A Facile Method for Activation of Carboxylic Acids

Shizuaki MURATA

Department of Chemistry, College of General Education, Nagoya University, Chikusa-ku, Nagoya 464

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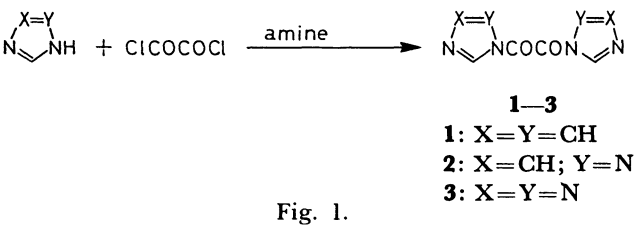
Synopsis. 1,1′-Oxalyldiimidazole, -1,2,4-triazole, and -1,2,3,4-tetrazole were prepared *in situ* from oxalyl dichloride and corresponding 1*H*-azoles. The 1,1′-oxalyldiazoles converted carboxylic acids and their salts into 1-acylazoles.

1-Acylazoles have been widely used as activated acyl species.[1] It was reported in a previous paper that 1,1′-oxalyldiimidazole[2] is a suitable reagent for the preparation of 1-acylimidazoles.[3] There remained, however, two problems worthy of further investigation; *i.e.* the isolation of the 1-acylazoles and the application to a variety of 1-acylazoles. In the present paper, these problems are examined and an effective method for the preparation of various 1-acylazoles is described.

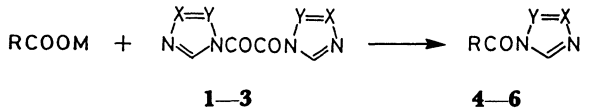
1,1′-Oxalyldiimidazole (**1**) was reported to be prepared by the reaction of 1*H*-imidazole and oxalyl dichloride in the presence of a tertiary amine.[3] This procedure was found to also be applicable for the synthesis of other 1,1′-oxalyldiazoles. 1,1′-Oxalyldi-1,2,4-triazole (**2**) and -1,2,3,4-tetrazole (**3**) were formed in a reaction involving the corresponding 1*H*-azole and oxalyl dichloride in the presence of *N,N*-diisopropylethylamine at 0—30 °C. *N,N*-Dicyclohexylmethylamine and 2,6-di-*t*-butylpyridine, as well as the 1*H*-azoles themselves, could be used for the hydrogen chloride acceptor. The resulting mixtures involving **2** and **3** were used in a follow-up reaction to prepare 1-acylazoles.



1—3

1: X=Y=CH
2: X=CH; Y=N
3: X=Y=N

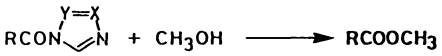
Fig. 1.



1—3 **4—6**

4: X=Y=CH
5: X=CH; Y=N
6: X=Y=N

Fig. 2.



7a—7c

7a: R=$CH_3(CH_2)_4$-$(CH{=}CHCH_2)_2$-$(CH_2)_6$-
7b: R=$CH_3(CH_2CH{=}CH)_3$-$(CH_2)_7$-
7c: R=$CH_3(CH_2)_4$-$(CH{=}CHCH_2)_4CH_2CH_2$-

Fig. 3.

Now, the reaction of **2** or **3** with a carboxylic acid, such as linoleic acid (C 18, Δ=2), linolenic acid (C 18, Δ=3), and arachidonic acid (C 20, Δ=4), in chloroform proceeded with CO and CO_2 evolution to give the corresponding 1-acyl-1,2,4-triazole (**5**) or -1,2,3,4-tetrazole (**6**) in high yields. In DMF, **2** and **3** converted the lithium and sodium salts of those fatty acids into **5** and **6**. The isolation and purification of produced 1-linoleoylimidazole (**4a**), -1,2,4-triazole (**5a**), and -1,2,3,4-tetrazole (**6a**) were performed successfully by extraction with a light petroleum followed by distillation.

