ORGANIC LETTERS

2003
Vol. 5, No. 5
753−755

Primary 1-Arylcyclopropylamines from Aryl Cyanides with Diethylzinc and Titanium Alkoxides†

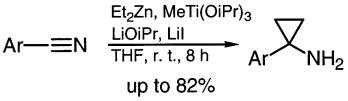
Stefan Wiedemann, Daniel Frank, Harald Winsel, and Armin de Meijere*

Institut für Organische Chemie der Georg-August-Universität Göttingen, Tammannstrasse 2, 37077 Göttingen, Germany

armin.demeijere@chemie.uni-goettingen.de

Received January 7, 2003

ABSTRACT



1-Aryl-substituted primary cyclopropylamines are conveniently prepared from aromatic nitriles and diethylzinc. The yields range from 40 to 56% for donor-substituted (five examples) to 62–82% for non- and acceptor-substituted substrates (nine examples).

The titanium-mediated reductive cyclopropanation of *N*,*N*-dialkylcarboxamides is now a well-established procedure for the synthesis of a wide range of *N*,*N*-dialkylaminocyclopropanes.[1,2] While alkyl-substituted primary cyclopropylamines can be prepared from thus accessible *N*,*N*-dibenzylcyclopropylamines by catalytic hydrogenation,[3] this deprotection obviously cannot be applied to alkenyl-substituted derivates. Not only the alkenyl substituents but also the conjugated cyclopropyl groups are hydrogenated with ring opening under such conditions, and this behavior is also observed for arylcyclopropylamines.[4] It was apparent early on that a titanium-mediated reductive cyclopropanation of nitriles would provide direct access to primary cyclopropylamines. However, early attempts to apply the established conditions for the conversion of carboxamides[1−3] to nitriles gave the corresponding primary cyclopropylamines only in poor yields.[4,5] In the meantime, Szymoniak et al. found that good yields can be achieved from aliphatic nitriles with alkylmagnesium halides and titanium tetraisopropoxide when the reaction mixture is treated with 2 equiv of BF_3·Et_2O before workup,[6] and α-alkoxy- as well as dialkylamino-substituted aliphatic nitriles are converted to the corresponding primary cyclopropylamines in good yields even without addition of a Lewis acid.[7] At the same time, we had turned our attention to the possible use of organozinc instead of Grignard reagents in the titanium-mediated cyclopropanation of carboxamides[8] as well as nitriles, and we report here our first results with nitriles and diethylzinc in the presence of methyltitanium triisopropoxide.

Before any nitriles were tried, the conditions for the use of diethylzinc instead of ethylmagnesium bromide were optimized for the conversion of dibenzylformamide (**1**) to *N*,*N*-dibenzylcyclopropylamine (**2**) (Scheme 1).

Under standard conditions, the expected cyclopropylamine (**2**) was obtained in a yield of only 21%.[5] This was attributed

† Part 90 in the series "Cyclopropyl Building Blocks for Organic Synthesis." For Part 89, see: Liu, C.; Tamm, M.; Nötzel, M. W.; de Meijere, A.; Schilling, J. K.; Kingston, D. G. I. *Tetrahedron Lett.* **2003**, in press. Part 88: Tebben, G.-D.; Stratmann, C.; Rauch, K.; Williams, C. M.; de Meijere, A. *Org. Lett.* **2003**, in press.

(1) (a) Chaplinski, V.; de Meijere, A. *Angew. Chem.* **1996**, *108*, 491−492. (b) Chaplinski, V.; Winsel, H.; Kordes, M.; de Meijere, A. *Synlett* **1997**, 111−114.

(2) Reviews: (a) de Meijere, A.; Kulinkovich, O. G. *Chem. Rev.* **2000**, *100*, 2789−2834. (b) de Meijere, A.; Kozhushkov, S. I.; Savchenko, A. I. In *Titanium and Zirconium in Organic Synthesis*; Marek, I., Ed.; Wiley-VCH: Weinheim, Germany, 2002; pp 390−434.

