Tetrahedron Letters,Vol.30,No.23,pp 3073-3076,1989
Printed in Great Britain

0040-4039/89 $3.00 + .00
Maxwell Pergamon Macmillan plc

REACTION OF TRIMETHYLSILYL DERIVATIVES WITH MELDRUM'S ACID : A NEW AND EASY MONOFUNCTIONALIZATION OF MALONIC ACID

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Abstract : Treatment of Meldrum's acid with silylated derivatives (amines, lactams or alcohols) yields very easily monofunctionalized malonic silyl esters. Hydrolysis of these silyl esters leads to the corresponding monoacids with a very good yield.

The problem of the synthesis of monofunctionalized malonic acids (1) is still very up in the air.[1-3] Sometimes, it can be solved by heating Meldrum's acid (2) with nucleophiles.[4,5] This is often a difficult reaction because of the thermal instability of Meldrum's acid or the decarboxylation of the monofunctionalized malonic acid.[5] We now report on an easy access to this type of compound, by treatment of Meldrum's acid with silylated derivatives of lactams, amines and alcohols : these silylated products (3) have no nucleophilic properties,[6,7] and this new reaction can be related to the opening of some oxygenated heterocycles by silylated amines or amides (epoxides,[8] butyrolactone,[9] maleic anhydride, oxazolidinone[10] and diketene[11]), but the mechanism of these reactions is not always the same : our results on the opening reaction of Meldrum's acid by silylated compounds suggest that "a cyclic transition state is probable because of the availability of the silicon 3d-orbital, into which an electron pair (from an oxygen) can be donated", as it has already been postulated for the reaction of silylamides with aldehydes,[14] while in some other cases, the silicon compound was transformed into a nucleophilic amide ion, by using a sodium methoxide catalyst.[8,14]

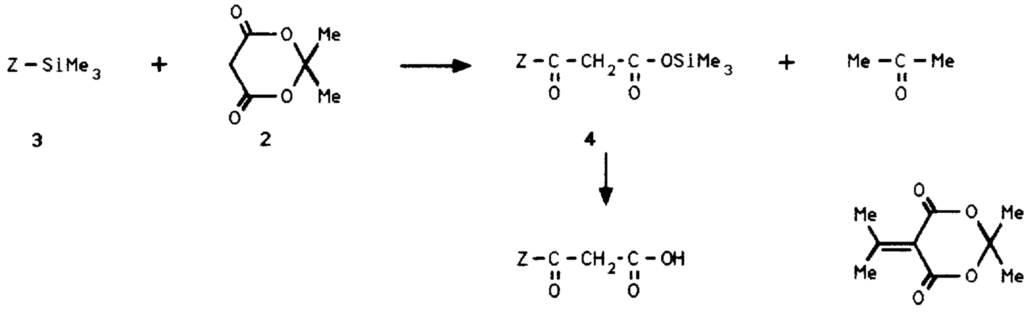
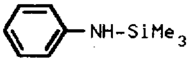
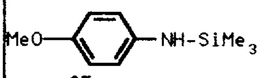
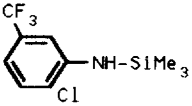
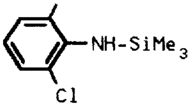
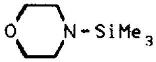
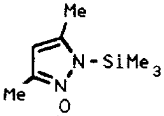
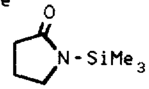
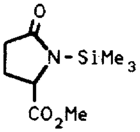
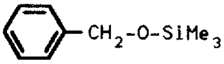
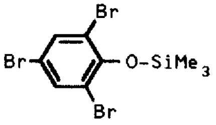


