ORGANIC LETTERS

2010
Vol. 12, No. 16
3648−3650

Preparation of Primary Amides from Functionalized Organozinc Halides

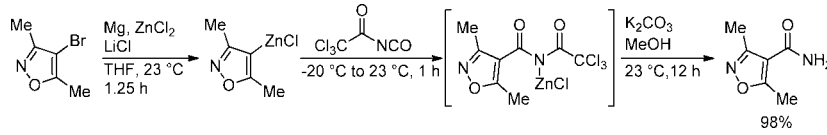
Matthias A. Schade, Georg Manolikakes, and Paul Knochel*

Department Chemie, Ludwig-Maximilians-Universität, Butenandtstrasse 5-13, 81377 München, Germany

Paul.Knochel@cup.uni-muenchen.de

Received June 25, 2010

ABSTRACT



Organozinc halides, which are prepared either by direct zinc insertion or halogen−magnesium exchange and subsequent transmetalation with $ZnCl_2$, react smoothly with commercially available trichloroacetyl isocyanate to give, after hydrolysis, the corresponding primary amides. This method is compatible with a variety of functional groups such as an ester or a cyano group. Also heterocyclic-, alkenyl, and acetylenic zinc reagents are converted to the corresponding primary amides under these conditions.

A primary amide funtionality ($CONH_2$) is found in a variety of natural products and pharmaceutically active substances.[1] The preparation of functionalized amides from readily available precursors is therefore of great interest. Among others, the reaction of carboxylic acid derivatives with ammonia and the hydration of nitriles are common methods for preparing primary amides.[2,3] Alternatively, organometallic routes starting from organomagnesium reagents require very low reaction temperatures, and sensitive functional groups or heterocycles are rarely tolerated.[4] In contrast, the use of organozinc reagents is compatible with a broad range of functional groups and sensitive heterocycles in the starting zinc organometallic.[5]

Recently, we have reported several methods for the preparation of highly functionalized organozinc reagents from the corresponding organic halides.[6] Herein, we wish to report that various organozinc halides of type **1** are converted into the primary amides (**2**) using commercially available trichloroacetyl isocyanate (Scheme 1).[7,8]

Thus, 4-cyanophenylzinc iodide (**1a**) prepared by the direct insertion of zinc into 4-iodobenzonitrile reacts with trichlo-

(1) For example: (a) *The Chemistry of Amides*; Zabicky, J., Ed.; Wiley-Interscience: New York, 1970. (b) Zhuo, L.; Liu, Y.; Zhang, W.; Wie, P.; Huang, C.; Pei, J.; Yuan, Y.; Lai, L. *J. Med. Chem.* **2006**, *49*, 3440. (c) Bhattcharaya, A.; Scott, B. P.; Nasser, N.; Ao, H.; Mahre, M. P.; Dubin, A. E.; Swanson, D. M.; Shankley, N. P.; Wickenden, A. D.; Chaplan, S. R. *J. Pharmcol. Exp. Ther.* **2007**, *323*, 665. (d) Pringle, W.; Peterson, J. M.; Xie, L.; Ge, P.; Gao, Y.; Ochterski, J. W.; Lan, J. WO 2006/089076 A2, Aug 24, 2006.

(2) (a) For the use of Mg_3N_2 as NH_3 source see: (a) Veitch, G. E.; Bridegwood, K. L.; Ley, S. V. *Org. Lett.* **2008**, *10*, 3623. For a Ru-catalyzed hydration of nitriles, see: (b) Cadierno, V.; Francos, J.; Gimeno, J. *Chem.—Eur. J.* **2008**, *14*, 6601. (c) Kukushkin, V. Y.; Pombeiro, A. J. L. *Inorg. Chim. Acta* **2005**, *1*, 1. For a $Bi(OTf)_3$-catalyzed Ritter reaction see :(d) Callens, E.; Burton, A. J.; Barrett, A. G. M. *Tetrahedron Lett.* **2006**, *47*, 8699. For a Pd-catalyzed aminocarbonylation of aryl halides see: (e) Schnyder, A.; Beller, M.; Mehltretter, G.; Nsenda, T.; Studer, M.; Indolese, A. F. *J. Org. Chem.* **2001**, *66*, 4311.