(3) de Meijere, A.; Williams, C. M.; Kourdioukov, A.; Sviridov, S. V.; Chaplinski, V.; Kordes, M.; Savtchenko, A. I.; Stratmann, C.; Noltemeyer, M. *Chem. Eur. J.* **2002**, *8*, 3789−3801.

(4) Stecker, B. Dissertation, Universität Göttingen, Göttingen, Germany, 2002.

(5) (a) Winsel, H. Diplomarbeit, Universität Göttingen, Göttingen, Germany, 1997. (b) Winsel, H. Dissertation, Universität Göttingen, Göttingen, Germany, 2000.

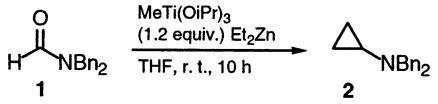
(6) Bertus, P.; Szymoniak, J. *Chem. Commun.* **2001**, 1792−1793.

(7) Bertus, P.; Szymoniak, J. *J. Org. Chem.* **2002**, *67*, 3965−3968.

(8) For cyclopropanations of *N*,*N*-dialkylcarboxamides with functionalized organozinc reagents, see: Wiedemann, S.; Marek, I.; de Meijere, A. *Synlett* **2002**, 879−882.

10.1021/ol034021k CCC: $25.00
Published on Web 02/04/2003

Scheme 1[a]



[a] For details, see Table 1.

to the lower nucleophilicity of diethylzinc[9] compared to ethylmagnesium bromide, and consequently the addition of sodium isopropoxide (NaOiPr) was tested.

Indeed, the yield increased to 52 and even 89% with 1 and 2 equiv, respectively, of NaOiPr being present (Table 1, entries 2 and 3). Similar yields were obtained with 2 equiv

Table 1. Reductive Cyclopropanation of Dibenzylformamide (**1**) with Diethylzinc under various conditions (see Scheme 1)

entry	additive (equiv)	Et_2Zn (equiv)	yield (%)
1	–	2	21
2	NaOiPr (1)	2	52
3	NaOiPr (2)	2	89
4	LiOiPr (2)	2	84
5	NaOMe (2)	2	10
6	NaOEt (2)	2	82
7	NaO*t*Bu (2)	2	76
8	NaOiPr (2)	1	82
9	NaOiPr (2)	0.5	43

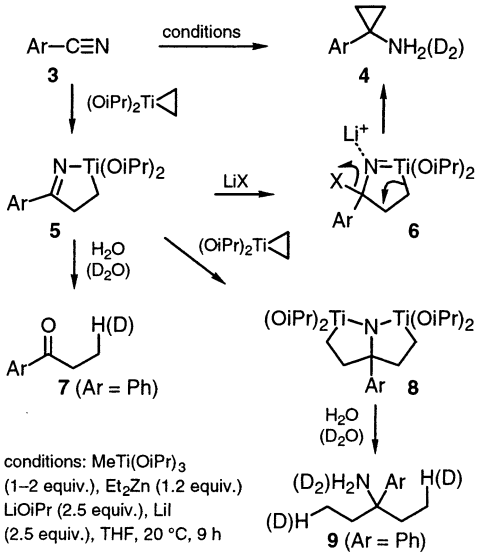
of LiOiPr, NaOEt, and NaO*t*Bu (entries 4, 6, and 7) but not with NaOMe, probably due to the poorer solubility of the formed titanium methoxide. With NaOiPr as an additive, the amount of diethylzinc could be lowered to 1 equiv without a significant loss in yield, but with 0.5 equiv of Et_2Zn, the yield dropped to 43% (Table 1, entries 8 and 9). The added alkoxide converts diethylzinc to a zincate complex of type $[Et_2Zn(OiPr)_2]^{2-}$ as corroborated by an ^1H NMR spectrum,[10] and the latter is much more nucleophilic than the uncoordinated diethylzinc.[9]

With the optimized protocol, benzonitrile (**3a**) was converted to 1-phenylcyclopropylamine (**4a**) in 25% yield, the major side products being propiophenone **7** (18%) and 3-amino-3-phenylpentane **9** (15%). Quenching the reaction with D_2O afforded all three products in their deuterated forms (Scheme 2). Thus, the azatitanacyclopentene **5** must be the intermediate en route to **4** and **7**, the latter being formed by direct hydrolysis of **5** without ring contraction. Apparently, **5** can undergo insertion with a second molecule of the titanacyclopropane intermediate to yield a 1-aza-2,8-dititanabicyclo[3.3.0]octane **8**, which upon hydrolysis or deuteriolysis yields 3-amino-3-phenylpentane (**9**) or its dideuterated analogue, the bisalkylation product of benzonitrile (**3a**).

