2-(2,6-DIMETHYLPIPERIDINO)ACETONITRILE AS AN ACYL CARBANION EQUIVALENT

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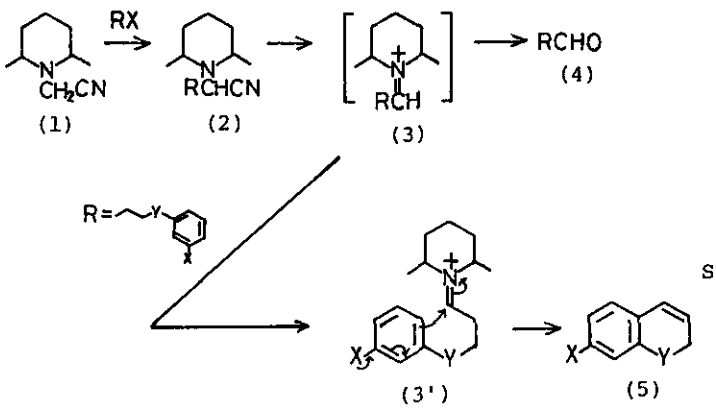
Abstract — Reaction of lithio 2-(2,6-dimethylpiperidino)acetonitrile with alkyl halides affords monoalkylation products which are easily hydrolyzed under mild conditions to give the homogeneous aldehyde or its acetal in moderate yield. In the case of alkyl halides having an electron donating group on aromatic ring the cyclization products are obtained.

One carbon elongation for the transfomation of alkyl halide into an aldehyde is a very useful sequence in organic synthesis.[1] In 1978, Stork and his coworkers[2] reported that N,N-diethylaminoacetonitrile as a latent acyl carbanion equivalent was more useful than the protected cyanohydrin of formaldehyde for the preparation of aldehydes and ketones.

In this communication, we wish to describe the details of our own results in this area which provided a convenient method for the preparation of an aldehyde(4) and an aromatic compound(5) via the iminium intermediate(3') (Scheme 1).



Scheme 1

2-(2,6-Dimethylpiperidino)acetonitrile(1)[3] which could be expected to increase the steric hindrance around the carbanion center was selected as a substrate with the reason for preventing the self-condensation reaction of aminoacetonitrile during anion formation.

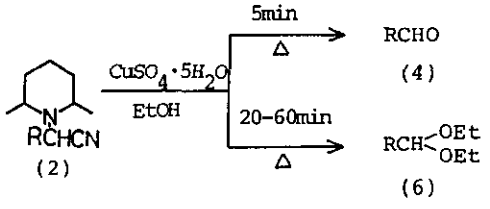
The features of the entitled compound are demonstrated in the following; a) The reagent[4] is readily available from condensation of 2,6-dimethylpiperidine and chloroacetonitrile; b) The alkylation followed by hydrolysis can be run with one pot operation; c) The hydrolysis of alkylated products can also be done under mild conditions.

The results for formation of an aldehyde and its acetal obtained in this way are compiled in Table 1.

Table 1 Preparation of Aldehyde and Its Acetal

entry	halide	product (% yield)	% of its acetal (6)
1	$C_6H_5(CH_2)_3Br$	$C_6H_5(CH_2)_3CHO$ (66)	45
2	$CH_3C(Me)_2CH_2CH(Me)(CH_2)_2Br$	$CH_3C(Me)_2CH_2CH(Me)(CH_2)_2CHO$ (42)	46
3	$CH_3(CH_2)_7Br$	$CH_3(CH_2)_7CHO$ (33)	48
4	$C_6H_{11}(CH_2)_2Br$	$C_6H_{11}(CH_2)_2CHO$ (45)	47

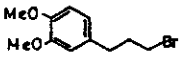
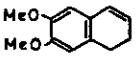
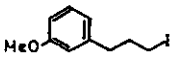
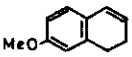
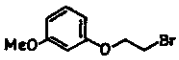
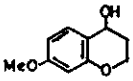
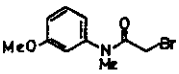
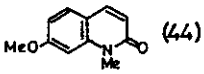
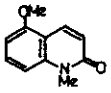
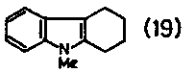
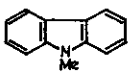
When the hydrolysis of monoalkylated aminoacetonitrile(2) with $CuSO_4 \cdot 5H_2O$ in ethanol[5] was carried out upon shorter reaction times(reflux,ca.5min), the corresponding aldehydes(4) were only obtained. On the other hand, the prolonged heating(20-60min) for the hydrolysis led exclusively to its acetals(6) in moderate yield (Table 1 and Scheme 2).