Table - Malonic acids derivatives

	Z-SiMe$_3$	Reaction Conditions		Yield of the acids 1 (%)	bp of the silyl esters 4 °C (mmHg)	mp of the malonic acids 1 (°C)
		t (hours)	T (°C)			
1		1	20	94[a]		137[b]
2		2	20	71		156
3		1.5	20	80		105
4		2	20	72		168
5		0.5	20	88		106
6	Me$_3$Si-NH-SiMe$_3$	0.5	20	78	76 (0.04)	49[c]
7		0.5	20	92[d]	120 (0.01)	
8		0.5	20	69[d]	114 (0.05)	
9		1.5	20	60[d]	130 (0.1)	
10	Me$_3$Si-O-SiMe$_3$	16	70	72[e]	44 (0.08)[f]	136[g]
11	Me-O-SiMe$_3$	5	60	77	78 (16)	80 (0.15)[h]
12		3	65	77	105 (0.1)	1.518[i]
13		4	80	65[j]		144

Satisfactory microanalyses obtained for new acids (C ± 0.4, H ± 0.4, N ± 0.4)

[a] Literature yield: 22% from malonic diester.[3] [b] Literature mp 134-136 °C.[3] [c] Literature mp 50 °C.[12] [d] Yield of silyl esters which were characterized by NMR. [e] 0.5% triflic acid as a catalyst. [f] Literature bp 63 °C (1).[13] [g] Literature mp 135-139 °C.[12] [h] bp of the acid °C (mmHg). [i] Index of refraction (n_d^{23}) of the acid. [j] 5% of ZnCl$_2$ as a catalyst.

Silylated amines and lactams (entry 1 to 9) reacted very easily with Meldrum's acid ; it was sometimes necessary to use a solvent (CH_2Cl_2) and a water bath at room temperature to avoid too exothermic a reaction and the spontaneous hydrolysis of the silylated esters (**4**) (by the traces of water contained in Meldrum's acid).[15] A limitation on this reaction was found with some silylated amines where a catalyzed condensation between acetone and Meldrum's acid gave compound 5.[11] Traces of this product were found in most of these reactions, and when silylated benzylamine and Meldrum's acid reacted in the usual way (CH_2Cl_2 solution), compound 5 was the main product, while the distillation of the reaction mixture obtained by performing the reaction under high vacuum conditions (to remove acetone) yield 85% N-benzylacetamide.

Silylated alcohols (entry 10 to 13) also opened Meldrum's acid when a mild heating was applied. With 2,4,6-tribromophenol, an acidic catalyst was necessary. Interestingly, even an absolutely non-nucleophilic compound like siloxane reacts in the presence of a catalytic amount of triflic acid.

In a typical experiment, silylaniline 3 (10 g, 69,4 mmol) was added via syringe through a septum cap to a solution of Meldrum's acid 2 (11.5g, 69.4 mmol) in 100 ml anhydrous CH_2Cl_2,[15] under nitrogen at room temperature. After one hour, the NMR yield was 100% : ^1H NMR ($CDCl_3$, 60 MHz) δ 0.32 (9H, s), 3.45 (2H, s), 6.81-7.69 (5H, m), 9.35 (1H, bs). MeOH (5 ml) was added to the solution of the silyl ester **4** and after 5 min the N-phenyl malonamic acid started to precipitate. The acid was washed with CH_2Cl_2, then with ether. The yield was 69%. Solvents were removed under reduced pressure, and crystallization of the residue augments the crude yield to 94% : ^1H NMR (acetone d_6, 60 MHz) δ 3.48 (2H, s), 6.90-7.70 (5H, m), 9.40 (1H, bs),[17] 10.20 (1H, s).[17,3]

From the results showns in the Table, it appears that the reaction is not sensitive to steric hindrance (entry 4, 13) and that monoprotected form (entry 12) or monoactivated form (entry 7, 13) of malonic acid can be easily obtained.

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(3) Entry 1 of the table : this acid was previously obtained with 22% yield from malonic ester : K. D. Paull , R. H. Boyd, J. L. Parson, P. A. Risbood, W. A. Barbera, M. N. Sharma, D. C. Baker, E. Hand, D. A. Scudiero, A. Monks, M. C. Alley and M. Grote, *J. Heterocyclic Chem.*, **25**, 911 (1988).

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(15) Methylene dichloride was dried on P_2O_5, then distilled ; Meldrum's acid was added and the solution was dried again by filtration on a neutral alumina column.

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(17) This peak disappears upon addition of deuterium oxide.

(Received in France 13 February 1989)