1-Linoleoylimidazole (**4a**) was converted into methyl linoleate (**7a**) by its treatment with methanol in the presence of potassium *t*-butoxide. It is known that the condensation of 1-acylimidazole **4** with an alcohol requires a basic catalyst.[1] Since the reaction of **5a** or **6a** with methanol proceeded smoothly in the absence of a basic catalyst, it may be concluded that **5** and **6** are more reactive than **4**. 1-Linolenoylimidazole (**4b**) and 1-arachidonoyltetrazole (**6c**) were converted into the methyl esters **7b** and **7c** by the same treatment. The results are summerized in Table 1.

Only 1,1-carbonyldiimidazole,which is fairly expensive for a large-scale reaction, and 1,1-carbonylditriazole,[4] whose preparation requires severe poisonous phosgene, have been used for the activation of

TABLE 1. REACTION OF 1,1′-OXALYLDIAZOLE (**1**, **2**, AND **3**) WITH A CARBOXYLIC ACID

substrate	oxalyldiazole	conditions solv	conditions temp/°C	product[a] (% yield[b])
Linoleic acid	**1**	$CHCl_3$	40	1-Linoleoylimidazole (89)
Sodium linoleate	**1**	DMF	60	1-Linoleoylimidazole (88)
Lithium linoleate	**1**	DMF	60	1-Linoleoylimidazole (74)
Linolenic acid	**1**	$CHCl_3$	40	1-Linolenoylimidazole (79[c])
Linoleic acid	**2**	$CHCl_3$	20	1-Linoleoyltriazole (82)
Sodium linoleate	**2**	DMF	30	1-Linoleoyltriazole (75)
Linoleic acid	**3**	$CHCl_3$	0	1-Linoleoyltetrazole (72)
Lithium linoleate	**3**	DMF	25	1-Linoleoyltetrazole (78)
Arachidonic acid	**3**	$CHCl_3$	0	1-Arachidonoyltetrazole (82[c])

a) Triazole and tetrazole refer to 1,2,4-triazole and 1,2,3,4-tetrazole, respectively. b) Isolated yield. c) Isolated yield of the methyl ester which was obtained in the treatment with methanol.

carboxylic acids. Since 1,1'-oxalyldiazoles **1**—**3** can be prepared safely from easily available reagents and work in the mild conditions almost same as 1,1-carbonyldiimidazole, the utilization of **1**—**3** is suggested to be more suitable for a large-scale experiment.

Experimental

General. IR spectra were recorded on a JASCO IR A-102 spectrometer. ^{1}H NMR spectra were measured on JEOL PMX-60Si and Fx-90Q instruments. GLC analyses were done on a Gasukuro Kogyo Model 370 instrument using a capillary column of PEG 20 M (0.25 mm×25 m). Elemental analyses were performed at the Analytical Center of Faculty of Agriculture in Nagoya University. 1*H*-Azoles were dried over P_2O_5 *in vacuo*.

A General Procedure for 1-Acylazoles ***4***—***6***. To a 1:1 mixture of a 1*H*-azole and *N,N'*-diisopropylethylamine in dry $CHCl_3$ or DMF (2—2.5 ml for 1 mmol) was added oxalyl dichloride (0.5 equiv), drop-by-drop, at −30—−10 °C. After 1—2h stirring, a fatty acid (or its salt) was added to the resulting mixture containing **1**, **2**, or **3**. This was stirred for 1 h at 0 °C, then warmed and maintained at an appropriate temperature for several hours. Three times the volume of petroleum ether or pentane was added to the solutions. A yellow-brown emulsion was separated into a colorless-yellow clear solution and a dark oil by centrifuge. Then, the oil was rinsed twice with the light petroleum. Concentration (40 °C, 6500 Pa) of the combined petroleum solutions yielded **4**—**6** as colorless-yellow oils. Bulb-to-bulb distillation of the oil gave an analytically pure sample.

1-Linoleoylimidazole[5] *(**4a**).* **4a** (89% (2.92 g) from linoleic acid, 88% (3.03 g) from sodium linoleate, 74% (0.28 g) from lithium linoleate): bp 230 °C (bath)/130 Pa; IR (neat) 1745 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$) 8.15 (1H, brs, H(C5) of imidazole), 7.43 (1H, dd, J=1.3 Hz, H(C2)), 7.08 (1H, m, H(C3)), 5.37 (4H, m, CH=CH), 2.82 (2H, m, =CCH_2C=), 2.05 (6H, m, CH_2C= and CH_2CO), 1.37 (16H, br, CH_2), 0.89 (3H, brt, CH_3).

