Pergamon

Tetrahedron Letters, Vol. 38, No. 7, pp. 1241-1244, 1997
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0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)00047-6

Organocerium Reactions of Benzamides and Thiobenzamides: A Direct Synthesis of Tertiary Carbinamines

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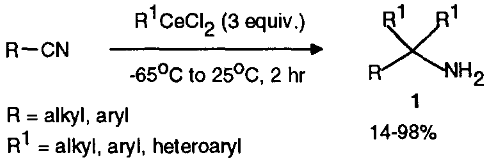
Abstract: A simple and efficient process has been developed for the direct conversion of benzamides and thiobenzamides into tertiary carbinamines. A synthesis of benzonitriles from simple benzamides and a thiobenzamide is also described. © 1997, Elsevier Science Ltd. All rights reserved.

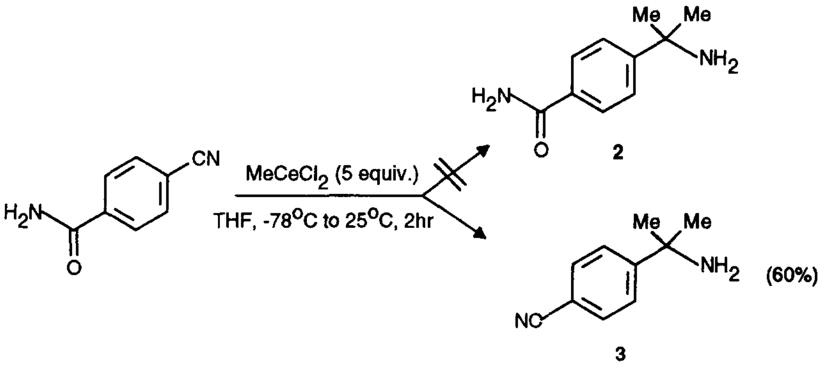
The field of organolanthanide chemistry has received considerable attention over the past 25 years and numerous review articles covering this field of chemistry have appeared.[1] In particular, organocerium reagents have found widespread use in carbon-carbon bond forming reactions.[2,3] These reagents readily undergo nucleophilic addition to carbonyl compounds,[4] αβ-unsaturated carbonyl compounds[5] and epoxides.[6] Addition to C-N π bonds, in particular chiral hydrazones,[7] has been shown to proceed in excellent yields and with high diastereoselectivity. Ciganek has also shown that organocerium reagents add to nitriles to generate tertiary carbinamines (**1**), often in excellent yields (Scheme1).[8, 9]

Scheme 1



As part of a discovery programme towards agents of potential antiinflammatory use[10] appropriately functionalised tertiary carbinamines (**1**, R=substituted phenyl, R^1=methyl) were required as synthetic intermediates. However, treatment of 4-cyanobenzamide under the described conditions did not give the expected amide (**2**) but instead gave the nitrile (**3**) (Scheme 2). That is, the organocerium reagent had either reacted at both electrophilic centres or the amide centre only. The possibility of reaction at the amide centre was investigated by examining independently the reactions of a variety of simple benzamides with the methylcerium reagent. As a result of these studies we describe a method for the dehydration of benzamides and a thiobenzamide to nitriles and also a direct method for their conversion into tertiary carbinamines.

Scheme 2



Thus, treatment of benzamide under optimised conditions[11] (2.5 equiv. MeCeCl$_2$, -78°C to 0°C, 1hr) gave an 87% G.L.C. yield of benzonitrile (48% isolated). The results of treating a range of benzamides and a thiobenzamide under these conditions are shown in Table 1.

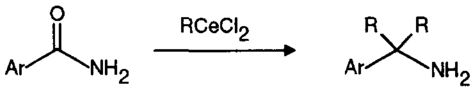
Table 1. Synthesis of Benzonitriles from Benzamides and a Thiobenzamide.

Entry	ArCXNH$_2$	ArCN (%)^a
1.	Ar = 4-Cl-C$_6$H$_4$, X=O	70
2.	Ar = 4-Cl-C$_6$H$_4$, X=S	68
3.	Ar = 4-MeO-C$_6$H$_4$, X=O	61
4.	Ar = 4-Me-C$_6$H$_4$, X=O	65
5.	Ar = 3-Me-C$_6$H$_4$, X=O	65
6.	Ar = 2-MeO-C$_6$H$_4$, X=O	50^b
7.	Ar = 2-Pyridyl, X=O	58

^{a} Isolated yields. (>95% purity by GLC) ^{b}2-(2-Methoxyphenyl)-2-methylethanamine (20% by G.L.C. of crude reaction mixture) was also isolated.

