An Easy Two-step Synthesis of 1-Imidazolylmethyl Esters

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A new synthesis of 1-imidazolylmethyl esters is described starting from the appropriate carboxylic acids *via* imidazolide intermediates.

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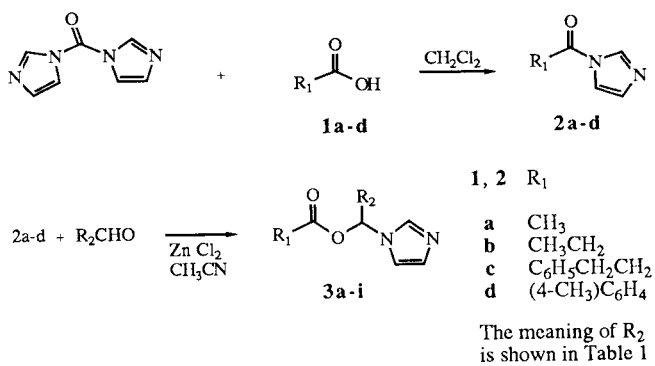
Imidazole plays a significant role in the preparation of pharmacologically active compounds. In the past few years a large number of 1-substituted imidazoles has been prepared in order to obtain new selective inhibitors of the production of thromboxane A_2 (TXA_2), a powerful pro-aggregatory and vasoconstrictor agent [1,2]. During the development of a program devoted to the synthesis of new TXA_2-inhibitors, we were interested in verifying how the presence of a carboxylic moiety into the side chain of the imidazole ring could influence the activity. At first we turned our efforts to the preparation of 1-imidazolylmethyl esters **3**. The reported approach to obtain these derivatives is carried out in a three-step synthesis starting from appropriate carboxylic acids **1**. Acid chlorides, originating from carboxylic derivatives, react with aliphatic and aromatic aldehydes in the presence of a catalytic amount of zinc chloride [3-6] to give the corresponding chloromethyl esters. The subsequent alkylation at position 1 of the imidazole ring affords desired compounds **3** [7].

In the present communication, we wish to report a new and simple two-step synthesis of 1-imidazolylmethyl esters **3**. Our synthetic route, shown in Scheme 1, starts from the reaction between appropriate carboxylic acids **1a-d** and *N,N'*-carbonyldiimidazole (CDI) and gives imidazolides **2a-d**. These derivatives often show a chemical behaviour like that of acid halides giving, for example, esters and amides when they are treated respectively with alcohols and amines. Moreover imidazolides are simple to prepare in good yields [8] and are frequently easier to purify than acid halides.

Scheme 1



The second step of our synthesis is the reaction between imidazolides **2a-d** and aldehydes in order to obtain 1-imidazolylmethyl esters **3**. At first we used aliphatic aldehydes, such as formaldehyde [9] and acetaldehyde. The preparation is carried out in dry acetonitrile at 60° using zinc chloride as the catalyst. 1-Imidazolylmethyl ester derivatives **3a-h** are obtained practically pure in good yields as oils [10] and only the analytical samples are purified by chromatography eluting with chloroform-acetone.

Afterwards we studied the possibility of using crotonaldehyde in order to prepare 1-imidazolylmethyl esters **3** containing a double bond in the side chain. Adopting the experimental conditions described for the synthesis of derivatives **3a-h**, the reaction gives very poor yields and the presence of desired derivatives **3** can be only detected by ^{1}H-nmr technique. We were able to isolate pure compounds **3i** as oil after chromatography only by carrying out the synthesis with imidazolide **2d**. In order to realize the nature of the synthetic problems found with crotonaldehyde, we studied the stability of compound **3i** by ^{1}H-nmr technique storing the pure chromatographed sample at room temperature. After few days the ^{1}H-nmr spectrum of a freshly prepared solution showed that derivative **3i** was completely decomposed. It is possible to think that the reaction between crotonaldehyde and imidazolides **2a-d** proceeds as previously described for aliphatic aldehydes obtaining, however, unstable 1-imidazolylmethyl derivatives.

At last we could not isolate any interesting compounds using aromatic aldehydes, such as benzaldehyde and 2-furaldehyde. We are now considering the possibility of changing the experimental conditions in order to make the reaction between imidazolides **2** and aldehydes more general.

EXPERIMENTAL

The ^{1}H-nmr spectra were recorded on a Varian Gemini 200, except the spectrum of compound **3i**, registered on a Varian CFT 20. Elemental analysis were carried out on Perkin-Elmer 240.

