# 170. A Mild, Facile Method for the Preparation of Amino-esters

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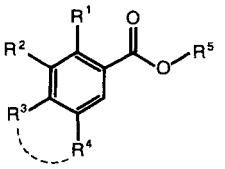
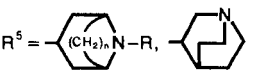
(18.VI.85)

Lithium alcoholates prepared *in situ* react spontaneously with imidazolides derived from substituted aromatic carboxylic acids to provide the amino-esters **4** in excellent yield.

In connection with our investigations of biologically useful compounds which are structurally related to metoclopramide [1] [2], we were interested in the synthesis of aromatic esters of type **1** containing a bicyclic basic sidechain.



**1**



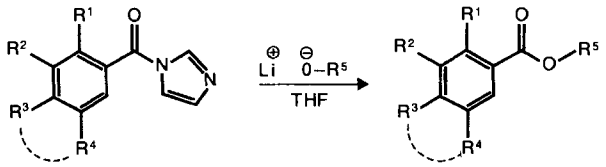
R = H, $CH_3$,
n = 2, 3

*Staab* [3] and his coworkers reported in 1961 that relatively strong bases such as sodium alcoholates react in catalytic amounts under mild conditions with imidazolides to provide the corresponding esters, and it recently occured to us that lithium alcoholates generated by BuLi and their corresponding hydroxy compounds could be a useful and simplified extension for esterifications of activated carboxylic acids [4].

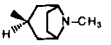
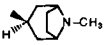
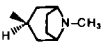
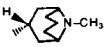
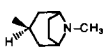
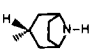
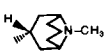
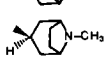
We now wish to report that lithium alcoholates **3** prepared *in situ* by use of BuLi and the amino alcohol in absolute tetrahydrofuran undergo reaction with aromatic imidazolides [5] [6] **2** to provide the corresponding amino-ester **4** in a clean and efficient manner at −10–0 °C. (see *Table*). The reactions proceed almost instantaneously and can usually be worked up after a short period of time by simply adding a slight excess of saturated $K_2CO_3$ solution and decanting the organic phase. Yields are generally good to excellent. Typical reactions are listed in the *Table*.

It is noteworthy that neither halogens nor $NO_2$ substituents are affected under these mild reaction conditions. Furthermore, no matter whether axial or equatorial lithium alcoholates are used for the transformation, no isomerisation has been observed in this process. However, we experienced self-condensation reactions with unprotected 4-aminoimidazolides using 3.5 equiv. of **3**, and it proved to be advantageous to treat the 4-*N*-(benzyloxycarbonyl)imidazolide at first with the nucleophile and to remove the protective Cbn group by catalytic hydrogenation in a further step. This reaction sequence provides the desired amino-ester **4h** in overall good yield. In conclusion, the described method of esterification represents a similar reaction type as reported by *Staab* [3] except for the use of lithium instead of sodium alcoholates as a strong base. However, it seems important to emphasize the convenient easy measurable application of a BuLi solution for the generation of lithium alcoholates and its sequential esterification. This mild and efficient procedure extends the usefulness of metallorganic esterifications of imidazolides basically investigated by *Staab et al.* in the late fifties.

Table. *Synthetic Scheme of Simple Aromatic Amino-esters*[a])