(3) (a) For related cyanations see: (a) Anbarasan, P.; Neumann, H.; Beller, M. *Chem.—Eur. J.* **2010**, *16*, 4725. For a Grignard addition-acylation route to enamides see: (b) Fleming, F. F.; Wei, G.; Zhang, Z.; Steward, O. W. *Org. Lett.* **2006**, *8*, 4903. For carbonylations of zinc reagents with CO_2, see: (c) Kobayashi, K.; Kondo, Y. *Org. Lett.* **2009**, *11*, 2035. (d) Metzger, A.; Bernhardt, S.; Manolikakes, G.; Knochel, P. *Angew. Chem., Int. Ed.* **2010**, *49*, 4665.

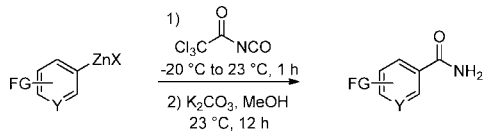
(4) Parker, K. A.; Gibbons, E. G. *Tetrahedron Lett.* **1975**, *12*, 981.

(5) (a) Zhu, L.; Wehmeyer, R. M.; Rieke, R. D. *J. Org. Chem.* **1991**, *56*, 1445. (b) Jackson, R. F. W.; Wishart, N.; Wood, A.; James, K.; Wythes, M. J. *J. Org. Chem.* **1992**, *57*, 3397. (c) Manolikakes, G.; Schade, M. A.; Hernandez, C. M.; Mayr, H.; Knochel, P. *Org. Lett.* **2008**, *10*, 2765. (d) Dong, Z.; Manolikakes, G.; Li., J.; Knochel, P. *Synthesis* **2009**, *4*, 681. (e) Crestey, F.; Knochel, P. *Synthesis* **2010**, 1097. (f) Mosrin, M.; Petrera, M.; Knochel, P. *Synthesis* **2008**, 3697. (g) Monzon, G.; Knochel, P. *Synlett* **2010**, 304.

(6) (a) Krasovskiy, A.; Malakhov, V.; Gavryushin, A.; Knochel, P. *Angew. Chem., Int. Ed.* **2006**, *45*, 6040. (b) Krasovskiy, A.; Knochel, P. *Angew. Chem., Int. Ed.* **2004**, *43*, 3333. (c) Piller, F. M.; Appukkuttan, P.; Gavryushin, A.; Helm, M.; Knochel, P. *Angew. Chem., Int. Ed.* **2008**, *47*, 6802. (d) Piller, F. M.; Metzger, A.; Schade, M. A.; Haag, B. A.; Gavryushin, A.; Knochel, P. *Chem.—Eur. J.* **2009**, *15*, 7192. (e) Metzger, A.; Argyo, C.; Knochel, P. *Synthesis* **2010**, 882. (f) Despotopoulou, C.; Gignoux, C.; McConnell, D.; Knochel, P. *Synthesis* **2009**, 3661.

10.1021/ol101469f
Published on Web 07/22/2010

Scheme 1. Reaction of Unsaturated Zinc Reagents with Trichloroacetyl Isocyanate Leading to Unsaturated Amides

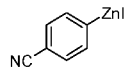
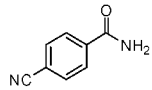
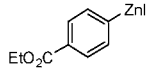
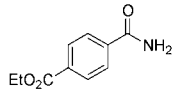
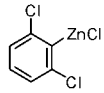
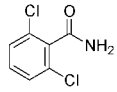
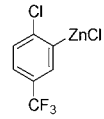
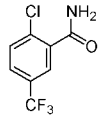
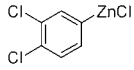
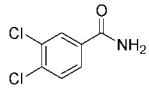
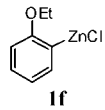
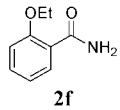
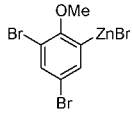
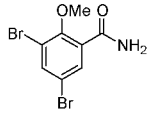
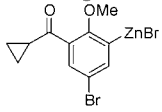
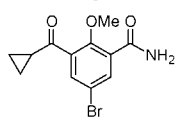


