ORGANIC LETTERS

2003
Vol. 5, No. 23
4257−4259

A Mild and Efficient One-Step Synthesis of Quinolines

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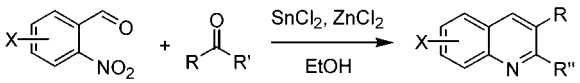
Received July 18, 2003

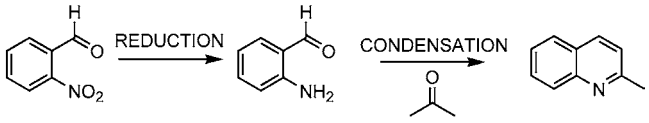
ABSTRACT



The Friedländer synthesis of quinolines is an extensively employed protocol, yielding the desired heterocycle in a two-step reduction–condensation sequence. We have developed a mild, efficient, high-yielding single-step variant of this methodology, which employs $SnCl_2$ and $ZnCl_2$ to effect the reaction.

The Friedländer synthesis of quinolines from *o*-aminobenzaldehydes is a staple reaction of organic synthesis.[1] This synthesis is usually carried out via a two-step procedure, in which reduction of an *o*-nitro aryl aldehyde (or 2-nitro vinyl aldehyde, for the analogous preparation of pyridines) is followed by condensation with an enolizable carbonyl compound in the presence of a Brønsted or Lewis acid catalyst (Scheme 1). A complicating factor in the reaction

Scheme 1



is the relative instability of the intermediate *o*-amino aldehyde, which can readily undergo self-condensation reactions. Modifications such as those developed by Borsche, in which the *o*-nitrobenzaldehyde is converted to an imine prior to reduction of the nitro group, are helpful in reducing problems due to *o*-aminobenzaldehyde instability but also increase the number of synthetic operations that must be performed.[2] Because of their importance as substructures in a broad range of natural and designed products, significant effort continues to be given over to the development of new quinoline-based structures[3] and new methods for their construction.[4]

As part of a continuing effort in our laboratory toward the development of new methods for the expeditious synthesis of biologically relevant heterocyclic compounds,[5] we became interested in the possibility of developing a one-pot analogue of the Friedländer synthesis, in which the intermediate *o*-aminobenzaldehyde was not isolated, but rather immediately converted in situ to a quinoline. We anticipated that, by analogy to our earlier work,[6] reaction of 2-nitrobenzaldehyde with catalytic amounts of $CrCl_2$ in the presence of Mn or Zn dust and TMSCl would provide for catalytic reduction of the nitroarene. If this were done in the presence of an enolizable carbonyl compound, we reasoned that formation of a Cr, Mn, or Zn enolate would

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(1) Cheng, C.-C.; Yan, S.-J. *Org. React.* **1982**, *28*, 37−200.
(2) Borsche, W.; Ried, W. *Justus Liebigs Ann. Chem.* **1943**, *554*, 269−272.
(3) Hoemann, M. Z.; Kumaravel, G.; Xie, R. L.; Rossi, R. F.; Meyer, S.; Sidhu, A.; Cuny, G. D.; Hauske, J. R. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 2675−2678.
(4) A subset of recent work in this area includes: (a) Du, W.; Curran, D. P. *Org. Lett.* **2003**, *5*, 1765−1768. (b) Lindsay, D. M.; Dohle, W.; Jensen, A. E.; Kopp, F.; Knochel, P. *Org. Lett.* **2002**, *4*, 1819−1822. (c) Matsugi, M.; Tabusa, F.; Minamikawa, J. *Tetrahedron Lett.* **2000**, *41*, 8523−8525. (d) Dormer, P. G.; Eng, K. K.; Farr, R. N.; Humphrey, G. R.; McWilliams, J. C.; Reider, P. J.; Sager, J. W.; Volante, R. P. *J. Org. Chem.* **2003**, *68*, 467−477.
(5) (a) Hari, A.; Rodrigues, W. C.; Karan, C.; Miller, B. L *J. Org. Chem.* **2001**, *66*, 991−996. (b) Hari, A.; Miller, B. L. *Org. Lett.* **2000**, *2*, 3667−3670.
(6) Hari, A.; Miller, B. L. *Org. Lett.* **2000**, *2*, 691−693.