**2** **3** **4**

| No. | $R^1$ | $R^2$ | $R^3$ | $R^4$ | Li-$OR_5$ used [Equiv.] | $R^5$ | Yield [%][b])[c]) | M.P. [°C][d]) |
|---|---|---|---|---|---|---|---|---|
| **4a** | $CH_3O$ | H | $NHCH_3$ | Cl | 2.5 |  | 89 (hml) | 193–195 |
| **b** | $CH_3O$ | H | H | Br | 1.3–1.5 |  | 83 (b) | 91–92 |
| **c** | Cl | H | $NO_2$ | H | 1.3–1.5 |  | 67 (hmo) | 132–133 |
| **d** | $CH_3O$ | H | $NHCH_3$ | Cl | 2.5 |  | 88 (b) | 183–184 |
| **e** | H | Cl | H | Cl | 1.3–1.5 |  | 84 (hmo) | 159–160 |
| **f** | $CH_3O$ | H | $NHCH_3$ | Cl | 2.5 |  | 100 (hmo) | 170–172 |
| **g** | $CH_3O$ | H | –NH– | | 1.3–1.5 |  | 70 (hmo) | 159–160 |
| **h**[e]) | $CH_3O$ | H | $NH_2$ | H | 2.5 |  | 72 (hml) | 166–167 |
| **i** | $CH_3O$ | H | $NHCH_3$ | I | 2.5 |  | 60 (b) | 164–166 |
| **k** | H | H | –NH– CH=CH– | | 2.5 |  | 75 (b) | 220–222 |

[a]) All imidazolides were prepared according to the method of *Staab et al.* [5] [6].

[b]) The yield are not optimized. Structure assignments were supported by $^1$H-NMR-spectroscopy (*Varian 90*, 360 MHz).

[c]) Abbreviations: hml, hydrogenmaleate; hmo: hydrogenmalonate; b, free base.

[d]) Melting points were obtained on a *Büchi* capillary melting-point apparatus and are uncorrected. Analytic samples gave satisfactory results and were within ±0.4% of the theoretical values.

[e]) **4h** was prepared by the reaction of the lithium-N-benzyltropin salt **3** with the 4-*N*-(benzyloxycarbonyl)-imidazolide [7–10] followed by catalytic debenzylation in the presence of $Pd/C/H_2$ in EtOH at r.t. and atmospheric pressure.

**A Typical Experimental Procedure.** – To a stirred soln. of 6.28 g (44 mmol) tropin (8-methyl-8-azabicyclo[3.2.1]octan-3-ol) in 100 ml of abs. THF were added dropwise under dry Ar 27 ml of BuLi soln. (1.6 m) in hexane at –10–0°. These mixture was stirred for 5 min and a soln. of 4.5 g (17 mmol) 3-chlor-4-methylamino-6-methoxybenzoic-acid-imidazolide [5] in 100 ml of abs. THF was added dropwise. The mixture was stirred for 15–20 min at 0° and 5 ml of a sat. soln. of $K_2CO_3$ (20%) was then added, and the org. layer decanted. The residue was triturated with two portions of THF, the combined org. layer was dried ($MgSO_4$), filtered and evaporated under reduced pressure. The residue was taken up in AcOEt and the org. phase was washed three times with $H_2O$, dried ($MgSO_4$), filtered, and the filtrate was evaporated under partial pressure to furnish 6.0 g almost pure amino-ester which was crystallized from Aceton/MeOH by addition of 1 equiv. maleicacid to give 6.55 g (89%) pure **4a**. M.p. 193–195°. $^1$H-NMR (90 MHz, $CDCl_3$): 1.95–2.8 (complex, 4 $CH_2$); 2.82 (*s*, $CH_3N$); 2.97 (*d*, $NHCH_3$); 3.8 (*m*, 2 CH–N); 3.9 (*s*, $CH_3O$); 4.95 (*d*, NH); 5.3 (*m*, CH–O); 6.12 (*s*, 1 arom. H); 6.3 (*s*, 2 arom. H), 7.78 (*s*, 1 arom. H) (3H, exchangeable). Anal. calc. for $C_{21}H_{27}ClN_2O_7$ (454.9): C 55.4, H 6.0, Cl 6.2, N 24.6, O 7.8; found: C 55.7, H 5.9, Cl 6.1, N 24.4, O 7.8.

The authors express their appreciation to *Harald Meigel* and *Roland Furler* for the experimental work.

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