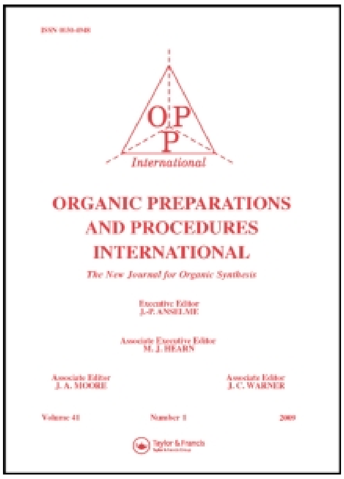

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FUNCTIONAL GROUP TRANSFORMATION. CONVERSION OF ALDEHYDES INTO AMIDES *via* α-CYANOENAMINES

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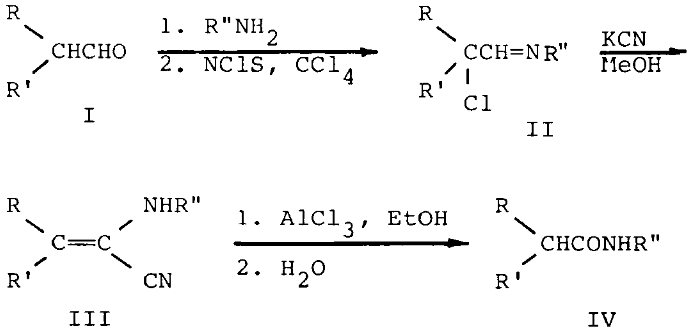
The conversion of aldehydes into amides is a potentially useful synthetic operation which can be performed by oxidation to a carboxylic acid followed by amidation *via* esters[1] or carboxylic acid halides. A number of oxidation reactions have already been developed[3] but this step in many cases limits the applicability of the sequence outlined above since oxidation often leads to side-products. Direct transformations of aldehydes into amides are limited to N-unsubstituted amides[4,5] and N-monosubstituted benzamide derivatives.[6,7]



(1)

We now report a convenient and mild synthesis of aliphatic N-monosubstituted amides IV starting from aliphatic aldehydes I. The method consists of treatment of α-cyanoenamines III with anhydrous aluminium chloride in absolute ethanol (reflux overnight).

TABLE I. Synthesis of Amides IV from α-Cyanoenamines III

	R	R'	R"	Reagent	Yield[a]	mp.[b] (lit. mp.)
IVa	Me	Me	Me	$AlCl_3$/EtOH	78 %	20° (20°)[9]
IVb	Me	Me	Me_2CH	$AlCl_3$/EtOH	80 %	104-105° (102°)[11]
IVc	Me	Me	Me_3C	$AlCl_3$/EtOH	86 %	118-119° (118-120°)[12]
IVd	Me	Et	Me_3C	$AlCl_3$/EtOH	83 %	114-115° (110-111°)[13]
IVd	Me	Et	Me_3C	$ZnCl_2$/EtOH	79 %	114-115° (110-111°)[13]
IVd	Me	Et	Me_3C	HCl/EtOH[d]	92 %	114-115° (110-111°)[13]
IVe	Me	Et	cyclohexyl	$AlCl_3$/EtOH	87 %	122-123°
IVf	Et	Et	Me_3C	$AlCl_3$/EtOH	83 %[e]	132-133°
IVg	$(CH_2)_5$		Me_3C	$AlCl_3$/EtOH	91 %	162°

a) Isolated yields starting from compounds III, except for compound IVf, which was prepared from the corresponding aldehyde without purifying any intermediate. All reactions were carried at reflux overnight except for IVd where the time was 4 hrs.

b) mps. are determined by means of a capillary and are uncorrecte

c) bp. 110-111°/17 mm (lit.[10] bp. 120-121°/27 mm)

d) A solution of 1 eq. hydrogen chloride in ethanol was prepared by mixing 0.5 eq. of thionyl chloride with a 10 % ethanolic solution of α-cyanoenamine III (containing 1.0 eq. of III).

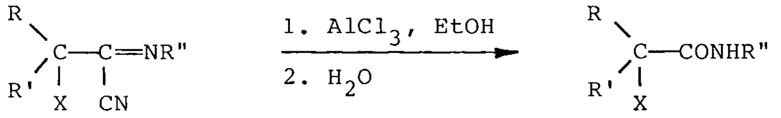
e) Overall yield starting from 2-ethylbutanal.

As α-cyanoenamines III are easily accessible from aliphatic aldehydes I via α-halogenated aldimines II[8] the reaction described represents a versatile functional group transformation. (Table I)

The use of alcohol as solvent seems necessary because the reaction of α-cyanoenamines III with $AlCl_3$ in diethyl ether or carbon disulfide at reflux resulted in a complete recovery of starting material. Good results were also obtained when zinc chloride was used instead of aluminium chloride (ethanolic solution). In this way, N-(t-butyl)-2-methylpropanamide IVc was obtained in 79 % yield starting from the corresponding α-cyanoenamine IIIc.

The activity of the $AlCl_3$-EtOH or $ZnCl_2$-EtOH complex was thought to be a polarization effect on the tautomeric form of α-cyanoenamines, i.e. an imidoylcyanide, thus creating an immonium-type compound. The validity of this proposal was checked by using hydrogen chloride in ethanolic solution (obtained from thionyl chloride in ethanol) as reagent. The reaction of IIId in HCl/EtOH proceeded more rapidly (reflux 4 h) resulting in a 92 % yield of amide IVd. All the reactions described here gave better results when absolute ethanol was used instead of 95 % ethanol.