The conversion of nitriles to tertiary carbinamines has been described by Ciganek (Scheme 1).[8] Consideration of his work together with the above observations suggested that it should be possible, given the correct conditions, to convert benzamides directly into tertiary carbinamines (Scheme 3).

Scheme 3



4

This proved to be the case. Thus, treatment of benzamide under optimised conditions[11] (5.0 equiv. $MeCeCl_2$, -78°C to 0°C, 2hr) gave a 73% isolated yield of **4** (Ar = C_6H_5, R = Me). The results of treating a range of substituted benzamides under the same conditions are shown in Table 2, and this methodology can be extended to thiobenzamides.[12]

Table 2. Synthesis of Tertiary Carbinamines from Benzamides.

Entry	**$ArCONH_2$**	**$ArC(Me)_2NH_2$ (%)[a]**
1.	Ar = 4-Cl-C_6H_4	66
2.	Ar = 4-MeO-C_6H_4	67
3.	Ar = 4-Me-C_6H_4	58
4.	Ar = 2-MeO-C_6H_4	70
5.	Ar = 2-Naphthyl	68

[a] Isolated yields (>95% purity by GLC)

The results for the latter type of substrate are shown in Table 3.

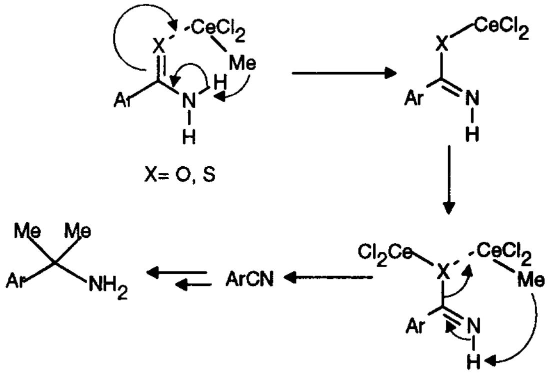
Table 3. Synthesis of Tertiary Carbinamines from Thiobenzamides.

Entry	**$ArCSNH_2$**	**$ArC(Me)_2NH_2$ (%)[a]**
1.	Ar = C_6H_5	68
2.	Ar = 4-Cl-C_6H_5	86
3.	Ar = 4-MeO-C_6H_5	75

[a] Isolated yields (>95% purity by GLC)

In this conversion of benzamides to tertiary carbinamines, benzonitriles have been identified (1-2% by G.L.C. of crude reaction mixture) as minor by-products and it is not unreasonable to speculate that they are intermediates in the reaction pathway. It is likely that the driving force for the dehydration of benzamides is the strong oxophilicity of the organocerium species. These results also emphasise that cerium is sufficiently thiophilic to enable this reaction to proceed with thioamides. A tentative mechanism for the amide to nitrile conversion is outlined in Scheme 4.

Scheme 4



In conclusion, we have shown that simple benzamides and thiobenzamides can be dehydrated to benzonitriles and also converted directly into tertiary carbinamines. This simple and efficient one step transformation of amides and thioamides into tertiary carbinamines adds significantly to the relatively few synthetic organometallic transformations of primary amides. The application of these findings to other amides using a range of organocerium reagents will be reported in due course.

Acknowledgements: We wish to thank Keith Robinson for analytical assistance, Prof. A. McKillop for stimulating discussion and Andrew Sachs for technical assistance.

References and Notes:

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9. Organocerium reagents are commonly referred to as $RCeCl_2$ although the authors are aware of a recent report by Evans who describes the presence of water in the $CeCl_3$/RLi alkylation system. See Evans, W.J.; Feldman, J. D.; Ziller, J. W. *J. Am. Chem. Soc.* **1996**, 118, 4581.
10. GB Appl. 93/12 893/1993 (*Chem. Abstr.* **1995**, 123, 198799s).
11. Unpublished results (H. L. Twigger and H. M. Whelan).
12. General work-up procedure (20mmol scale): The solution was quenched at -78°C with NH_4OH (100ml), warmed to room temperature, filtered through a pad of celite and the solvent evaporated to leave an oil. The oil was taken up in EtOAc (100ml) and, after an acid / base extraction procedure, the organics were dried, filtered and evaporated to leave an oil. Compounds were identified by ^1H NMR, IR, elemental analysis and mass spectral analysis. Purity was determined by GLC.

(*Received in UK* 30 *October* 1996; *revised* 2 *January* 1997; *accepted* 10 *January* 1997)