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N,N-DIETHYLAMINOACETONITRILE
A GENERALLY USEFUL LATENT ACYL CARBANION

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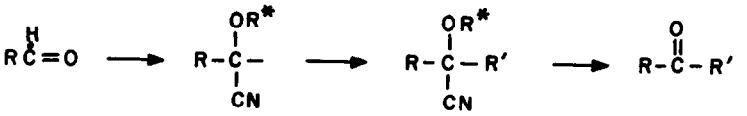
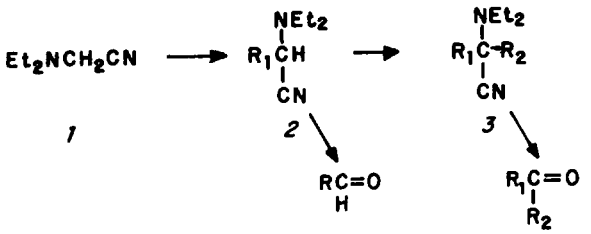
The protected cyanohydrin sequence for the transformation of an aldehyde into a ketone[1] by the alkylation of a latent acyl carbanion has proved useful.



The method is, however, not universal. It fails in the case where R=H, because the ethers of the cyanohydrin of formaldehyde self-condense during anion formation.

We anticipated that the self-condensation reaction could be prevented by increasing the steric hindrance around the carbanion center of the heterosubstituted nitrile. This should be easily achieved by changing the alpha substituent in the nitrile from a monosubstituted oxygen to a disubstituted nitrogen. This expectation has been fulfilled, and we now report that N,N-diethylaminoacetonitrile[2] serves as an excellent latent formaldehyde anion[3], thus permitting the easy transformation of an alkyl halide to the homologous aldehyde. Sequential alkylation with two different halides naturally leads to ketones[4].



These transformations can also be done with dithiane anions[5], rather than diethylaminoacetonitrile, but the latter has unique properties which may make it preferable in a given situation. N,N-diethylaminoacetonitrile is a much more economical starting material than dithiane; the second alkylation to generate a ketone can be done by Michael addition rather than alkylation (dithiane anions do not normally undergo conjugate addition) and alkylation can be done with secondary halides such as cyclohexyl bromide, whereas the dithiane anion leads to elimation to cyclohexene.

One other feature of considerable potential interest is that it is pos-

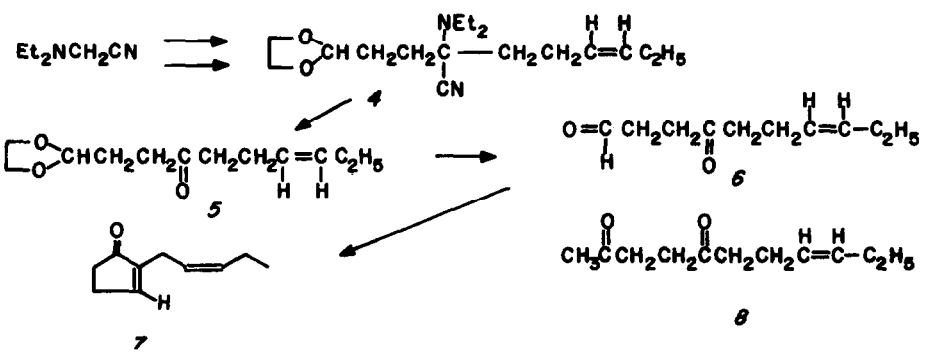
sible to liberate a ketone from its α-diethylaminonitrile equivalent under conditions which do not affect an acetal. These various features are illustrated in the representative syntheses below.

General Procedure for Alkylation

1) Synthesis of aldehydes. N,N-diethylaminoacetonitrile in tetrahydrofuran was added at -78°C to 1 equiv of lithium diisopropylamide in THF to which had been added ∿ 1 equiv of hexamethylphosphoramide. Addition of 1 equiv of 1-iodooctane and work up after 1 hr gave the alkylated aminonitrile 2 R = octyl, b.p. ∿ 87° (0.09 mm) in 90% yield. Hydrolysis by refluxing with equal volumes of 30% aqueous oxalic acid and THF[6] for ten min gave nonanal in essentially quantitative yield (vpc comparison and 2,4-dinitrophenylhydrazone).

2) Synthesis of ketones. Ketones are readily accessible by the alkylation of monosubstituted dialkylaminoacetonitriles which arise either as shown in 1→2 above, or by synthesis from an aldehyde. The dimethylamino analog of 2 (from the appropriate aldehyde, dimethylamine hydrochloride and alkali cyanide) is particularly convenient in that case.

When the dialkylated aminonitrile 3 is made starting with N,N-diethylaminoacetonitrile, the isolation of the monoalkylation product is unnecessary. We give an example which also illustrates the use of 3-haloacetal to give a 1,4 keto aldehyde. Alkylation was conducted, exactly as above, with 1 equiv of 3-(2-bromoethyl) dioxolane. After 1 hr at -78°C and ½ hr at room temperature, the solution was transferred (through a steel needle) to a flask containing another equiv of lithium diisopropylamide in the usual THF-HMPA solution at -78°C, and this was followed by 1 equiv of cis 3-hexenyliodide. Isolation after a final hour at room temperature, gave the crude amino nitrile 4 which was hydrolyzed to the keto acetal 5 by refluxing 1 hr with 2.5 equiv of $CuSO_4 \cdot 5\ H_2O$ in 95% ethanol[7]. This procedure was used for all ketone syntheses. It is noteworthy that it allows retention of an acetal function[8]. Conversely,

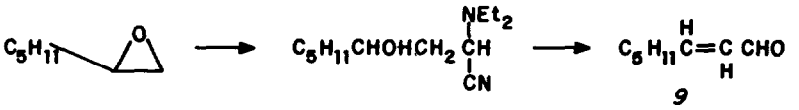


disubstituted aminonitriles are stable to the aqueous oxalic acid conditions which (vide supra) are usually satisfactory for aldehyde generation from the monosubstituted aminonitriles. It would thus seem possible to generate carbonyl groups independently of one another in substances in which they might be stored as acetal, alkoxynitrile or aminonitrile functions.