1a-w **2a-w**: 56 - 99%

FG = CO_2Et, COR, CN, OR, Br, Cl, F
X = Br, Cl;
Y = CH, N, O, S

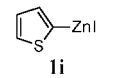
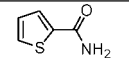
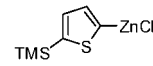
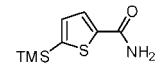
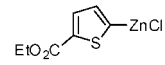
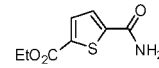
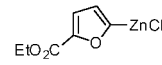
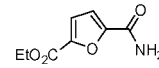
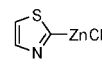
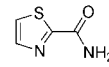
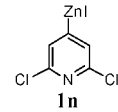
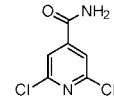
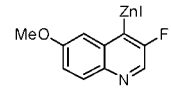
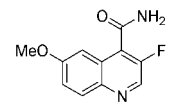
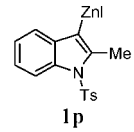
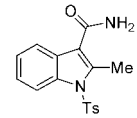
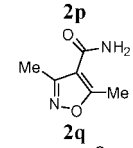
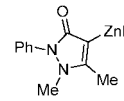
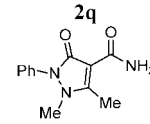
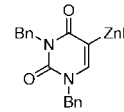
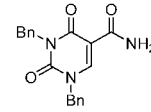
roacetyl isocyanate (1.1 equiv) at −20 to 25 °C to the corresponding zinc imidate. After basic hydrolysis using K_2CO_3 (1.5 equiv) and MeOH, 4-cyanobenzamide (**2a**) was isolated in 95% yield (Table 1, entry 1).

Table 1. Reaction of Organozinc Halides with Trichloroacetyl Isocyanate Leading to Aromatic Amides of Type **2**

entry	zinc reagent[a]	primary amide[b]	yield[c]
1	 **1a**	 **2a**	95%
2	 **1b**	 **2b**	90%
3	 **1c**	 **2c**	60%
4	 **1d**	 **2d**	98%
5	 **1e**	 **2e**	71%
6	 **1f**	 **2f**	98%
7	 **1g**	 **2g**	78%
8	 **1h**	 **2h**	66%

[a] For the sake of clarity, additional complexed salts are omitted. [b] All reactions were hydrolyzed at 23 °C 12 h. [c] Isolated yield of analytically pure product.

Table 2. Reaction of Heterocyclic Zinc Halides with Trichloroacetyl Isocyanate Providing Heterocylcic Amides of Type **2**

entry	zinc reagent[a]	primary amide[b]	yield[c]
1	 **1i**	 **2i**	99%
2	 **1j**	 **2j**	99%
3	 **1k**	 **2k**	61%
4	 **1l**	 **2l**	78%
5	 **1m**	 **2m**	82%
6	 **1n**	 **2n**	63%
7	 **1o**	 **2o**	69%
8	 **1p**	 **2p**	73%
9	 **1q**	 **2q**	98%
10	 **1r**	 **2r**	70%
11	 **1s**	 **2s**	78%

[a] For the sake of clarity, additional complexed salts are omitted. [b] All reactions were hydrolyzed at 23 °C 12 h. [c] Isolated yield of analytically pure product.

Using this method, other substituted benzamides have been prepared. Thus, 4-(ethoxycarbonyl)phenylzinc iodide (**1b**) reacts smoothly with trichloroacetyl isocyanate to produce the expected primary amide **2b** in 90% yield (entry 2). Furthermore, chloro- or trifluoromethyl-substituted arylzinc reagents react with trichloroacetyl isocyanate furnishing the expected primary amides in 60−98% yield (entries 3−5). Starting from 2-ethoxyphenylzinc chloride (**1f**), ethenzamide[9] (**2f**), an analgesic and anti-inflammatory drug, is obtained in almost quantitative yield (98%, entry 6).

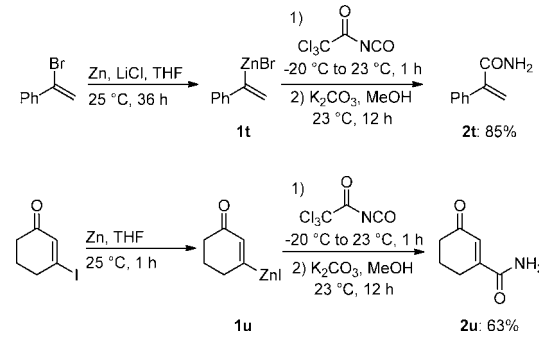
The directed zinc insertion in polybrominated protected phenols[10,6d] gives regioselectively the arylzinc reagents **1g** and **1h** which then react with trichloroacetyl isocyanate affording the corresponding benzamides **2g** and **2h** in 66−78% yield (entries 7 and 8).