Scheme 2

Similarly, treatment of alkyl halides having electron donating group on aromatic ring with lithio derivative of (1) gave directly the cyclization products(5)[6] but none of the aldehydes could be observed among the reaction products (Table 2).

Table 2 Reaction of alkyl halides containing electron donating group on aromatic ring with 2-(2,6-dimethylpiperidino)-acetonitrile

entry	halide	product[a] (% yield)
1		 (70)
2		 (61)
3		 (30) *
4		 (44)  (21)
5		 (19)  (20)

a Hydrolysis was carried our upon heating unless otherwise cited.

* Hydrolysis was run at room temperature.

General procedure for alkylation and hydrolysis is described in the following.

Synthesis of 4-phenylbutanal

To a solution of lithium diisopropypamide(6.8mM) in THF was added slowly at -78°C 2-(2,6-dimethylpiperidino)acetonitrile(716mg,5mM) in 5 ml of THF and the mixture was stirred at -78°C for 30 min. After the addition of phenylpropyl bromide(1.10g, 5.5mM) in THF-HMPA(1:1,20ml) to this solution, the whole mixture was stirred at room temperature for 15 h. Removal of the solvent in vacuo and heating for 5 min with $CuSO_4 \cdot 5H_2O$(1.25g,5.0mM) in 20 ml of ethanol gave 4-phenylbutanal(489mg,66%) after purification by chromatography on silica gel.

Synthesis of 6,7-dimethoxy-1,2-dihydronaphthalene

To a solution of lithium diisopropylamide(0.7mM) in THF was slowly added at -78°C 2-(2,6-dimethylpiperidino)acetonitrile(110mg,0.7mM) in 3 ml of THF. After an additional stirring at the same temperature for 25 min, HMPA(0.1ml,0.64mM) and then 3,4-dimethoxyphenylpropyl bromide(150mg,0.58mM) in THF were added. The mixture was stirred at -78°C for 2 h. After evaporation of the solvent, hydrolysis was carried out on heating with equal volumes of 30% aqueous oxalic acid in THF[7] (3ml/3ml) for 15 min to give 6,7-dimethoxy-1,2-dihydronaphthalene(77mg,70%), mp 44.5-45.5°C.

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REFERENCES AND NOTES

1. For dithian anion see, D. Seebach and E.J. Corey, J. Org. Chem., 40, 231(1975).
2. G. Stork, A.A. Ozorino, and A.Y.W. Leong, Tetrahedron Lett., 5175(1978). Some success was reported on the alkylation of α-aminoacetonitriles; Z. Welvart, Bull. Soc. Chim. France, 1653(1961). Recent reports on the applications of the α-aminoacetonitriles have appeared; H. Ahlbrecht and K. Pfaff, Synthesis, 897 (1978); G. Stork, R.M. Jacobson, and R. Levitz, Tetrahedron Lett., 771(1979); H. Reutrakul, P. Patananukul, and S. Nimgirawath, Chem. Lett., 71(1980). The reaction of α-aminoacetonitriles derived from aromatic and heterocyclic aldehydes is also reported; C.R. Hauser, H.M. Taylor, and T.G. Ledford, J. Am. Chem. Soc., 82, 1979(1960); E. Leete, M.R. Chedekel, and G.B. Bodem, J. Org. Soc., 37, 4465(1972); S.F. Dyke, E.P. Tily, A.W.C. White, and D.P. Gale, Tetrahedron, 31, 1219(1975); E. Leete, J. Org. Chem., 41, 3438(1976); F.J. McEvoy and J.D. Albright, J. Org. Chem., 44, 4597(1979); V. Reutrakul, S. Nimgirawath, S. Panichanun, and P. Patananukul, Chem. Lett., 399(1979).
3. Second alkylation of monoalkylated piperidinoacetonitrile(2) is not accessible. In the case of pyrrolidinoacetonitrile, alkylation of the corresponding carbanion even with 1 equiv. of alkyl halides gave exclusively dialkylated products.
4. F. Hoffmann-La Roche and Co., Chem. Abstr., 2960h(1965).
5. G. Büchi and H. Wüest, J. Am. Chem. Soc., 96, 7573(1974); G. Büchi, P.H. Liang, and H. Wüest, Tetrahedron Lett., 2763(1978).
6. This reaction sequence represents that the carbon atom next to amino-substituted nitrile served concurrently as nucleophile plus electrophile. For a similar reaction sequence see, Y. Oikawa and O. Yonemitsu, Tetrahedron, 30, 2653(1974).
7. L.N. Mander and J.V. Turner, J. Org. Chem., 38, 2915(1973).

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