Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron Letters 49 (2008) 2225–2227
Tetrahedron Letters

A remarkably simple N-formylation of anilines using polyethylene glycol ☆

Biswanath Das *, Maddeboina Krishnaiah, P. Balasubramanyam, Boyapati Veeranjaneyulu, D. Nandan Kumar

Organic Chemistry Division-I, Indian Institute of Chemical Technology, Hyderabad 500 007, India

Received 10 December 2007; revised 31 January 2008; accepted 10 February 2008
Available online 13 February 2008

Abstract

N-Formylation of anilines has efficiently been carried out at room temperature in excellent yields by treatment with formic acid in polyethylene glycol (PEG-400). No additional solvent and catalyst are required.

Keywords: N-Formylation; Anilines; Formic acid; PEG-400; Catalyst- and solvent-free reaction

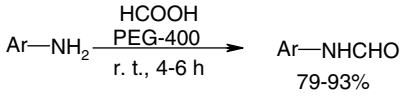
1. Introduction

Formylation of amines is a useful reaction in synthetic organic chemistry. Formamides are valuable intermediates in the construction of various pharmaceutically important compounds.[1,2] They are also useful reagents in Vilsmeier formylation reactions.[3] Moreover, they are Lewis bases and can catalyze several organic transformations.[4] The formyl group is also an important aminoprotecting group in peptide synthesis.[5]

Various methods are available for N-formylation of amines.[6–15] However, many of these methods suffer from different drawbacks such as the application of expensive and toxic formylating agents and catalysts, long reaction times, high temperatures and the formation of by-products.

2. Results and Discussion

In continuation of our work[16,17] on the application of polyethylene glycol (PEG) to carry out organic synthesis, we have observed that the N-formylation of aniline can efficiently be accomplished in this reaction medium by treatment with formic acid at room temperature (Scheme 1).



Scheme 1.

A series of anilines were converted into the corresponding *N*-formyl amines in high yields following the above procedure (Table 1). No additional solvent or catalyst was used. Different functionalities such as alkyl, nitro, halogens and carbonyl remained intact. Anilines containing both electron-donating and electron-withdrawing groups underwent the conversion smoothly. Previously, the N-formylation of anilines having electron-withdrawing groups was found to be difficult.[18] The present conversion is also chemoselective. O-Formylation of phenols did not take place. Thus, the aminophenols (entries o and p) furnished only the N-formylation products under the present reaction conditions. However, benzylamine afforded the N-formylation product in poor yield while the open-chain aliphatic amines did not undergo any conversion.

Polyethylene glycol (PEG-400)[19–21] is a biologically acceptable inexpensive polymer and is eco-friendly. Its

☆ Part 165 in the series, 'Studies on novel synthetic methodologies'.
* Corresponding author. Tel./fax: +91 40 27160512.
E-mail address: biswanathdas@yahoo.com (B. Das).

0040-4039/$ - see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2008.02.050

Table 1
N-Formylation of anilines using PEG-400[a]