Furthermore, heterocyclic zinc reagents, such as the thiophenylzinc derivatives **1i**−**1k** provide the expected primary amides **2i**−**2k** in 61−99% yield (Table 2, entries 1−3). Moreover, ethyl 5-carbamoylfuran-2-carboxylate (**2l**) and thiazole-2-carboxamide (**2m**) have been prepared by this way in 78−82% yield (entries 4 and 5). Also electron-deficient 6-membered ring N-heterocyclic zinc reagents have been reacted with trichloroacetyl isocyanate leading to the corresponding primary amides. 2,6-Dichloro-4-pyridylzinc iodide (**1n**) is converted to the isonicotinamide **2n** in 63% yield (entry 6). Also, the substituted quinoloylzinc iodide **1o** and the protected indole **1p** have been smoothly converted to the benzamides **2o** and **2p** in 69−73% yield (entries 7 and 8). Also, 3,5-dimethylisoxazolylzinc chloride **1q** provides the amide **2q** in almost quantitative yied (98%, entry 9). Moreover, sensitive 5-membered heterocyclic zinc reagents, such as pyrazolylzinc iodide **1r** or the zinc reagent derived from the benzyl protected bromo-uracil derivative **1s**, react with trichloroacetyl isocyanate to their corresponding primary amides **2r** and **2s** in 70−78% yield (entries 10 and 11).

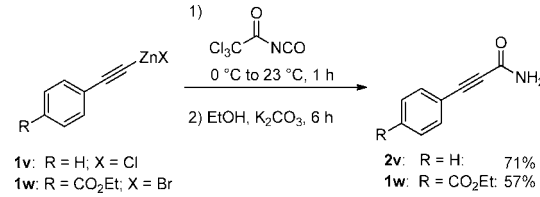
Also α,*β*-unsaturated amides can be prepared from the corresponding zinc reagents. Thus, the unsaturated zinc reagents derived from α-bromostyrene[6a] and 3-iodocyclohex-2-enone[11] react with trichloroacetyl isocyanate to give **2t** and **2u** in 63−85% yield (Scheme 2).

Finally, acetylenic amides can also be prepared by this method. Phenylacetylenezinc chloride (**1v**) reacts with trichloroacetyl isocyanate at room temperature and the acetylenic amide **2v** was isolated in 71% yield (Scheme 3). The ester substituted phenylacetylene derived zinc reagent **1w** can be converted to the primary amide **2w** in 57% yield (Scheme 3).

Scheme 2. Preparation of Unsaturated Primary Amides



Scheme 3. Reaction of Alkynylzinc Halides with Trichloroacetyl Isocyanate



In summary, we have developed a new and efficient method for the preparation of primary amides from the corresponding organozinc halides. This method is suitable for a one-pot preparation of functionalized aromatic, heterocyclic, alkenyl and alkynyl primary amides. Further extensions of this method are currently underway in our laboratories.

Acknowledgment. We thank the DFG (SFB749) and the European Research Council (ERC) for a financial support. We also thank Chemetall GmbH (Frankfurt) and BASF SE (Ludwigshafen) for the generous gift of chemicals.

Supporting Information Available: Experimental details and full spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL101469F

(7) (a) Deng, M.-Z.; Caubère, P.; Senet, J. P.; Lecolier, S. *Tetrahedron* **1988**, *44*, 6079. (b) Manolikakes, G.; Dong, Z.; Mayr, H.; Li, J.; Knochel, P. *Chem.—Eur. J.* **2009**, *15*, 1324. For a recent overview on the addition of organozinc reagents to carbonyl compounds, see: (c) Salvi, L.; Kim, J. G.; Walsh, P. J. *J. Am. Chem. Soc.* **2009**, *131*, 12483.

(8) Zinc reagents prepared by direct C-H activation using TMPZnCl·LiCl or TMP_2Zn·2 $MgCl_2$·2 LiCl do not give the desired products. Also, the use of the corresponding organomagnesium reagents either do not yield in the desired primary amides or only in low yields.

(9) Buschmann, H.; Christoph, T.; Friderichs, E. *Analgesics: From Chemistry and Pharmacology to Clinical Application*; Wiley-VCH: Weinheim, 2002.

(10) Boudet, N.; Sase, S.; Sinha, P.; Liu, C.-Y.; Krasovskiy, A.; Knochel, P. *J. Am. Chem. Soc.* **2007**, *129*, 12358.

(11) Knochel, P.; Rao, C. J. *Tetrahedron* **1993**, *49*, 29.