

Preparation of primary arylamines via arylzinc chlorides in good yields

Tahir Daşkapan*

Ankara University, Science Faculty, Department of Chemistry, 06100 Beşevler, Ankara, Turkey

Received 28 November 2005; revised 16 February 2006; accepted 23 February 2006

Available online 13 March 2006

Abstract—Primary arylamines can be prepared easily by electrophilic amination of arylzinc chlorides with acetone *O*-(2,4,6-trimethylphenylsulfonyl)oxime in the presence of DMPU as additive and CuCN as catalyst in good yields.

© 2006 Elsevier Ltd. All rights reserved.

The amino group is a common building block in synthetic organic, medicinal and agricultural chemistry. Biologically active molecules, which have been targeted by pharmaceutical and agricultural companies, include different types of amines. Among these, arylamines are especially important since they are a fundamental structural motif in Nature. So, development of an efficient method for the preparation of such compounds is important and continues to be an active area of research.^{1–3}

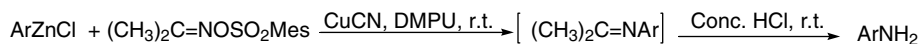
Arylamines are usually prepared using nucleophilic amination methods. The scope of these methods is limited due to difficulties in synthesizing functionalized electrophilic precursors and also requires harsh reaction conditions. On the other hand, amongst modern methods,^{4–8} electrophilic amination of an easily available and functional group tolerant organometallic reagent appeared to be a viable alternative method.^{9–13} For this reason, we planned to develop a practical electrophilic amination procedure employing organozinc reagents for the preparation of functionalized primary arylamines.

To date, there have been limited publications on electrophilic amination of organozinc reagents.^{14–21} In 1998,

Rieke's group²² described a process for electrophilic amination of organozinc halides with di-*tert*-butyl azodicarboxylate (DBAD) to synthesize primary amines in three steps. Recently, Erdik and Koçoğlu²³ reported a procedure for preparation of primary arylamines in moderate yields by electrophilic amination of organozinc reagents with benzenediazonium tetrafluoroborate. Berman and Johnson have described^{24,25} the preparation of tertiary arylamines via the copper-catalyzed electrophilic amination of diorganozinc reagents.

Previously, we reported a new amination protocol for organozinc reagents using acetone *O*-(2,4,6-trimethylphenylsulfonyl)oxime **1**, which produced primary amines in moderate yields.²⁶ In the amination of phenylzinc chloride the highest yield (40%) of aniline was obtained when the molar ratio of phenylzinc chloride/**1** was 2:1 and in the presence of 20 mol % CuCN, at room temperature in 3 h.

Herein the preparation of arylamines is described in good yields by copper-catalyzed electrophilic amination of arylzinc chlorides in the presence of 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (DMPU) (Scheme 1). DMPU is a Lewis base and coordinating solvent, which



1

Ar : Phenyl, 4-tolyl, 4-anisyl, 3-bromophenyl, 1-naphthyl.

Scheme 1. Amination of arylzinc chlorides with acetone *O*-(2,4,6-trimethylphenylsulfonyl)oxime.

Keywords: Electrophilic amination; Organozinc reagents; Oxime; Arylamines.

* Tel.: +90 312 2126720/1514; fax: +90 312 2232395; e-mail: daskapan@science.ankara.edu.tr

has been used as a co-solvent to promote the reactions of organozinc reagents. In this connection, we decided to investigate the effect of DMPU in the electrophilic amination of arylzinc chlorides with **1**.

In the first part of this work, we aimed to determine the optimal reaction conditions using the amination reaction of phenylzinc chloride with **1** as a model reaction. Phenylzinc chloride was prepared by transmetallation of phenylmagnesium bromide with ZnCl₂ in THF. The final product, aniline, was removed from the reaction mixture as its benzanilide derivative. The results are given in Table 1.