Imidazolides **2a-d**.

Derivatives **2a-d** were obtained as already described [8,11].

Imidazolylmethyl Esters **3a-i**.

Table 1

Compound No.	R_1	R_2	Yield (%)	Formula	^{1}H-NMR (ppm, deuteriochloroform)	Elemental Analysis Calcd. (%)/Found (%) C	H	N
3a	CH_3	H	72	$C_6H_8N_2O_2$	7.55 (s, 1H), 6.96 (s, 1H), 6.90 (s, 1H), 5.71 (s, 2H), 1.94 (s, 3H)	51.42 51.27	5.75 5.65	19.99 19.87
3b	C_2H_5	H	50	$C_7H_{10}N_2O_2$	7.59 (s, 1H), 7.01 (s, 1H), 6.96 (s, 1H), 5.77 (s, 2H), 2.26 (q, 2H), 1.03 (t, 3H)	54.54 54.50	6.54 6.55	18.17 18.09
3c	$(CH_2)_2C_6H_5$	H	50	$C_{13}H_{14}N_2O_2$	7.62 (s, 1H), 7.28-7.06 (m, 5H), 7.19 (s, 1H), 7.01 (s, 1H), 5.77 (s, 2H), 2.88 (t, 2H), 2.61 (t, 2H)	67.81 67.60	6.13 5.99	12.17 12.08
3d	4-$CH_3C_6H_4$	H	79	$C_{12}H_{12}N_2O_2$	7.55 (AA' BB' System, 4H), 7.81 (s, 1H), 7.17 (s, 1H), 7.08 (s, 1H), 6.06 (s, 2H), 2.38 (s, 3H)	66.65 66.56	5.59 5.42	12.95 12.88
3e	CH_3	CH_3	40	$C_7H_{10}N_2O_2$	7.66 (s, 1H), 7.04 (s, 1H), 6.97 (s, 1H), 6.63 (q, 1H), 1.96 (s, 3H), 1.70 (d, 3H)	54.54 54.39	6.54 6.50	18.17 18.00
3f	C_2H_5	CH_3	53	$C_8H_{12}N_2O_2$	7.65 (s, 1H), 7.03 (s, 1H), 6.96 (s, 1H), 6.64 (q, 1H), 2.22 (q, 2H), 1.69 (d, 3H), 1.01 (t, 3H)	57.13 56.95	7.19 6.99	16.66 16.51
3g	$(CH_2)_2C_6H_5$	CH_3	69	$C_{14}H_{16}N_2O_2$	7.81 (s, 1H), 7.28-7.06 (m, 5H), 7.21 (s, 1H), 7.02 (s, 1H), 6.66 (q, 1H), 2.87 (t, 2H), 2.59 (t, 2H), 1.70 (d, 3H)	68.83 68.71	6.60 6.52	11.47 11.31
3h	4-$CH_3C_6H_4$	CH_3	54	$C_{13}H_{14}N_2O_2$	7.57 (AA' BB' System, 4H), 7.92 (s, 1H), 7.18 (s, 1H), 7.06 (s, 1H), 6.68 (q, 1H), 2.38 (s, 3H), 1.76 (d, 3H)	67.81 67.77	6.13 6.15	12.17 12.06
3i	4-$CH_3C_6H_4$	CH=CH-CH_3	15	$C_{15}H_{16}N_2O_2$	7.52 (AA' BB' System, 4H), 7.90 (s, 1H), 7.51 (dd, 1H), 7.24 (m, 2H), 7.14 (m, 2H), 2.47 (s, 3H), 2.42 (d, 3H)	70.29 70.20	6.29 6.07	10.93 10.84

Typical Procedure.

A catalytic amount of zinc chloride was added at room temperature to a stirred solution of imidazolide **2** (3 mmoles) and aldehyde (3 mmoles) in dry acetonitrile (10 ml). The reaction mixture was stirred at 65° for 16 hours. After evaporation of the solvent, the residue was treated with methylene chloride, filtered and washed with 5% aqueous sodium bicarbonate solution. The organic layer was dried and evaporated to give desired product **3**. Analytical data of compounds **3a-i** are presented in Table 1.

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[9] The reaction is carried out using trioxymethylene.

[10] Imidazolylmethyl ester **3d** is obtained as a solid, mp 99-100° (ethyl acetate) determined on a Büchi SMP-20 apparatus and uncorrected.

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