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A FACILE SYNTHESIS OF ACID-ESTERS

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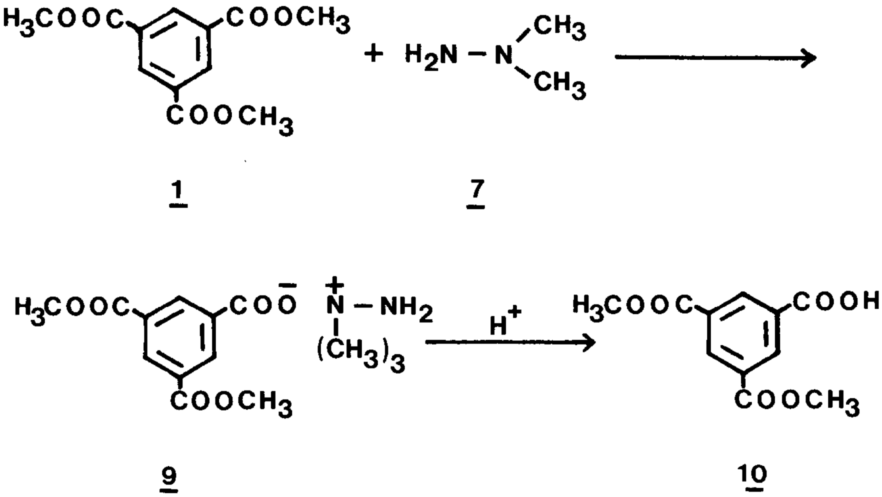
We have reported[1,2] that 1,1-dimethylhydrazine reacts with various dimethyl esters (vicinal and nonvicinal) to effect monodemethylation; providing a facile method for the synthesis of acid-esters.

This report is the result of our investigation on the monodemethylation of a series of polycarboxylates, shown in Table I. The selectivity of such demethylation – in the least hindered site – together with its significantly facile and high yield features provide a method to synthesize monoacid-polyesters and mixed esters not previously attainable.

The reaction of trimethyl 1,3,5-benzenetricarboxylate (1) with 1,1-dimethylhydrazine (7) (excess 7 at room temperature or under carefully controlled reflux temperature) is depicted as an example (Scheme 1).

Scheme 1

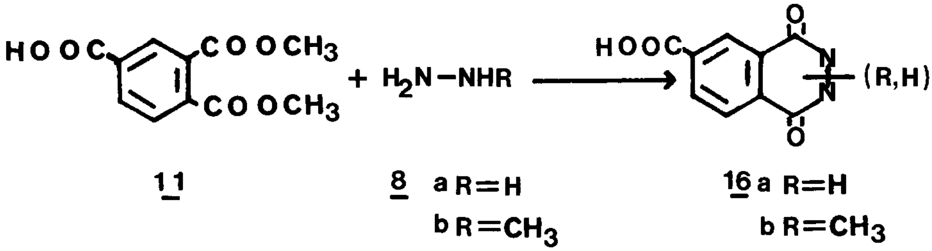


A general synthetic procedure for acid esters consists of the following steps: A mixture of 1:5 molar ratio of the polyester and 1,1-dimethylhydrazine was left at room temperature for 24-36 hours or heated under reflux for 6-12 hours (completion of the reaction was monitored by using TLC). The mixture was then evaporated *in vacuo*. After washing several times with CCl_4, the residue was collected to yield 75-90% of 1,1,1-trimethylhydrazinium salt of the acid-ester (characterized by using spectrometries). By adding 5% HCl, the salt was converted to the acid-ester in 80-90% yield. A mixture of benzene and methanol was used as a solvent for crystallization. For preparation of 15, due to its tendency to undergo a facile didemethylation, a slightly different procedure[7] was adopted.

In contrast to the possible formation of only one monodemethylated product from 1 or 5, those from 2, 3, 4 and 6 required unequivocal structure proof for the position of COOH.

The acid-ester from 2 was allowed to react both with hydrazine and with methylhydrazine (excess, at reflux temperature for 3 hours). The facile formation of benzopyridazines[3] (exemplified by 16a and 16b in Scheme 2), which could only result from 2 vicinal ester groups, led to the assignment of the structure dimethyl 4-carboxy-1,2-benzenedicarboxylate (11) to this product.

Scheme 2



For acid-ester from 3, similar reaction gave 5-carboxybenzopyridazines 17a and 17b to establish the structure as 12.

