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C-C - CONNECTIVE SYNTHESIS OF α-DIALKYLAMINO - KETONES FROM ALDEHYDES AND SEC.-AMINES

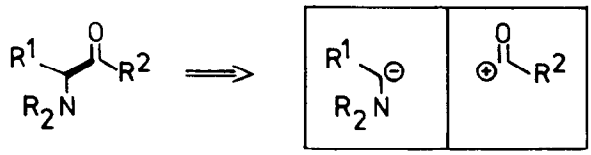
Dieter Enders[★] *and Hermann Lotter*

Institut für Organische Chemie und Biochemie, Rheinische Friedrich - Wilhelms - Universität
Gerhard - Domagk - Str. 1, D-5300 Bonn, Germany

Summary: A simple and efficient 3 - step synthesis of α-dialkylamino - ketones 3 starting from aldehydes and sec.-amines is described. The unsymmetrically aminoketones are obtained as pure regioisomers via reaction of metalated α-aminonitriles 1 with aldehydes, followed by thermal HCN-elimination/tautomerization.

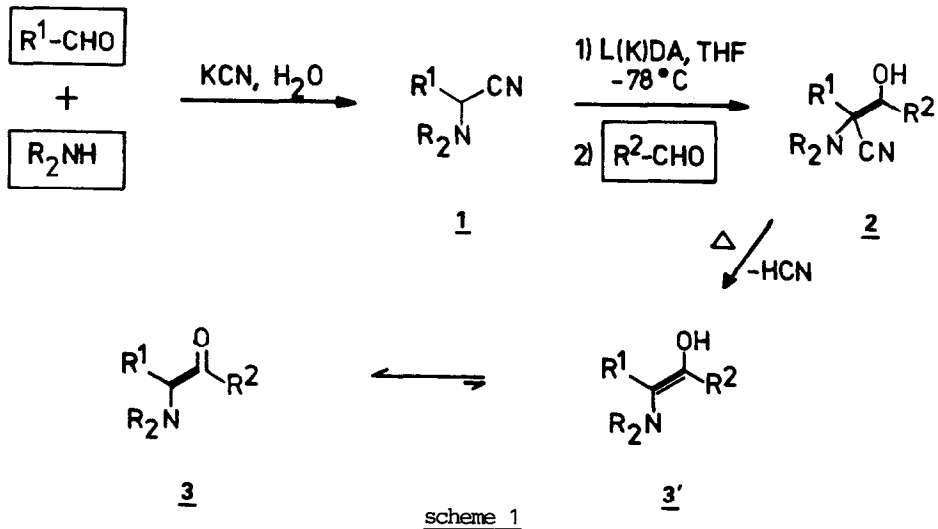
α-Aminoketones of the general structure A constitute an important class of compounds in preparative organic chemistry[1] and as biologically significant substances[2]. They are valuable starting materials of N - containing heterocycles, diamines, and aminoalcohols, such as biologically active ethanolamines. Although many routes to these compounds, for instance the reaction of α-haloketones with amines[1], the Dakin - West - reaction[3], the Neber - rearrangement[4], etc.,have been described, most of these methods are not generally applicable and/or suffer from unsatisfactory yields, inaccessible starting materials, and lack of regioselectivity[1].

From the retrosynthetic point of view, α-aminoketones A should in principle be obtainable via C-C bond formation using an α-aminocarbanion synthon B and an acylcation synthon C.



A **B** **C**

It turned out, that indeed such a process is possible, and we now report a simple and efficient 3-step synthesis of α-dialkylamino ketones starting from easily accessible aldehydes and sec.-amines. As is shown in scheme 1, the procedure involves the transformation of an aldehyde and a sec.-amine into the corresponding α-aminonitrile 1[5], followed by metalation with lithium (or potassium) diisopropylamide (LDA or KDA) in tetrahydrofuran at -78°C (0.5 - 5h) and addition of a second aldehyde. During distillation of the adducts 2,[6] formed in very good yields, HCN-elimination occurrs and the resulting aminoenol - forms 3' immediately tautomerize to the desired α-aminoketones 3[7].

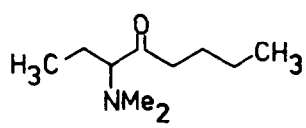


1 2 3 3'

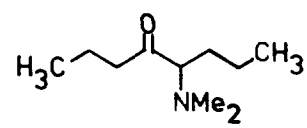
scheme 1

Thus, the deprotonated α-aminonitriles function as equivalents of B, already demonstrated by Stork et al., and the aldehydes R^2CHO as equivalents of acylcations C. Since the reaction of metalated α-aminonitriles with aldehydes can alternatively be used to prepare aminoalcohols[8] or α-hydroxyketones[9], this new route again enlarges the already great synthetic potential of these compounds[10].

One major advantage of the method described above is the possibility to prepare α-dialkylamino derivatives of unsymmetrically ketones as pure regioisomers simply by synthon control. This may be demonstrated by the synthesis of the two regioisomers 3-dimethylamino-(3b) and 5-dimethylamino-octanon-4 (3c), starting from dimethylamine and either n-propanal/n-pentanal or two equivalents of n-butanal as building blocks in 67% and 60% yield respectively.



