Pergamon

Tetrahedron Letters, Vol. 38, No. 13, pp. 2367-2368, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)00350-X

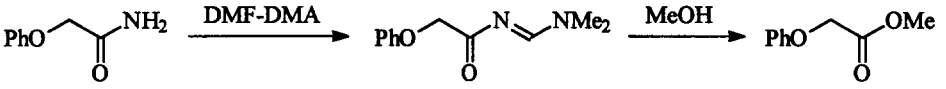
Mild Conversion of Primary Carboxamides into Carboxylic Esters

Pier Lucio Anelli, Marino Brocchetta,* Daniela Palano and Massimo Visigalli

Milano Research Centre, Bracco spa, via E. Folli 50, 20134 Milano, Italy

Abstract: Primary carboxamides are converted into the corresponding alkyl carboxylates by treatment with dimethylformamide dimethylacetal in the appropriate alcohol at 25-45 °C. Yields are very good to excellent. © 1997 Elsevier Science Ltd.

The existing methods for the conversion of primary carboxamides into the related carboxylic esters usually call for harsh reaction conditions. Most preferred methodologies involve treatment, at high temperature for several hours, of the carboxamide in the suitable alcohol in the presence of large amounts of acidic catalysts such as HCl,[1] BF_3,[2] or Amberlyst® 15 resin.[3] However, an attractive procedure which makes use of HCl (1 mol. equiv.) and $TiCl_4$ (0.1 mol. equiv.) has been reported.[4] We recently found that treatment of phenoxyacetamide **1** with dimethylformamide dimethylacetal (DMF-DMA) at room temperature affords *N*-acylformamidine **2**, which, in its turn, is converted into methyl phenoxyacetate **3** by simple dissolution in MeOH (Scheme).[5]



1 **2** **3**

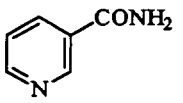
Scheme

Here we report that reaction of **1** with DMF-DMA (3 mol. equiv.) in MeOH, after 1 h at room temperature, directly leads to **3** in excellent yield.[6] Furthermore, we have found that such reaction conditions can be advantageously applied to the conversion of a variety of primary carboxamides into the corresponding methyl esters (Table).[7] For most substrates the formation of the transient *N*-acylformamidine species[8] can be observed by monitoring the reaction course by HPLC or GC.

This synthetic methodology, still using DMF-DMA, can be extended to the preparation of carboxylic esters other than methyl from the corresponding primary carboxamides. Thus **1** in EtOH in the presence of 2 mol. equiv. of DMF-DMA at 45 °C for 3 h affords ethyl phenoxyacetate in 85% yield. Likewise *i*-propyl (25°C, 22 h, 60%), *n*-butyl (50°C, 6 h, 76%) and benzyl (25°C, 15 h, 91%) phenoxyacetates are easily prepared.[9]

This methodology appears of quite broad application: for example it can be successfully used with substrates containing hydroxy groups (see last entry in the Table). However, a limitation to its use is the presence in the substrate of functional groups (*e. g.* NH_2, NHR, COOH) which are reactive towards DMF-DMA.[10]

Table. Conversion of primary carboxamides into the corresponding methyl carboxylates

Substrate	T (°C)	t (h)	Ester yield, %[a]
$PhOCH_2CONH_2$	25	1	92[b] (89)
$PhCH_2CONH_2$	25	4	99[b] (94)
$PhCONH_2$	45	5	98[b] (96)
	25	2	100[b] (92)
CH_3CONH_2	25	4	97[c]
$CH_3(CH_2)_3CONH_2$	45	1	99[c] (95)
$CH_3CHOHCONH_2$[d,e]	25	4	96[c]

[a] Chromatographic yield (isolated yield). [b] HPLC yield, determined using an authentic sample of the ester as the standard. [c] GC yield, determined using an authentic sample of the ester as the standard. [d] (*RS*)-2-hydroxypropanamide was used. [e] 2 mol. equiv. of DMF-DMA were used.

References and Notes

1. Bobbit, J. M.; Scola, D. A. *J. Org. Chem.* **1960**, *25*, 560-564. Kumler, P. L.; Dybas, R. A. *Ibid.*, **1970**, *35*, 125-131.
2. Hamilton, D. J.; Price, M. J. *J. Chem. Soc., Chem. Commun.* **1969**, 414.
3. Greenlee, W. J.; Thorsett, E. D. *J. Org. Chem.* **1981**, *46*, 5351-5353.
4. Fisher, L. E.; Caroon, J. M.; Stabler, S. R.; Lundberg, S.; Zaidi, S.; Sorensen, C. M.; Sparacino, M. L.; Muchowski, J. M. *Can. J. Chem.* **1994**, *72*, 142-145.
5. Species **2** has been fully characterized by ^1H and ^{13}C NMR, MS, elemental analysis and X-ray crystal structure: Anelli, P. L.; Brocchetta, M.; Palano, D.; Paoli, P.; Visigalli, M. Book of Abstracts of the 11th ICOS, Amsterdam, The Netherlands, 30 June - 4 July 1996; Abs. PO-304.
6. Use of smaller DMF-DMA/amide ratios and longer reaction times favours the formation of *N,N*-dimethylphenoxyacetamide. This compound is formed by reaction of **3** with dimethylamine which is generated in the cleavage of **2**.
7. Typical procedure: To a 0.2-0.5 M solution of the primary amide in MeOH was added DMF-DMA (3 mol. equiv.). The reaction was stirred at 25 or 45°C for 1-5 h (see Table). The progress of the reaction was monitored by either HPLC or GC. After neutralization (HCl in MeOH) and evaporation of the solvent the residue was dissolved in Et_2O (CH_2Cl_2) and extracted with H_2O. The organic phase was dried and evaporated to give a crude which was distilled. All isolated products showed analytical data (b.p., ^1H and ^{13}C NMR, MS and elemental analysis) in agreement with the assigned structure.
8. To the best of our knowledge the only mention of a potential use of *N*-formylamidines as precursors of carboxylic esters is contained in: Brace, N. O. *J. Org. Chem.* **1993**, *58*, 1804-1811. *N*-Acylamidinium salts and suitably activated formamidines derived from secondary carboxamides have been reported to undergo alcoholysis to the corresponding alkyl carboxylates (see: Glocker, M. O.; Shrestha-Davadi, P. B.; Küchler-Krischun, J.; Hofmann, J.; Fischer, H.; Jochims, J. C. *Chem. Ber.* **1993**, *126*, 1859-1865; Ono, M.; Araya, I.; Todoriki, R.; Tamura, S. *Chem. Pharm. Bull.* **1990**, *38*, 1824-1831).
9. Differently from the typical procedure (ref. 7), for the preparation of these esters it is recommended to use a 0.05-0.15 M solution of **1** in the appropriate alcohol. Under such conditions the competitive formation of the methyl ester **3** is minimized (less then 7 %).
10. Abdulla, R. F.; Brinkmeyer, R. S. *Tetrahedron* **1979**, *35*, 1675-1735.

(*Received in UK* 6 *January* 1997; *revised* 14 *February* 1997; *accepted* 21 *February* 1997)