. We assume that the benzylic H-atoms, which are readily abstracted by TEMPO at high temperature, may be the reason for the decreased yield.

(19) Marque, S.; Le Mercier, C.; Tordo, P.; Fischer, H. *Macromolecules* **2000**, *33*, 4403. Marque, S.; Fischer, H.; Baier, E.; Studer, A. *J. Org. Chem.* **2001**, *66*, 1146.

(20) Skene, W. G.; Connolly, T. J.; Scaiano, J. C. *Tetrahedron Lett.* **1999**, *40*, 7297. Coseri, S.; Ingold, K. U. *Org. Lett.* **2004**, *6*, 1641.

(21) Ananchenko, G. S.; Fischer, H. *J. Polym. Sci., Part A: Polym. Chem.* **2001**, *39*, 3604.