Completion of the hydrolysis of the isolated ketoacetal 5 was effected by the oxalic acid procedure (30 min reflux), thus producing the ketoaldehyde 6 in 83% overall yield. The structure of 6 was proved by conversion to the known cyclopentenone 7 (two phase system of 1% sodium hydroxide-ether, 3 days at room temperature, 91% yield)[9].

The second alkylation can also be done by Michael addition: Sequential alkylation, exactly as above, first with cis 3-hexenyl iodide, and then with methyl vinyl ketone, gave, after the copper sulfate hydrolysis, 72% overall yield of the known cis undec-8-en-2,5-dione (8)[10]. Although bromides and iodides are most effective in these alkylations, chlorides or tosylates can also be used: 1,5-dichloropentane gave (4 hr at 0°C) a 73% yield of the cyclic bis-alkylation product, 1-N,N-diethylaminocyclohexanecarbonitrile (convertible into cyclohexanone as usual).

We draw attention to the fact that in addition to alkylation with alkyl halides and Michael acceptors, epoxides can be used, thus leading to α,β-unsaturated aldehydes with one more carbon than the epoxide: Addition of the epoxide of 1-heptene to the lithium salt prepared as above (3 hr, 0°), followed by refluxing with aqueous methanolic oxalic acid for 20 min gave, in 50% yield, trans 2-ocetenal (9). Styrene oxide similarly gave cinnamaldehyde in 65% yield.



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We conclude by comparing diethylaminoacetonitrile with the protected cyanohydrins in the synthesis of carbonyl compounds. The cyanohydrin method must be used for the alkylation of α,β-unsaturated aldehydes (RC=CCHO→ RC=CCR'). It is also useful when the final cyanohydrin is chemically equivalent to what would be an unstable ketone and can thus be used in its place for a subsequent step. Either method can be used for the alkylation of an aldehyde to a ketone, but only the diethylaminoacetonitrile method is suitable for the transformation alkyl halide → homologous aldehyde, or for ketone synthesis involving sequential dialkylation.

Acknowlegement: We thank the National Science Foundation and the Petroleum Fund of the American Chemical Society for the support of this work.

References and Notes

1. G. Stork and L. Maldonado, J. Am. Chem. Soc., 93, 5286 (1971).
2. Organic Synthesis Coll. Vol. III, John Wiley and Sons, New York, N.Y. 1955, p. 275.
3. There is essentially no self-condensation with α-unsubstituted dialkylaminoacetonitriles derived from diethylamine or its homologs. With dimethylaminoacetonitrile, about 50% of the aminonitrile undergoes self-condensation, although it is still possible to achieve monoalkylation in 50% yield with primary iodides (Takashi Takahashi, unpublished work in this laboratory).
4. There has been no previous report of the monoalkylation or sequential dialkylation of formaldehyde via dialkylaminoacetonitriles. Some success was achieved (Z.Welvart, Bull. Soc. Chim. France, 1653 (1961) in the alkylation of aminonitriles derived from aliphatic aldehydes, but the lack of generality of the method has restricted its use to a few cases in which the aminonitriles were derived from aromatic and heterocylic aldehydes: See, inter alia, C.R. Hauser, H.M. Taylor and T.G. Ledford, J. Am. Chem. Soc., 82, 1976 (1960); E. Leete, M.R. Chedekel and G.B. Bodem, J. Org. Chem., 37, 4465 (1972); E. Leete, J. Org. Chem., 41, 3438 (1976).
5. Cf. D. Seebach and E.J. Corey, J. Org. Chem., 40, 231 (1975).
6. Cf. L.N. Mander and J. V. Turner, J. Org. Chem., 38, 2915 (1973).
7. Cf. G. Büchi and H. Wüest, J. Am. Chem. Soc., 96, 7573 (1974); Tetrahedron Lett., 2763 (1978).
8. Carbonyl liberation can also be done simply by silica gel chromatography (30 x weight of aminonitrile and elution with 80-20 hexane-ether). This transformed the monoalkylated dialkylaminoacetonitriles into the corresponding cyanohydrins. The latter are easily converted to the corresponding aldehydes with dilute base. The same silica gel procedure transforms α-disubstituted aminoacetonitriles directly into ketones. The process may be useful to liberate carbonyl compounds which contain acid-sensitive groups.
9. This cyclopentenone is an important intermediate toward either methyl jasmonate or cis jasmone: G. Büchi and B. Egger, J. Org. Chem., 36, 2021 (1971); P.A. Grieco, ibid 37 2363 (1972); A. I. Meyers and N. Nazarenko, ibid., 38, 175 (1973); K. Oshima, H. Yamamoto and H. Nozaki, J. Am. Chem. Soc. 95, 4446 (1973).
10. The structure of this 1,4-diketone (Cf. G. Stork and R. Borch J. Am. Chem. Soc., 86, 936 (1964) was confirmed by cyclization to cis jasmone.

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