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One-Step Dialkylation of Phenylacetonitrile in the Presence of Tertiary Amines

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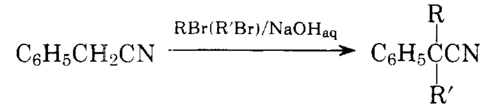
The alkylation of the activated methyne carbon atom is known to occur in aqueous organic medium under standard "phase-transfer" conditions, catalyzed by quaternary ammonium salts.[1-3]

In the course of our studies dealing with the use of macromolecular amines and derived ammonium salts as phase transfer catalysts[4] we have pointed out the activity of tertiary heteroaromatic bases in the monoalkylation of phenylacetonitrile (PAN).[5]

In the previously reported conditions[5] (molar ratio: alkylating agent/PAN = 1.2), the formation of a small amount (<15%) of dialkylated product became appreciable only at PAN conversions larger than 60%.

When an excess of alkylating agent with respect to the starting PAN [5/1 (mol/mol)] was used, conversions to dialkylation product of preparative value were obtained in the same time scale as for standard monoalkylation in the presence of both aliphatic and heteroaromatic amines (Table I).



$$C_6H_5CH_2CN \xrightarrow{RBr(R'Br)/NaOH_{aq}} C_6H_5C(R)(R')CN$$

(R = or ≠ R′)

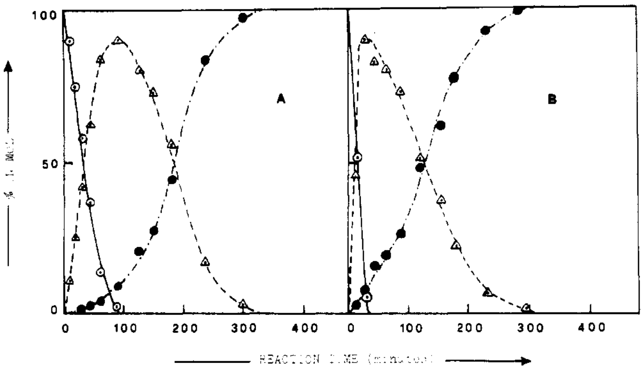


Figure 1. Mono- and dialkylation of phenylacetonitrile (PAN) in the presence of tri-*n*-butylamine (A) and tetra-*n*-butylammonium bromide (B): (– ○ –) PAN disappearance curve; (- ▲ -) 2-phenylbutanonitrile formation and disappearance curve; (- · ● - ·) 2-ethyl-2-phenylbutanonitrile formation curve.

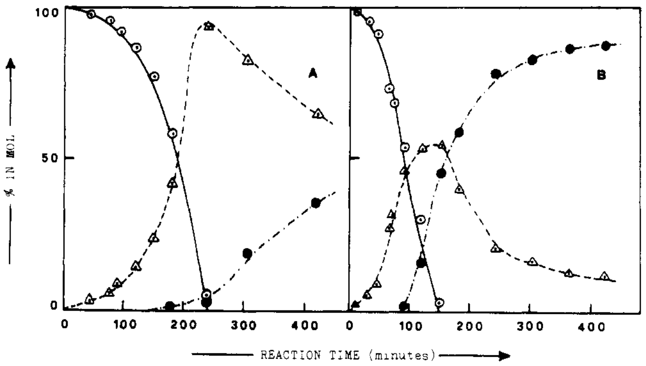


Figure 2. Mono- and dialkylation of phenylacetonitrile (PAN) in the presence of poly(4-vinylpyridine) (A) and 4-methylpyridine (B): (– ○ –) PAN disappearance curve; (- ▲ -) 2-phenylbutanonitrile formation and disappearance curve; (- · ● - ·) 2-ethyl-2-phenylbutanonitrile formation curve.

In the case of asymmetric dialkylation of PAN (R ≠ R′) an excess of the less reactive alkyl bromide (n-C_4H_9Br) was used and the reaction was temporarely stopped at PAN conversion >98% (monoalkylation 90–95% and dialkylation 5–10%). After the removal of the unreacted alkyl bromide under vacuum (no further workup of the reaction mixture) an excess of the more reactive alkyl bromide was added and the reaction was carried on until completion.