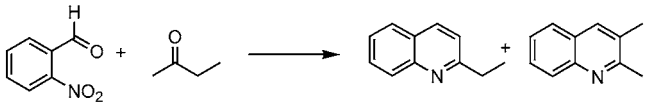
10.1021/ol035333q CCC: $25.00
Published on Web 10/21/2003

lead to concomitant condensation with the reduced arene, providing the quinoline in a single synthetic operation.

To our surprise, however, reaction of 2-nitrobenzaldehyde with $CrCl_2$, Mn(0), and TMSCl in DMF in the presence of 2-butanone produced none of the desired quinoline (Table 1, entry 1). Similarly, substitution of Zn(0) for Mn(0) (Table 1, entry 2) was unsuccessful. Numerous other metal salts have been employed in the reduction of nitroarenes;[7] $SnCl_2$ is one in particular that has found wide usage.[8] We found that while $SnCl_2$ indeed caused the disappearance of the starting nitrobenzaldehyde, none of the desired quinoline was obtained. However, reduction of nitrobenzaldehyde followed by condensation with 2-butanone in the presence of excess $ZnCl_2$ was successful, albeit low yielding (Table 1, entry 4). Incorporation of 4 Å molecular sieves into the second step provided a substantial increase in the yield. Most gratifyingly, highest yields were obtained when the reaction was carried out as a single operation (Table 1, entry 6). Reduction in the number of equivalents of $SnCl_2$ and $ZnCl_2$ to 2 each resulted in a complex mixture of unreacted starting material, *o*-nitrobenzaldehyde, and quinoline products.

We next examined the utility of this process to synthesize a range of quinolines (Table 2). Simple ketones, both *n*-alkyl

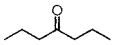
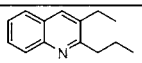
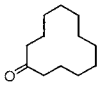
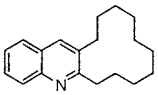
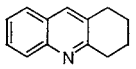
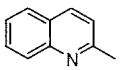
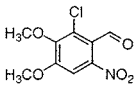
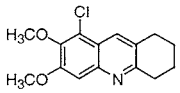
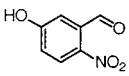
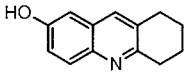
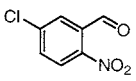
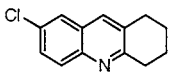
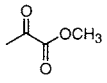
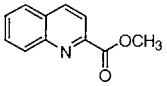
Table 1. Reagent Screening for One-Pot Quinoline Synthesis



2 **3**

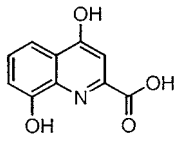
entry	conditions	yield of **2** + **3**
1	$CrCl_2$ (0.25 equiv) $Mn^{(0)}$ (16 equiv) TMSCl (16 equiv) DMF, 50 °C	0
2	$CrCl_2$ (0.25 equiv) $Zn^{(0)}$ (16 equiv) TMSCl (16 equiv) DMF, 50 °C	0
3	$SnCl_2 \cdot 2H_2O$ (10 equiv) EtOH, 70 °C	0
4	(1) $SnCl_2$ (5 equiv) EtOH, 70 °C (2) $ZnCl_2$ (5 equiv) 2-butanone (1 equiv) EtOH, 70 °C	40%
5	(1) $SnCl_2$ (5 equiv) EtOH, 70 °C (2) $ZnCl_2$ (5 equiv) 2-butanone (1 equiv) EtOH, 70 °C, 4 Å mol sieves	80%
6	$SnCl_2$ (5 equiv) $ZnCl_2$ (5 equiv) 2-butanone (1 equiv) EtOH, 70 °C, 4 Å mol sieves	90%
7	$CrCl_2$ (5 equiv) $ZnCl_2$ (5 equiv) 2-butanone (1 equiv) EtOH, 70 °C, 4 Å mol sieves	23%
8	$SnCl_2$ (5 equiv) $FeCl_2$ (5 equiv) 2-butanone (1 equiv) EtOH, 70 °C, 4 Å mol sieves	42%
9	$SnCl_2$ (5 equiv) $AlCl_3$ (5 equiv) 2-butanone (1 equiv) EtOH, 70 °C, 4 Å mol sieves	51%

