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SHORT AND CONVENIENT SYNTHESIS OF TRIETHOXY-[^{2}H]METHANE AND ETHOXY-[^{2}H]METHYLENE MALONONITRILE

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SUMMARY

Triethoxy-deuteriomethane is synthesized simply from deuteriochloroform and monodeuterio-ethanol. The previously not described ethoxy-[^{2}H]methylene malononitrile can be prepared from the deuterated orthoester and dideuterio-malononitrile. Ring closure with acetamidine in ethanol yields 4-amino-5-cyano-2-methyl-[6-^{2}H]pyrimidine without any loss of deuterium label.

INTRODUCTION

Triethoxy methane and ethoxymethylene malononitrile are well known starting materials for the synthesis of thiamine (1) as well as a variety of heterocycles (2,3,4) . In the course of our studies of the mechanism of the cleavage of thiamine (5,6) we had the task to synthesize ethoxy deuteriomethylene malononitrile 2 . The undeuterated material is conveniently prepared from triethoxymethane and malononitrile (7). A previous publication describing

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the synthesis of triethoxy-deuteriomethane 1 started from trimethoxymethane (8). A three step reaction with methylmercaptane, butyllithium and deuteriohydrogenchloride, and finally zincchloride in ethanol should give the deuterated material in 37 % overall yield. Besides an important wrong indication of the reaction temperature [a] in the exchange reaction with butyllithium, however, the zincchloride catalyzed substitution of the methylmercaptogroups with ethanol resulted - at least in our experiments - in a loss of deuterium to give only a 78 % deuterated product 1.

RESULTS

To get a higher labelled orthoester we tried the simple and well known triethoxymethane synthesis from deuteriochloroform and sodium ethoxide (9). But the procedure described in Organic Synthesis using sodium ethoxide in ethanol resulted in a 55% loss of deuterium label. Our other attempts using ethanol-free sodium ethoxide in toluene or ether (10) yielded surprisingly again only low deuterated material. This deuterium loss can only be explained by an exchange reaction with an ethyl hydrogen of either orthoester or ethanolate. Finally we succeeded with a modified and optimised procedure using monodeuterio ethanol and deuterio- chloroform. It was not possible however to separate the deuterated product 1 directly from the excess ethanol by means of distillation from the reaction mixture in more than 5 % yield. Surprisingly, the completely analogous reaction with undeuterated material had yielded several times about 25% pure orthoester. An aqueous workup solved the problem to separate the excess of deuterioethanol

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[a] Two attempts to run the reaction as indicated (8) at -25 to -30°C led to very impure product. The same reaction carried out at -35 to -40 °C yielded the desired trithiomethoxy deuteriomethane without any problems.

Table 1. Optimation of the yield of deuteriotriethoxymethane 1

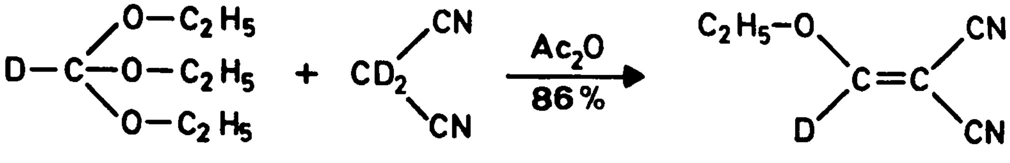
Test	C_2H_5OD		Na	$CDCl_3$		Yield[c]	
	(ml)	(mol)	(mol)	(g)	(mol)	(g)	(%)
1	50	0.86	0.15	16.87	0.14	1.98	10
2	50	0.86	0.21	8.43	0.07	1.03	10
3[a]	25	0.43	0.21	25.30	0.21	4.90	15
4	50	0.86	0.15	8.43	0.07	1.67	16
5[b]	50	0.86	0.30	16.87	0.14	3.56	17
6	50	0.86	0.30	16.87	0.14	4.23	20
7	50	0.86	0.30	16.87	0.14	4.53	22
8	50	0.86	0.45	16.87	0.14	6.39	31

[a] These concentrations led to a 20 % loss of deuterium label

[b] At first formation of sodium ethoxide and than addition of chloroform.