The acid-ester resulting from 6 was assumed to have the structure of trimethyl 4-carboxy-1,2,3-benzenetricarboxylate (15), analogous to 11 and 12 and the fact that its NMR spectrum depicted 2 conspicuously nonequivalent phenyl protons (2 peaks[6], δ=8.20 and 8.25).

The position of COOH group in the acid-ester from 4 was determined to be at 4 by the NMR spectral comparison (the 2 singlets with 2:1 ratio, ascribed to the $COOCH_3$ protons at positions 3 and 4 and at position 2 of the ester respectively, was collapsed to 2 singlets with 1:1 ratio in its acid-ester) and its amenability to react with 8b to give pyrrolopyridazine[3] (18) analogous to 17.

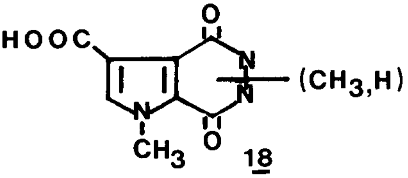
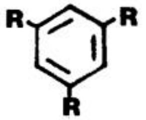
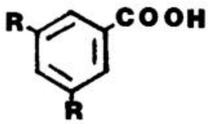
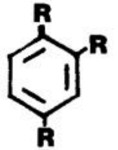
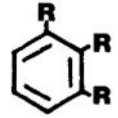
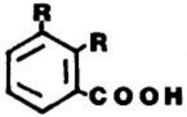
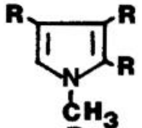
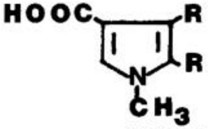
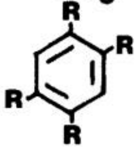
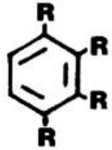


Table I. Yields and Physical Properties of the Acid-Esters

Starting Polyesters R=COOCH$_3$	Products Acid-Esters	Yield[a], %	Mp. °C (lit. Mp.)	IR(KBr), cm^{-1} C=O	NMR,δ,ppm(TFA-TTP)[b] CH$_3$	NMR,δ,ppm(TFA-TTP)[b] Ph
 1	 10	92	145-147	1690, 1730	4.10	9.08
 2	 11	73[c]	114-117[c] (115.5-117)	1690, 1720	4.08	7.70-8.80
 3	 12	80[d]	163-165[d] (162-163)	1690, 1730	4.04, 4.09	7.55-8.65
 4	 13	75	192-193	1670, 1715, 1740	3.90, 3.95, 4.0 (N-CH$_3$)	7.53 (Pyrrole)
 5	 14	75	108-111	1700, 1730	4.07	8.15, 8.45
 6	 15	70	129-131	1690, 1725	4.05	8.20, 8.25

[a] Partially purified over-all yield with Mp. lower than that of the analytical samples. [b] Solvent, trifluoroacetic acid (TFA); reference, sodium 2,2,3,3-tetradeutero-3-(trimethylsilyl) propionate (TTP); instrument, 60 Hz, NMR (not sensitive enough to resolve all phenyl proton peaks and splittings). [c,d] References 4 and 5 (the yields are 26% and 10% respectively).

Among the acid-esters shown in Table I only the synthesis of 11 and 12 have been reported[4,5]. The methods, however, were laborious and the yields somewhat poor (26% and 10% respectively).

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References and Notes

1. S. Kasina, K. Ng and J. Nematollahi, J. Pharm. Sci., 63, 1155 (1974).
2. J. Nematollahi and S. Kasina, J. C. S. Chem. Comm., 775 (1974).
3. Preliminary structure elucidation of the acid-esters and benzopyridazines was carried out by using IR, NMR, and Mass Spec. Additionally, compounds 10, 13, 17b and 18 were microanalyzed and compounds 14, 15, 16a, 16b, and 17a were analyzed by using high resolution mass spectrometry; providing satisfactory results. In the N-methylpyridazines fused to benzene or pyrrole, the position of CH_3 has not been determined.
4. R. Wegscheider, H. Perndanner, and O. Auspitzer, Monatsh. Chem., 31, 1267 (1910).
5. E. Wenkert, D. Johnston and K. Dave, J. Org. Chem., 29, 2534 (1964).
6. The expected splitting due to coupling of 2 nonequivalent protons (an A B system) was not observed, probably due to insufficient resolution power of 60 Hz NMR instrument.
7. For preparation of 15, it was necessary to modify slightly the general procedure. A 1:1.5 molar ratio of 6 and 7 was heated for 2 hours. The unreacted ester was separated by washing the reaction mixture with CCl_4. The residue was then treated as described above, (following Scheme 1).

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