(9) (a) Tochtermann, W. *Angew. Chem* **1966**, *78*, 355−375; *Angew. Chem., Int. Ed. Engl.* **1966**, *5*, 351−371. (b) Uchiyama, M.; Kameda, M.; Mishima, O.; Yokoyama, N.; Koike, M.; Kondo, Y.; Sakamoto, T. *J. Am. Chem. Soc.* **1998**, *120*, 4934−4946.

(10) Cf.: Mobley, T. A.; Berger, S. *Angew. Chem.* **1999**, *111*, 3256−3258; *Angew. Chem., Int. Ed.* **1999**, *38*, 3070−3072.

Scheme 2[a]



[a] For details, see Table 2.

The obvious solution to this problem would be to favor formation of the saturated azatitanacyclopentane intermediate **6** by addition of a better nucleophile to the reaction mixture. Indeed, with added lithium iodide (2.5 equiv) and slow addition of Et_2Zn to avoid formation of the intermediate **8**, the yield of 1-phenylcyclopropylamine (**4a**) went up to 62%. With this improved protocol, various 1-arylcyclopropylamines **4** were obtained from aryl cyanides in moderate to good yields (Table 2). Acceptor-substituted aromatic nitriles

Table 2. Various 1-Arylcyclopropylamines from Aromatic Nitriles, Diethylzinc, and Methyltitanium Triisopropoxide (See Scheme 2)

nitrile **3**	Ar	yield **4** (%)
a	Ph	62
b	2-Me-C_6H_4	54
c	3-Me-C_6H_4	53
d	4-Me-C_6H_4	56
e	2-MeO-C_6H_4	47
f	2,4-$(MeO)_2$-C_6H_3	40
g	4-F-C_6H_4	65
h	4-Cl-C_6H_4	75
i	4-Br-C_6H_4	72
j	3-CF_3-C_6H_4	73
k	3-*t*BuO_2C-C_6H_4	73
l	3-NC-C_6H_4	75
m	2-Py	80
n	3-Py	82
o	2-Naph	71

consistently gave better yields than donor-substituted ones. Yields were particularly high for 1-pyridylcyclopropylamines **4m**,**n** (80 and 82%, respectively).[11] Nitro groups are incompatible with these conditions;[12] thus, 4-nitrobenzonitrile did

not give any of the corresponding 1-(4-nitrophenyl)cyclopropylamine.

Under the same conditions, aliphatic nitriles such as acetonitrile and phenylacetonitrile gave the corresponding primary cyclopropylamines in poor yields only (12 and 16%, respectively). This new protocol for the synthesis of 1-arylcyclopropylamines thus ideally complements the recently published methods of Szymoniak et al., which with one exception provide only 1-alkyl-substituted primary cyclopropylamines from aliphatic nitriles.[6,7]

(11) 1-(2-Pyridyl)cyclopropylamine has also been obtained from 2-cyanopyridine and ethylmagnesium bromide in the presence of $Ti(OiPr)_4$ by Szymoniak et al., yet in lower yield (54%). Cf. ref. 7.

(12) For a review on organozinc reagents, see: Knochel, P.; Singer, R. D. *Chem. Rev.* **1993**, *93*, 2117−2188.

Acknowledgment. This work was supported by the Niedersächsisches Ministerium für Wissenschaft und Kunst and the Fonds der Chemischen Industrie. The authors are indepted to Witco GmbH for a generous gift of diethylzinc, Prof. Paul Knochel, München, for valuable discussions, and Dr. Burkhard Knieriem, Göttingen, for his careful proofreading of the final manuscript.

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

OL034021K