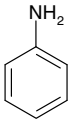
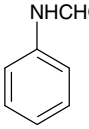
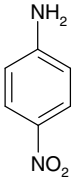
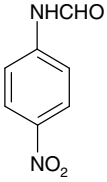
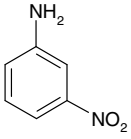
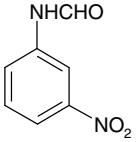
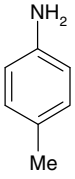
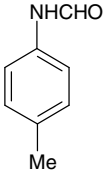
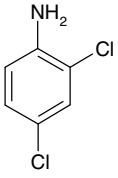
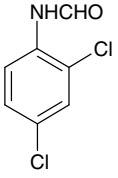
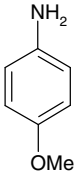
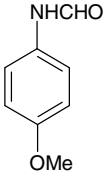
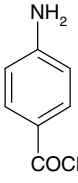
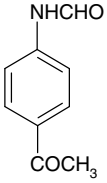
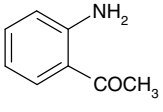
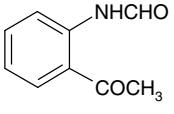
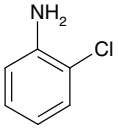
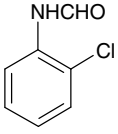
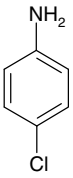
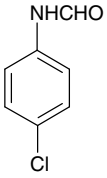
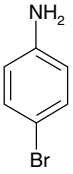
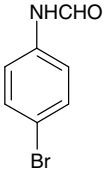
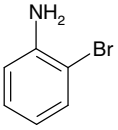
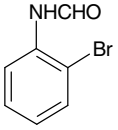
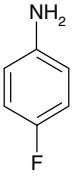
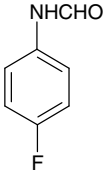
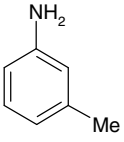
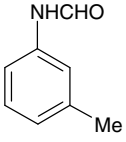
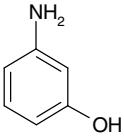
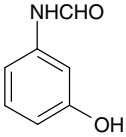
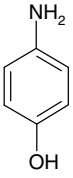
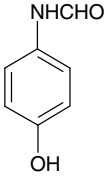
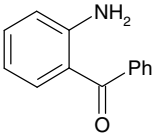
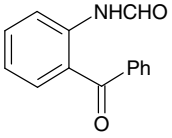
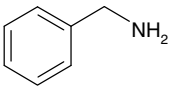
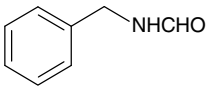
Entry	Aniline	Product	Isolated yield (%)	Ref.[b]
a			91	14
b			86	14
c			85	14
d			90	15
e			89	—
f			92	13
g			85	14
h			83	—
i			79	14

Table 1 (*continued*)

Entry	Aniline	Product	Isolated yield (%)	Ref.[b]
j			86	15
k			91	14
l			83	14
m			81	14
n			93	14
o			89	14
p			90	14
q			82	—
r			42	14

[a] The structures of the products were established from their spectral (IR, ^{1}H NMR and MS) and analytical data.
[b] The compound reported in the literature.

applications in organic synthesis have not yet been fully explored. In the present conversion, it has efficiently been utilized for the preparation of *N*-formyl anilines. The experimental procedure is highly convenient. The structures of the products were established from their spectral (^{1}H NMR and MS) and analytical data.

3. General experimental procedure

To a mixture of aniline (1 mmol) and HCOOH (3 mmol), PEG-400 (2 g) was added. The mixture was stirred at room temperature and the progress of the reaction was monitored by TLC. After completion, the mixture was diluted with water (10 mL) and extracted with EtOAc (3×10 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated. The residue was subjected to column chromatography to obtain the pure *N*-formyl aniline.

The spectral (IR, ^{1}H NMR and MS) and analytical data of novel compounds **e**, **h** and **q** are given below. In the ^{1}H NMR spectra of all these compounds, the formyl proton appeared as *cis* to the proton of the –NH-group.

3.1. N-(2,4-Dichlorophenyl) formamide (entry *e*)

White solid. mp 57–58 °C. IR (KBr): 3242, 2903, 1665, 1527, 1395, 1293 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz): 9.52 (br s, 1H), 8.38 (br s, 1H), 8.28 (d, $J = 8.0$ Hz, 1H), 7.39 (d, $J = 2.0$ Hz, 1H), 7.22 (dd, $J = 8.0$, 2.0 Hz, 1H); EI-MS: $m/z = 189$, 191, 193; Anal. Calcd for $C_7H_5NOCl_2$: C, 44.24; H, 2.62; N, 7.33. Found: C, 43.89; H, 2.56; N, 7.39.

3.2. N-(2-Acetylphenyl) formamide (entry *h*)

White solid; mp 79–80 °C. IR (KBr): 3254, 2925, 1695, 1527, 1395, 1293 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz): 11.62 (br s, 1H), 8.79 (d, $J = 8.0$ Hz, 1H), 8.52 (br s, 1H), 7.90 (d, $J = 8.0$ Hz, 1H), 7.49 (t, $J = 8.0$ Hz, 1H), 7.08 (t, $J = 8.0$ Hz, 1H), 2.60 (s, 3H); EI-MS: $m/z = 163$; Anal. Calcd for $C_9H_9NO_2$: C, 66.25; H, 5.52; N, 8.58. Found: C, 66.30; H, 5.48; N, 8.52.