As show in Table 1, this yield of aniline after one hour using 3.35 equiv of DMPU (entry 1) was 40% and when the reaction time was extended to 3 h the yield increased to 65% (entry 3). The highest yield of aniline (78%) was obtained at room temperature in 3 h when 10 mol % CuCN and 2 equiv of DMPU were used (Table 1, entry 7). It was observed that, when less than 2 equiv of PhZnCl or DMPU was used, or when the amount of CuCN was below 10 mol %, the yield decreased.

In the second part of this study, to broaden the scope of this procedure, we investigated the amination of naphthylzinc chloride and some functionalized arylzinc chlorides with **1** under the optimal reaction conditions²⁸ (Table 2). As seen, functionalized arylamines were prepared in good yields in the presence of 2 equiv of DMPU. Previously,²⁶ *p*-toluidine and *p*-anisidine were obtained in 49% and 54% yields, respectively, without the use of DMPU. Using the improved method the yields of these amines were 72% and 75%, respectively (entries 2 and 3).

Table 1. Amination of phenylzinc chloride with **1** in the presence of DMPU

PhZnCl ^a + 1 $\xrightarrow[2. \text{ Conc. HCl, r.t.}]{1. \text{ THF, CuCN, DMPU, r.t., 1-3 h}}$ ArNH ₂				
Entry	1 (equiv)	CuCN (%)	DMPU:PhZnCl	Yield of ArNH ₂ ^b (%)
1 ^c	2	20	3.35	40
2 ^d	2	20	3.35	43
3	2	20	3.35	65
4	2	10	3.35	58
5	2	5	3.35	40
6	2	20	2	42
7	2	10	2	78
8	2	5	2	67
9	2	5	1	57
10	2	10	1.7	60
11	1	10	2	30
12	1.25	10	2	35
13	1.5	10	2	65

^a Phenylzinc chloride was prepared by Mg-to-Zn transmetallation.

^b Aniline was isolated as its benzanilide and this known compound was identified from its melting point²⁷ and FT-IR analysis.

^c Reaction time was 1 h.

^d Reaction time was 2 h.

Table 2. Scope of the copper-catalyzed amination reaction of arylzinc chlorides with **1** in the presence of DMPU

ArZnCl ^a + 1 $\xrightarrow[2. \text{ Conc. HCl, r.t.}]{1. \text{ THF, 10 mol\% CuCN, 2 equiv. DMPU, r.t., 3 h}}$ ArNH ₂		
Entry	Ar	Yield of ArNH ₂ ^b (%)
1	C ₆ H ₅	78
2	4-CH ₃ C ₆ H ₄	72
3	4-CH ₃ OC ₆ H ₄	75
4	3-BrC ₆ H ₄	70
5	1-C ₁₀ H ₇	79

^a Organozinc reagents were prepared by transmetallation of the corresponding arylmagnesium bromides with ZnCl₂ in THF.

^b Yield of amines isolated as the *N*-benzoyl derivatives and these known compounds were identified from their melting point²⁷ and FT-IR analysis.

In conclusion, we have described an easy and good yielding preparation for primary arylamines by electrophilic amination of arylzinc chlorides with acetone *O*-(2,4,6-trimethylphenylsulfonyl)oxime in the presence of DMPU. Our investigations are continuing on this subject and the results will be published when our studies are complete.

Acknowledgement

I thank the Ankara University Research Fund for financial support.

