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LETTERS

A novel approach to amidines from esters

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Abstract—A mild and efficient method for the direct conversion of aromatic, benzylic and aliphatic esters to amidines—in the form of their hydrochlorides—has been developed. © 2002 Elsevier Science Ltd. All rights reserved.

Amidines are versatile building blocks for the synthesis of various heterocyclic compounds.[1] Nevertheless, the methods currently available for the preparation of amidines often involve multistep processes.[2] The most common precursors are nitriles, which are often expensive or have to be synthesized prior to the amidine formation. With carboxyclic acids as starting materials, temperatures above 230°C are needed for the transformation using benzenesulfonamide as reagent.[3]

We have developed a mild and efficient route to amidinium hydrochlorides from the corresponding esters employing a variation of Garigipati's reaction,[4] which is based on Weinreb's procedure[5] for the conversion of esters to amides.

In 1990 Garigipati reported on the conversion of alkyl and aryl nitriles to amidines in a single step using methylchloroaluminium amide which was prepared by addition of ammonium chloride to commercially available trimethylaluminium.[4] This procedure was developed by Weinreb et al.[5] for the conversion of esters to amides, using 3 equiv. of the aluminium reagent with subsequent quenching with 5% hydrochloric acid. In contrast to that, Garigipati employed a slurry of silica gel in chloroform as quenching agent for the preparation of amidines.[4]

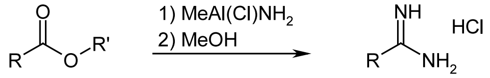
We observed the conversion of esters to amidines with 1–5 equiv. methylchloroaluminium amide which was prepared in situ, followed by hydrolysis of the aluminium complexes with methanol (Scheme 1). Therefore, the quenching conditions seem to be crucial for the isolation of either amidines or amides, the amides would then be the hydrolysis products of the amidines.

We have employed this method for the preparation of aromatic, heteroaromatic, benzylic and aliphatic amidinium hydrochlorides in moderate to high yields (Table 1). Even nitriles as further substituents are tolerated (entries 4 and 5), in contrast to previous studies which described the selective transformation of nitriles to amidines in the presence of esters.[6]

In conclusion, we have developed a mild and efficient route to amidines from readily available esters using methylchloroaluminium amide and methanol as quenching agent.

General experimental procedure

1–5 equiv. ammonium chloride was suspended in dry toluene under an argon atmosphere, and the mixture was cooled to 0°C. 1–5 equiv. of a 2 M solution of trimethylaluminium in hexane was added dropwise and the reaction mixture was stirred at room temperature until no more evolution of gas was observed. After addition of 1 equiv. of the ester, the mixture was stirred at 80°C bath temperature overnight. It was then cooled down to 0°C and methanol was added with consequent stirring for 1 h at room temperature. After filtration, the solid was washed with methanol several times, the solution evaporated to dryness in vacuo and the residue washed with methanol. The product can be purified by crystallization from methanol/dichloromethane or by flash chromatography.



Scheme 1.

Keywords: amidine; ester; methylchloroaluminium amide.

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Table 1. Preparation examples

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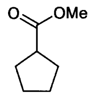
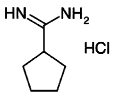
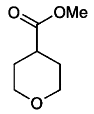
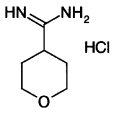
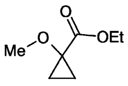
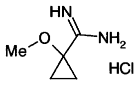
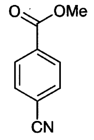
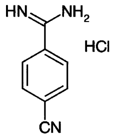
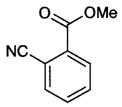
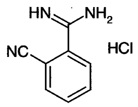
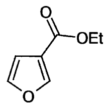
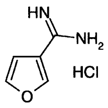
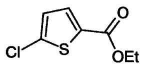
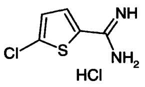
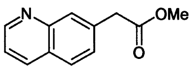
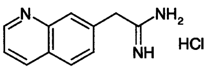
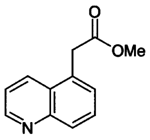
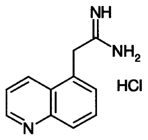
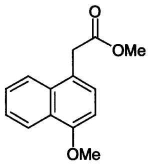
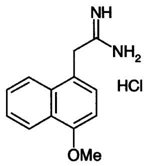
1			2	47
2			5	87
3			5	87
4			1	50
5			2	43
6			2	57
7			5	71
8			5	50
9			5	47
10			5	77

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