3.3. N-(2-Benzoylphenyl) formamide (entry *q*)

Light yellow viscous oil. IR (KBr): 3319, 2924, 1699, 1638, 1514, 1262 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz): 10.79 (br s, 1H), 8.77 (d, $J = 8.0$ Hz, 1H), 8.54 (br s, 1H), 7.80–7.44 (m, 7H), 7.08 (t, $J = 7.0$ Hz, 1H); EI-MS: $m/z = 225$; Anal. Calcd for $C_{14}H_{11}NO_2$: C, 74.66; H, 4.88; N, 6.22. Found: C, 74.72; H, 4.91; N, 6.26.

Acknowledgements

The authors thank CSIR and UGC, New Delhi, for financial assistance.

References and notes

1. Kobayashi, K.; Nagato, S.; Kawakita, M.; Morikawa, O.; Konishi, H. *Chem. Lett.* **1995**, 575.
2. Chen, B. C.; Bednarz, M. S.; Zhao, R.; Sundeen, J. E.; Chen, P.; Shen, Z.; Skoumbourdis, A. P.; Barrish, J. C. *Tetrahedron Lett.* **2000**, *41*, 5453.
3. Downie, I. M.; Earle, M. J.; Heaney, H.; Shuhaibar, K. F. *Tetrahedron* **1993**, *49*, 4015.
4. (a) Kobayashi, S.; Nishio, K. *J. Org. Chem.* **1994**, *56*, 6620; (b) Kobayashi, S.; Yasuda, M.; Hachiya, I. *Chem. Lett.* **1996**, 407.
5. Martrniez, J.; Laur, J. *Synthesis* **1982**, 979.
6. Strazzolini, P.; Giumanimi, A. G.; Cauci, S. *Tetrahedron* **1990**, *46*, 1081.
7. Neveux, M.; Bruneaum, C.; Dixneuf, P. H. *J. Chem. Soc., Perkin Trans. 1* **1991**, 1197.
8. Duczek, W.; Deutsch, J.; Vieth, S.; Niclas, H.-J. *Synthesis* **1996**, 37.
9. Green, T. W.; Wuts, P. G. M. *Protecting Groups in Organic synthesis*, 3rd ed.; Wiley-Interscience: New York, 1999.
10. Reddy, P. G.; Kumar, G. D. K.; Baskaran, S. *Tetrahedron Lett.* **2000**, *41*, 9149.
11. Mihara, M.; Ishino, Y.; Minakara, S.; Komatsu, M. *Synthesis* **2003**, 2317.
12. Luca, L. D.; Giacomelli, G.; Porcheddu, A.; Salaris, M. *Synlett* **2004**, 2570.
13. Desai, B.; Danks, T. N.; Wagner, G. *Tetrahedron Lett.* **2005**, *46*, 955.
14. Hosseini-Sarvari, M.; Sharghi, H. *J. Org. Chem.* **2006**, *71*, 6652.
15. Pratap, T. V.; Baskaran, S. *Tetrahedron Lett.* **2001**, *42*, 1983.
16. Das, B.; Reddy, V. S.; Krishnaiah, M. *Tetrahedron Lett.* **2006**, *47*, 8471.
17. Das, B.; Reddy, V. S.; Tehseen, F.; Krishnaiah, M. *Synthesis* **2007**, 666.
18. Jung, S. H.; Ahn, J. H.; Park, S. K.; Choi, J.-K. *Bull. Korean Chem. Soc.* **2002**, *23*, 149.
19. Dickerson, T. J.; Reed, N. N.; Janda, K. D. *Chem. Rev.* **2002**, *102*, 3325.
20. Chandrasekhar, S.; Narasihmulu, Ch.; Sultana, S. S.; Reddy, N. R. *Chem. Commun.* **2003**, *9*, 1716.
21. Kamal, A.; Reddy, D. R.; Rajendar. *Tetrahedron Lett.* **2006**, *47*, 2261.