The activity of amines, in the examined cases, appears to be comparable to that of the corresponding ammonium salts (Figure 1). When poly(4-vinylpyridine) was used, the reaction rate was markedly lower than that observed for the corresponding low molecular weight analogue (4-methylpyridine) (Figure 2) as previously observed in PAN monoalkylation.[5] This is perhaps obvious because of steric reasons and/or heterogeneity of the reaction medium. The effect of the former factor on rate control is confirmed by the fact that a longer reaction time is required to obtain 50% theoretical yields of 2-ethyl- and 2-butyl-2-phenylhexanonitriles than for 2-ethyl-2-phenylbutanonitrile.

This differentiated reactivity and the reproducibility of the investigated systems, in spite of the complexity of the reaction

Table I. Dialkylation of Phenylacetonitrile[d] (PAN) in Alkaline Aqueous Organic Medium[a]

Amine or quaternary ammonium salt	Registry no.	Alkyl bromide, alkyl =	Registry no.	Time for total disappearance of PAN, min	Time for 50% dialkylation, min	Dialkylated product after 325 min, mol %
Poly(4-vinylpyridine)	25232-41-1	C_2H_5	74-96-4	245	450	19
4-Methylpyridine	108-89-4	C_2H_5		155	160	85
Tri-*n*-butylamine	102-82-9	C_2H_5		95	190	100
		C_4H_9	109-65-9	125	355	40
		C_4H_9, C_2H_5[b]		90	255	94[c]
Tetra-*n*-butylammonium bromide	1643-19-2	C_2H_5		45	125	100

[a] Runs carried out at 70 °C under stirring. Molar ratios: alkyl bromide/PAN = 5, NaOH/PAN = 37.5, and catalyst/PAN = 0.167. [b] Run carried out in two steps. Alkylation with n-C_4H_9Br until 98% PAN conversion (90% monoalkylation and 10% dialkylation) then after removal of excess 1-bromobutane C_2H_5Br was added and the reaction carried out again as in footnote *a*. [c] Constituted by 10% of 2-butyl-2-phenylhexane nitrile and 90% of 2-ethyl-2-phenylhexanenitrile. [d] Registry no. 140-29-4.

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mixture, are particularly convenient from a preparative viewpoint as an asymmetrically dialkylsubstituted PAN derivative can be obtained in good yields and practically free from the symmetrically substituted ones, especially if care is taken in the first step of alkylation to maximize the PAN conversion with a minimum extent of symmetric dialkylation. This can be selectively performed by using a relatively small excess of alkylating agent and therefore longer reaction times.

The in situ formation of the quaternary ammonium salt is not the only factor controlling the catalytic activity of amines in the dialkylation and monoalkylation of PAN, at least in the reported conditions. In fact, the extent of quaternization (determined kinetically) of tri-*n*-butylamine reaches only a 30% value after 400 min and therefore does not suffice to explain the kinetic feature of PAN mono- and dialkylation.

Experimental Section

Starting and final product were characterized by a Varian T60 NMR spectrophotometer with Me_4Si as internal standard.

Gas-chromatographic analyses were done on a Perkin-Elmer F 30 gas chromatograph equipped with a 6 ft × ⅛ in. 2% silicon gum rubber SE 30 on high performance Chromosorb W (AW-DMCS) 80–100 mesh columns.

Viscometric measurements were carried out in methanol at 25 °C by using a Desreux-Bishoff dilution viscometer.

Reagents. Commercial grade phenylacetonitrile (PAN), bromoethane, 1-bromobutane, and tri-*n*-butylamine were purified by distillation.

Poly(4-vinylpyridine) was prepared by polymerization of 4-vinylpyridine in bulk at 40 °C in the presence of AIBN. The polymeric product was purified by dissolution in methanol and reprecipitation in diethyl ether (conversion >90%). The average molecular weight ($\overline{M}_v$) as determined by viscometric measurements was 3.15×10^5.[6]

Tetra-*n*-butylammonium Bromide.[7] A mixture of 4.62 g (25 mmol) of tri-*n*-butylamine and 17.1 g (125 mmol) of 1-bromobutane was heated at 70 °C in a sealed vial. After 70 h the reaction product was precipitated into diethyl ether and recrystallized from absolute ethanol–pentane (2:3) as white crystals.