The mechanism of the reaction may be interpreted as derived from protonation (HCl/EtOH) or complex formation of α-cyanoenamines III to afford immonium type compounds, which will be readily attacked by ethanol. Expulsion of hydrogen cyanide produces imidates which hydrolyze during work-up to give the final amides IV. Similar results were obtained with α-haloge-



V → VI (2)

nated imidoylcyanides V[14] which were transformed into α-halogenated amides VI. (Table II)

TABLE II. Synthesis of α-Halogenated Amides VI

	R	R'	R"	X	Yield[a]	mp[b] (lit. mp.)
VIa	Me	Me	Me_3C	Cl	76 %	67°
VIb	Me	Me	Me_3C	Br	87 %	88° (85-88°)[15]
VIc	Me	Et	phenethyl	Cl	72 %	43-46°[c]

a) Isolated yields starting from V and $AlCl_3$/EtOH
b) mps are determined by means of a capillary (uncorrected)
c) bp. 103-104°/0.02 mm.

The net result of the transformation of an α-cyanoenamine III into a N-monosubstituted amide IV consists only of the displacement of the nitrile moiety by an hydroxyl function. This prompted us to examine the reaction of α-cyanoenamines III with sodium hydroxide in ethanolic solution. Treatment of 2-(t-butylamino)-3-methyl-2-butenenitrile IIIc with excess (5 eq.) sodium hydroxide in absolute ethanol under reflux gave rise to N-(t-butyl)-2-methylpropanamide IVc in 57 % yield. However, the final product was less pure than in the case of the $AlCl_3$/ethanol system.

In order to evaluate the synthetic utility of the functional group transformation described in this paper, the reaction sequence outlined in equation 1 was carried out without purification of any intermediate. Thus, 2-ethylbutanal III (R=R'=Et) was converted into N-(t-butyl)-2-ethylbutanamide IVf in 83 % overall yield (using the $AlCl_3$/ethanol reagent).

In conclusion, we feel that this mild transformation might be useful in organic syntheses of polyfunctional molecules.

EXPERIMENTAL

All compounds described in this paper have been fully characterized by spectroscopic methods (IR, NMR, MS) and showed satisfactory analytical data. α-Cyanoenamines III were prepared from aliphatic aldehydes I *via* α-chloroaldimines.[8] α-Chloro- and α-bromoimidoylcyanides V were obtained as described.[14]

Conversion of α-Cyanoenamines III into N-Monosubstituted Amides IV

To a stirred solution of 0.1 mol α-cyanoenamines III in 100-150 ml absolute ethanol was added portionwise 0.1 mol dry aluminium chloride over a period of 10 minutes. When the vigorous reaction ceased, the mixture was refluxed overnight, after which most of the ethanol was evaporated *in vacuo*. The residue was poured into water and extracted three times with ether. The combined ethereal extracts were dried over $MgSO_4$ and evaporated to leave a crystalline material which was recrystallized from carbon tetrachloride/pentane. Yields and physical data of the N-monosubstituted amides IV thus obtained are listed in Table I.

Some of the amides IV have been compared with an authentic sample, obtained by acylation of a primary amine in dichloromethane in the presence of triethylamine.[15]

Direct Conversion of Aldehydes into N-Monosubstituted Amides IV

The general procedure is illustrated by the conversion of 2-ethylbutanal into N-(t-butyl)-2-ethylbutanamide IVf. A mixture of 10.0 g (0.1 mol) 2-ethylbutanal I (R=R'=Et) and 7.3 g (0.1 mol) t-butylamine were stirred during 10 minutes. After addition of 100 ml CCl_4, the solution was dried ($MgSO_4$) and filtered. To this clear solution, 13.5 g (0.11 mol) N-chlorosuccinimide was added portionwise at ambient temperature and stirring was continued for 4 hrs. Filtration of succinimide and evaporation of CCl_4 afforded crude N-1-(2-chloro-2-ethylbutylidene)t-butylamine IIf, which was dissolved in 150 ml dry methanol and treated with 14.3 g potassium cyanide. After refluxing overnight, the solution was concentrated to half its volume and the reaction mixture was poured into water. Three extractions with ether followed by evaporation yielded crude 2-(t-butylamino)-3-ethyl-2-pentenenitrile IIIf. This crude α-cyanoenamine IIIf was further treated with 13.35 g (0.1 mol) dry aluminium chloride in 180 ml absolute ethanol as described above to give 14.2 g (83 %)[8] N-(t-butyl)-2-ethylbutanamide IVf.

Conversion of α-Halogenated Imidoylcyanides V into α-Halogenated amides VI. A procedure similar to that described above for the reaction of α-cyanoenamines III with aluminium chloride in absolute ethanol was used. The results are given in Table II.

Reaction of 2(t-Butylamino)-3-methyl-2-pentenenitrile IIId with Hydrogen Chloride in Ethanol. A solution of 0.010 mol hydrogen chloride in 16 ml absolute ethanol was prepared by mixing 0.6 g (0.005 mol) thionyl chloride and 16 ml absolute ethanol.

After addition of 1.66 g of IIId (0.01 mol), the solution was refluxed for 5 hrs, cooled, evaporated and treated with 10 ml water. Three extractions with ether and drying ($MgSO_4$) gave, after evaporation, a 92 % yield of amide IVd.

Reaction of 2-(t-Butylamino)-3-methyl-2-butenenitrile IIIc with Aquous Sodium Hydroxide. To a solution of 7.6 g (0.05 mol) 2-(t-butylamino)-3-methyl-2-butenenitrile IIIc in 80 ml absolute ethanol was added 10 g (0.25 mol) solid sodium hydroxide and the mixture was refluxed overnight. Filtration and evaporation gave a residue which was treated with little water and extracted with ether. Drying ($MgSO_4$) and evaporation yielded a solid, which was recrystallized from CCl_4/pentane. N-(t-butyl)-2-methylpropanamide IVc was obtained in 57 % yield.

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