[c] Yield based on deuterio-chloroform; the yield of the Organic Synthesis procedure (9) was 27 -31 % .

from 1 satisfactory. This way is simple, cheap and convenient. The table shows some results using different ratios of reagents. Version 8 seems to be the upper concentration limit of sodium and chloroform yielding 31% orthoester. Higher concentrations of chloroform in ethanol led again to a partial loss of deuterium label (version 3).



1

2

Reaction of orthoester 1 with undeuterated malononitrile to form ethoxy deuterio-methylene malononitrile 2 led surprisingly again to a loss of about 18 % of deuterium label. Therefore deuterated malononitrile (11), which can be made simply by exchange in D_2O was used to give finally a 96 % deuterium labelled 2 . Ring closure of 2 with acetamidine led to 4-amino-5-cyano-2-methyl- 6-^{2}H - pyrimidine[1] without any loss of deuterium.

EXPERIMENTAL

Triethoxy-[^{2}H]methane 1

To a cooled solution of mono deuterio-ethanol (50 ml, 0.86 mol,99% D) and deuterio-chloroform (16.9 g, 0.14 mol, 99.8% D) in a dry 100-ml flask fitted with a magnetic stirrer, a condenser and a drying tube are added successively clean pieces of sodium (10.35 g, 0.45 moles) . After 12 hours the reaction mixture is poured into a solution of sodium hydrogencarbonate (4g) in water (100ml). The mixture is extracted twice with n-hexane (60ml). The organic layer is dried over magnesium sulfate and the hexane is removed by gentle distillation, otherwise there is a notable loss of orthoester. The residue is fractionated through a short Vigreux column and the fraction boiling at 142-145^0 is collected; yield: 6.39 g (31 %; 96 % D estimated by a 200MHz ^{1}H-NMR spectrum).

Ethoxy-[^{2}H]methylene malononitrile 2

In a dry 50-ml round-bottomed flask fitted with a condenser and a drying tube deuterio-malononitrile (11) (1.82 g, 27.6 mmol) , deuterioorthoester 1 (6 g, 39 mmol) and acetic anhydride (6.71g, 76.2 mmol) are refluxed for 6.5 hours. The reaction mixture is then evaporated and the dark residual solid is first washed with hexane, then with ice cold ethanol (3ml). The grade of deuteration is 96-97 % ; yield: 2.42 g (86 %) mp.: 69-71^0.

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REFERENCES

1. Grewe R.- Hoppe-Seylers Z. physiol. Chem. 242: 89 (1936)
2. DeWolfe R.H.- Carbocyclic Ortho Acid Derivatives, Academic Press, New York, 1970
3. Freeman F.- Synthesis 1981: 925
4. Schmidt H.-W., Schipfer R. and Junek H.- Liebigs Ann. Chem. 1983: 695
5. Zoltewicz J.A., Kauffman G.M. and Uray G.- Ann. New York Acad. Sci. 1982: 7
6. Uray G., Kriessmann I. and Zoltewicz J.A.- J. Org. Chem. 49: 5018 (1984)
7. Jones R.G.- J.Am.Chem.Soc. 74: 889 (1952)
8. Eliel E.L., Hartmann A.A. and Abatjoglou, A.G.- J.Am.Chem. Soc.96: 1807 (1974)
9. Kaufmann W.E. and Dreger, E.E.- Organic Syntheses 5: 55 (1925)
10. Castells J. and Soler J.- An. Quim. 65: 685 (1969); Chem.Abstr. 72: 31179f.
11. Hirota E. and Marino, Y.- Bull. Chem. Soc. Japan 33: 158 (1960)