Dialkylation Reactions. The reactions were carried out under nitrogen in a 100-mL two-necked flask equipped with a condenser and a serum cap. To a mixture of PAN (15 mmol) and alkyl bromide (75 mmol) heated at 70 °C (temperature of the heating oil bath) were added under magnetic stirring 2.5 mmol of catalyst (amine or quaternary ammonium salt) immediately followed by 45 mL of aqueous 50% NaOH preheated at 70 °C. At intervals small samples of the organic layer were withdrawn directly from the mixture through the serum cap by a hypodermic syringe and analyzed by gas chromatography.

In the case of asymmetric dialkylation the same procedure was used as far as the amount of reagents and other operative conditions are concerned. When PAN conversion was higher than 98% the reaction mixture was cooled to room temperature and after removal of the unreacted excess alkyl bromide under vacuum 75 mmol of the more reactive alkyl bromide was added and the mixture was heated again at 70 °C until there was complete dialkylation.

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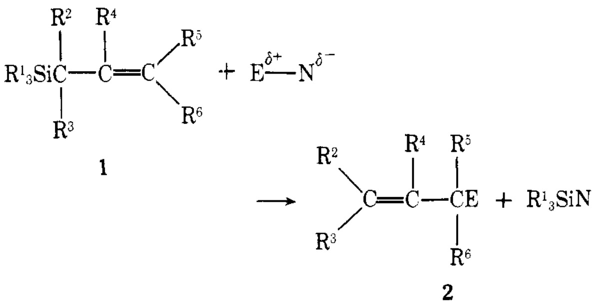
Communications

α-Siloxyallylsilanes as Homoenolate Anion Equivalents. A Novel Synthesis of γ-Keto Aldehydes[1,2]

Summary: This paper reports a versatile method of formation of γ-keto aldehydes by the reaction of α-siloxyallysilanes with acid chlorides, which takes place under mild conditions to give products in high yields.

Sir: In earlier papers,[3] we have described new synthetic reactions using allylsilanes (**1**), in which allyl transfer accompanied by transposition of the allyl group took place very smoothly from **1** to electrophilic carbons of carbonyl compounds or acetals activated by a Lewis acid such as $TiCl_4$ in the direction shown in eq 1.



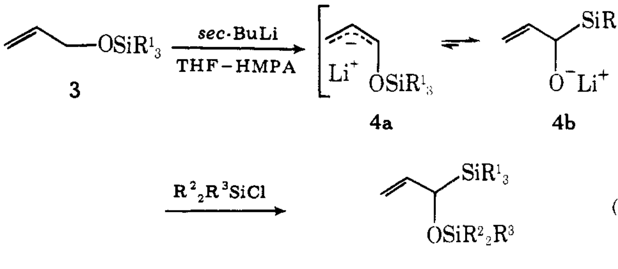
(1)

Introduction of a functionality in the allyl group of **1** will expand the scope of the reaction. For example, introduction of a silyloxy group at the α carbon of **1** (R^2 = silyloxy) could result in the formation of a silyl enol ether which should give a carbonyl compound on hydrolysis. In this paper, we report the synthesis of γ-keto aldehydes,[4] which can serve as valuable precursors for the synthesis of natural cylopentanoids, furans, and pyrroles.

For this strategy of synthesis, we have prepared a variety of α-siloxyallylsilanes, the requisite precursors, by silylation of allyloxy carbanions.[5,6]

Still and Macdonald[6] have suggested that while allyloxy carbanions (**4a**) were in rapid equilibrium with the corresponding silyl alkoxide (**4b**), alkylation of **4** resulted in the formation of only C-alkylated products. We have found, however, that silylation of **4** with chlorosilane occurred exclusively at oxygen to give **5**.[7] Several examples of **5** are shown in Table I.[8]

The reaction of **5** with a variety of acid chlorides in the presence of titanium tetrachloride gave the corresponding γ-keto aldehydes (**6**) after hydrolysis, as shown in Table II.



(2)

5a, $R^1 = R^2 = R^3 = Me$
b, $R^1 = Me$; $R^2 = R^3 = Et$
c, $R^1 = R^2 = Me$; $R^3 = t\text{-}Bu$
d, $R^1 = Et$; $R^2 = R^3 = Me$
e, $R^1 = R^2 = R^3 = Et$

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