Found: C, 76.53; H, 10.58; N, 8.23%. Calcd for $C_{21}H_{34}N_2O$: C, 76.31; H, 10.37; N, 8.48%.

*1-Linoleoyl-1,2,4-triazole (**5a**).* **5a** (82% (0.29 g) from linoleic acid, 75% (0.03 g) from sodium linoleate): bp 180 °C (bath)/130 Pa; IR (neat) 1760 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$) 8.90 (1H, s, H(C5) of triazole), 8.00 (1H, s, H(C3)), 5.37 (4H, m, HC=CH), 3.11 (2H, dd, J=7.2 Hz, =CCH_2C=), 2.78 (2H, brt, CH_2CO), 2.05 (4H, m, CH_2C=), 1.36 (14H, m, CH_2), 0.88 (3H, brt, CH_3).

Found: C, 72.21; H, 10.05; N, 12.41%. Calcd for $C_{20}H_{33}N_3O$: C, 72.46; H, 10.03; N, 12.68%.

*1-Linoleoyl-1,2,3,4-tetrazole (**6a**).* **6a** (72% (0.28 g) from linoleic acid, 78% (0.03 g) from lithium linoleate): bp 180 °C (bath)/7 Pa; IR (neat) 1770 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$) 9.28 (1H, s, H(C5) of tetrazole), 5.40 (4H, m, HC=CH), 3.33 (2H, dd, J=6.0 Hz, =CCH_2C=), 2.82 (2H, brt, CH_2CO), 2.1 (4H, m, CH_2C=), 1.4 (16H, m, CH_2), 0.93 (3H, brt, CH_3).

Found: C, 68.93; H, 9.85; N, 16.55%. Calcd for $C_{19}H_{32}N_4O$: C, 68.64; H, 9.70; N, 16.85%.

*Reaction of **4** with Methanol.* A mixture of **4**, which was prepared *in situ* or isolated, and 0.05 M *t*-C_4H_9OK/CH_3OH (0.5 ml for 1 mmol) was stirred at 25 °C for 6 h. A column of silica gel eluting with 5% ethyl acetate in petroleum ether gave **7**.

*Reaction of **5** and **6** with Methanol.* Methanol (0.5 ml for 1 mmol) was added to the solution of **5** or **6** prepared *in situ*. After 3—8 h at 25 °C, **7** was obtained by a silica-gel column.

*Methyl Linoleate (**7a**).* **7a** (93% from **4a**): IR (neat) 1740 cm^{-1} (C=O); ^{1}H NMR (CCl_4) 5.33 (4H, m, CH=CH), 3.66 (3H, s, CH_3O), 2.78 (2H, m, =CCH_2C=), 2.05 (6H, m, CH_2C= and CH_2CO), 1.35 (16H, br, CH_2), 0.90 (3H, brt, CH_3); GLC (170 °C) t_R=10.5 min (authentic sample[6] 10.5 min).

*Methyl Linolenate (**7b**).* **7b** (79% from linolenic acid): IR (neat) 1743 cm^{-1} (C=O). ^{1}H NMR (CCl_4) 5.35 (6H, m, HC=CH), 3.63 (3H, s, CH_3O), 2.79 (4H, m, =CCH_2C=), 2.4—1.9 (6H, m, CH_2CO and CH_2C=), 1.7—1.2 (10H, m, CH_2), 0.98 (3H, t, CH_3); GLC (170 °C) t_R=10.3 min (10.3 min[6]).

*Methyl Arachidonate (**7c**).* **7c** (82% from arachidonic acid): IR (neat) 1745 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$) 5.36 (8H, m, HC=CH), 3.68 (3H, s, CH_3O), 2.80 (6H, br, =CCH_2C=), 2.4—1.5 (6H, m, CH_2CO and CH_2C=), 1.3 (8H, br, CH_2), 0.89 (3H, brt, CH_3); GLC (185 °C) t_R=12.7 min (12.7 min[6]).

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