Table 2. Synthesis of Quinolines via the $SnCl_2/ZnCl_2$ Procedure

entry	aryl aldehyde	ketone	**product**	yield (%)
1			 **5**	89
2			 **6**	82
3			 **7**	94
4			 **8**	90
5			 **9**	98
6			 **10**	80
7			 **11**	90
8			 **12**	70

(7) Wei, G. P.; Phillips, G. B. *Tetrahedron Lett.* **1998**, *39*, 179−182.
(8) Bellamy, F. D.; Ou, K. *Tetrahedron Lett.* **1984**, *25*, 839−842.

and cyclic, give uniformly high yields. Since the number of commercially available *o*-nitrobenzaldehydes is exceedingly small, we have only begun to examine the substrate scope of the reaction with regard to this moiety. However, as may be seen in entries 5−7, the reaction readily tolerates both methoxy and chloro substitutions, as well as hydroxy and chloro monosubstitution. Likewise, methyl pyruvate works well (entry 8), potentially providing a simple entry into compounds related to xanthurenic acid (**4**), a critical regulator of malaria development.[9]



4

To verify that the ketone partner was not at fault in our inability to prepare quinolines using a Cr(II)-based process, we treated a mixture of *o*-nitrobenzaldehyde and cyclohexanone as described above, replacing the 5 equiv of $SnCl_2$ + $ZnCl_2$ with 5 equiv of $CrCl_2$ + $ZnCl_2$. This provided **7** in a modest 23% yield, with unreacted *o*-nitrobenzaldehyde and *o*-aminobenzaldehyde constituting the bulk of the remaining material. This difference in reactivity is striking, and is likely a result of differences in the Lewis acidity of Cr(II) and Sn(II).

(9) Billker, O.; Lindo, V.; Panico, M.; Etienne, A. E.; Paxton, T.; Dell, A.; Rogers, M.; Sinden, R. E.; Morris, H. R. *Nature* **1998**, *392*, 289−292.

In conclusion, we have developed a rapid, high-yielding procedure for the conversion of *o*-nitrobenzaldehydes to quinolines.[10] This method provides a significant improvement over the venerable Friedländer synthesis, by obviating the need to prepare and isolate *o*-aminobenzaldehydes. We anticipate that this methodology will be readily applicable to solid-phase and combinatorial library synthesis; efforts along those lines are currently in progress.

Acknowledgment. The authors thank the sponsors of the Center for Future Health, University of Rochester, for generous financial support, and thank Prof. Steven Ley, Cambridge University, for helpful discussions.

Supporting Information Available: Spectral data for compound **9**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) **Representative experimental procedure:** The procedure for the reaction of cyclohexanone with *o*-nitrobenzaldehyde (entry 3) is illustrative. A 150-mL round-bottom flask equipped with a stir bar and reflux condenser was flame dried under an atmosphere of N_2. *o*-Nitrobenzaldehyde (0.5 g, 3.3 mmol) and cyclohexanone (0.325 g, 3.3 mmol) were added, followed by 20 mL of anhydrous ethanol. $SnCl_2$ (3.138 g, 16.55 mmol, 5 equiv), $ZnCl_2$ (2.257 g, 16.55 mmol, 5 equiv), and approximately 0.5 g of 4 Å molecular sieves were added to the solution. This mixture was then heated at 70 °C under an atmosphere of nitrogen for 3 h. The reaction was then cooled to room temperature and rendered basic (pH 8) with 50 mL of 10% sodium bicarbonate (aq). The mixture was transferred to a separatory funnel, and was extracted with 3 × 20 mL of ethyl acetate. Organics were combined and washed thoroughly with saturated NaCl (aq), dried over Na_2SO_4, and filtered through Celite. Following reduction of the solvent in vacuo, the material remaining was subjected to chromatography on silica (20% ethyl acetate in hexane). The desired quinoline (**7**) was obtained in 94% yield as an orange oil.