3b



3c

In all cases the HCN-elimination was quantitative and took place in the desired direction. The pure aminoketones, prepared in this way in good over all yields, are summarized in the table[11].

In the case of optically active 3g the diastereomeric excess was low(de = 15%, NMR)[12]. With cinnamonaldehyde exclusively 1.2-addition occurred leading to 3h in excellent over all yield.

Further development of the skope of this method and the analogous procedure using metalated α-cyanohydrines are now in progress.

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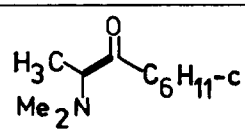
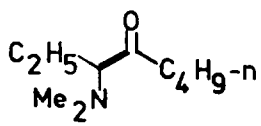
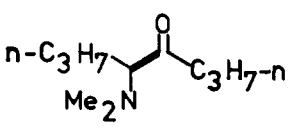
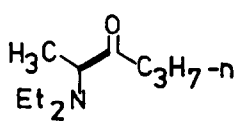
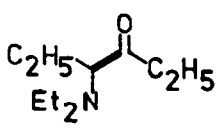
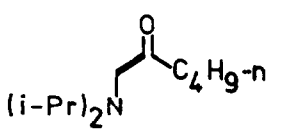
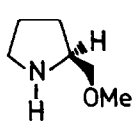
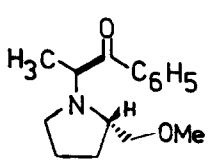
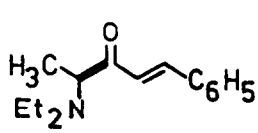
Table. α - Dialkylamino - ketones 3 prepared from aldehydes and sec. - amines

	R^1-CHO	R^2-CHO	R_2NH	3	b.p.[°C,torr][a]	yield[%][b]
a	H_3C-CHO	c-C_6H_{11}-CHO	Me_2NH		96-97/5[c]	72[d] (95)
b	C_2H_5-CHO	n-C_4H_9-CHO	Me_2NH		72-73/10	67 (85)
c	n-C_3H_7-CHO	n-C_3H_7-CHO	Me_2NH		68-69/8	60 (84)
d	H_3C-CHO	n-C_3H_7-CHO	Et_2NH		78/15	75 (89)
e	C_2H_5-CHO	C_2H_5-CHO	Et_2NH		67-68/15	d,e 55 (71)
f	H-CHO	n-C_4H_9-CHO	$(i\text{-}Pr)_2NH$		102-104/12	44[d] (56)
g	H_3C-CHO	C_6H_5-CHO			115/0.1[f]	81 (85)
h	H_3C-CHO	C_6H_5-CH=CH-CHO	Et_2NH		105-106/0.2	79 (90)

a) Distillation over a 10 cm Vigreux - column. - b) Yield of distilled pure (97-99%, capillary-gc) aminoketones 3 based on 1; yield of crude adducts 2 in parenthesis. - c) Lit.:[13] 220 - 240 °C. - d) Yield after a second Kugelrohr - distillation. - e) Contains ca. 3% 1e (gc). - f) Oven temperature during Kugelrohr - distillation.

References and Notes

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2) For a recent synthesis of α-aminoalkyl-aryl-ketones from α-amino acids see: T.F.Buckley III and H.Rapoport, J.Am.Chem.Soc. 103, 6157(1981).

3) W.Steglich and G.Höfle, Angew.Chem. 81, 1001(1969) and lit. cited therein.

4) C.O'Brien, Chem.Reviews 64, 81(1964).

5) The aminonitriles were prepared as follows: 1. $R_2NH \cdot HCl/H_2O$ 2. KCN/H_2O, 0°C 3. 1.1 equiv. R^1CHO, 2h, 25°C(yields after distillation: 72 - 92%); 1f was obtained via the bisulfite adduct: 1. $R^1CHO/NaHSO_3/H_2O$, 25°C - 1h, 50°C 2. R_2NH, 25°C - 5h, 70°C 3. KCN/H_2O, 5h,70°C; 12h, 25°C(76%).

6) To prevent any aminonitril hydrolysis to the corresponding α-hydroxyketones[9], mild work up conditions were used: quenching at -78°C with sat.NH_4Cl-solution, work up of the cold mixture with ether, drying over $Na_2SO_4/MgSO_4$(30 min) and concentration under inert gas. All compounds 2 were characterized by ^{1}H-NMR- and IR-spectra.

7) The formation of an α-aminoketone after distillation of the adduct of metalated N-methyl-N-phenylamino-acetonitrile and benzaldehyde was reported in 1976, C.Vonderheid, Dissertation, Universität Giessen; Prof.Ahlbrecht, Giessen, private communication, 1981.

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11) The spectroscopic data(NMR,IR,MS) and elementary analyses of all new compounds are in agreement with the structures given.

12) Metalated α-aminonitriles of type 1g can be used as chiral d^1-reagents in asymmetric nucleophilic acylations; D.Enders and H.Lotter, to be published.

13) T.Thomson and T.S.Stevens, J.Chem.Soc. 1932, 2608.

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