References and notes

- Ley, S. V.; Thomas, A. W. *Angew. Chem., Int. Ed.* **2003**, *42*, 5400–5449.
- Mitsunobu, O. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Winterfeldt, E., Eds.; Pergamon: Oxford, 1991; Vol. 6, p 65.
- Hottori, T.; Sakamoto, J.; Hayashizaka, N.; Miyano, S. *Synthesis* **1994**, 199–202.
- Bishop, R. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon: Oxford, 1991; Vol. 6, p 261.
- Du Bois, J.; Tomook, C. S.; Hong, J.; Carreira, E. M. *Acc. Chem. Res.* **1997**, *30*, 364–372.
- Bruncko, M.; Schlingoff, G.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **1997**, *36*, 1483–1486.
- Antilla, J. C.; Baskin, J. M.; Barder, T. E.; Buchwald, S. L. *J. Org. Chem.* **2004**, *69*, 5578–5587.
- Hartwig, J. F. In *Handbook of Organopalladium Chemistry For Organic Synthesis*; Negishi, E.-I., Ed.; Wiley: New York, 2002; Vol. 1, p 1051.
- Erdik, E.; Ay, M. *Chem. Rev.* **1989**, *89*, 1947–1980.
- Mulzer, J.; Altenbach, H. J.; Brown, M.; Krohn, K.; Reissi, H. U. *Organic Synthesis Highlights*; VCH: Weinheim, 1991, p 45.
- Boche, G. In *Houben-Weyl, Methods of Organic Chemistry*; Heimchen, G., Hoffman, R. W., Mulzer, J., Schumann, E., Eds.; Thieme: Stuttgart, 1995; Vol. E21e, p 5153.
- Ricci, A. *Modern Amination Methods*; Wiley-VCH: Weinheim, 2000.
- Dembeck, P.; Seconi, G.; Ricci, A. *Chem. Eur. J.* **2000**, *6*, 1281–1286.

14. Coleman, G. H.; Andersen, H. P.; Hermanson, J. L. *J. Am. Chem. Soc.* **1934**, *56*, 1381–1382.
15. Coleman, G. H.; Hermanson, J. L.; Johnson, H. L. *J. Am. Chem. Soc.* **1937**, *59*, 1896–1897.
16. Curtin, D. Y.; Ursprung, J. A. *J. Org. Chem.* **1956**, *21*, 1221–1225.
17. Hagopian, R.; Therien, M. J.; Murdoch, J. R. *J. Am. Chem. Soc.* **1984**, *106*, 5753–5754.
18. Cane, F.; Brancaleoni, D.; Dembech, P.; Ricci, A.; Seconi, G. *Synthesis* **1997**, 545–548.
19. Zheng, N.; Armstrong, J. D.; McWilliamson, J. C., III; Volante, R. P. *Tetrahedron Lett.* **1997**, *38*, 2817–2820.
20. Beak, P.; Selling, G. W. *J. Org. Chem.* **1989**, *54*, 5574–5580.
21. Mitchel, H.; Leblanc, J. *J. Org. Chem.* **1994**, *59*, 682–687.
22. Vlarde-Ortiz, R.; Guijarro, A.; Rieke, R. D. *Tetrahedron Lett.* **1998**, *39*, 9157–9160.
23. Erdik, E.; Koçoğlu, M. *Main Group Met. Chem.* **2002**, *25*, 621–627.
24. Berman, A. M.; Johnson, J. S. *J. Am. Chem. Soc.* **2004**, *126*, 5680–5681.
25. Berman, A. M.; Johnson, J. S. *J. Org. Chem.* **2005**, *70*, 364–366.
26. Erdik, E.; Daşkapan, T. *J. Chem. Soc., Perkin Trans. 1* **1999**, 3139–3142.
27. *Handbook of Tables for Organic Compound Identification*; Zvi Rappoport, Ed.; CRC Press: Florida, 1980.
28. *General procedure for the preparation of arylamines*: A solution of ZnCl₂ (0.546 g, 4 mmol) in anhydrous THF (4 ml) was cooled to –3 °C under argon and 4 mmol of arylmagnesium bromide in THF was added dropwise via syringe. The reaction mixture was stirred for an additional 5 min, the cooling bath was removed and the resulting white suspension was allowed to warm to room temperature. To this mixture, CuCN (0.0358 g, 0.4 mmol), DMPU (0.0966 ml, 8 mmol) and a solution of **1** (0.51 g, 2 mmol) in dry THF (3 ml) were added. The reaction mixture was stirred at room temperature for 3 h and then worked up by addition of concd HCl with stirring at room temperature for 4 h. The aqueous phase was washed with diethyl ether, made basic with concd NaOH and the free amine was extracted with diethyl ether (3 × 50 ml). The organic layer was dried over Na₂SO₄, the solvent was evaporated and the crude product was converted to its *N*-benzoyl derivative by reaction with benzoyl chloride in the presence of NaOH. The product was recrystallized from ethanol–water (4:1).