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P(RNCH$_2$CH$_2$)$_3$N-Catalyzed α,*β*-Dimerization of Unsaturated Nitriles: Formation of 2-Alkylidene-3-alkylglutaronitriles

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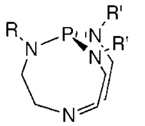
Introduction

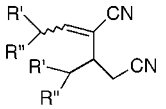
The oligomerization and polymerization of olefins has been of interest to researchers for decades. Of specific interest are processes that lead to the formation of dimers that can be utilized in copolymerization reactions. Such dimers are often observed as byproducts in Michael addition reactions. Dimerization reactions for unsaturated nitriles include electrolytic processes[1,2] and those catalyzed by transition metal complexes,[3,4] trialkyl phosphines,[4] isocyanide−copper(I) oxide binary systems,[4−6] and bases.[7] Reactions catalyzed by trialkyl phosphines or transition metal complexes suffer from the major drawback that they are restricted to the dimerization of *β*-unsubstituted-α,*β*-unsaturated acrylonitrile and the corresponding acrylates. Moreover, the isocyanide−copper(I) system requires a lengthy reaction time and a high temperature, and the conversion ratio is disappointing. Electrolytic reactions produce glutaronitriles as a minor product and are therefore inefficient routes to this class of compounds. Reports of the use of ionic bases in the dimerization of nitriles are scanty. The report by White[7] et al. describes a rapid reaction that is catalytic in R$_4$NCN but provides very low to modest yields (15−54%) along with several byproducts. Shabtai[8] and co-workers reported on the dimerization of crotononitrile and allyl cyanide using a catalyst system consisting of potassium/benzylpotassium. However, these reactions produce the corresponding dimers in apparently very low (unreported) yields along with other products including trimers. The method reported by Daweal[9] utilizes a condensation between propionaldehyde and cyanoacetic acid to produce 3-ethyl-2-propylideneglutaronitrile in low yield.

Results and Discussions

We have shown previously that acetonitrile can be deprotonated by the nonionic bases **1a**,[10] **1b**,[11] and **1c**,[12] giving a low concentration[13,14] of the $^{-}$CH$_2$CN anion. It has also been demonstrated that this anion adds to carbonyl compounds to form α,*β*-unsaturated nitriles[13] or *β*-hydroxynitriles.[14] In the formation of α,*β*-unsaturated nitriles we reported that aldehydes lacking an α-hydrogen (e.g., trimethylacetaldehyde and aromatic aldehydes) react to form α,*β*-unsaturated nitriles while primary aldehydes form the aldol products.[13] Here we show that secondary aldehydes in the presence of **1a** or **1b** afford 2-alkylidene-3-alkylglutaronitriles (**2**) which are α,*β*-dimers of the α,*β*-unsaturated nitriles we expected originally. We observed no *β*,*β*-dimer in our reaction (a product that accompanies the copper(I) oxide−isocyanide process[4]).



1a: R = R' = Me
1b: R = H, R' = *i*-Pr
1c: R = R' = *i*-Pr



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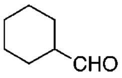
Furthermore, only the α-carbon atom of the delocalized anion Michael adds to a second molecule of the unsaturated nitrile. We believe that this is due to the stability of $\mathrm{MeCH{=}CH\bar{C}HCN}$ relative to $\mathrm{Me\bar{C}HCH{=}CHCN}$ since the negative charge in the former can be stabilized by the nitrile group.

Commercially available **3**−**6** are converted in high yields to the corresponding glutaronitriles **7**−**10**, respectively (Table 1). These products are assumed to form via the corresponding α,*β*-unsaturated nitriles (eq 1), which are subsequently deprotonated by **1a** or **1b** to form an allylic anion that can then undergo Michael addition to a second molecule of the α,*β*-unsaturated nitrile. This process is depicted in Scheme 1. The isomerization of the double bond as shown in this scheme is consistent with our previous observation that **1a** and **1b** are capable of conjugating methylene-interrupted double bonds.[14] In accord with this finding, we expected nonionic bases of type **1** to be able to produce Michael addition products



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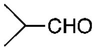

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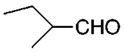

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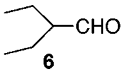

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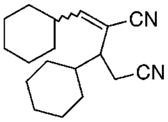

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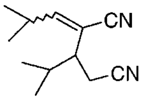

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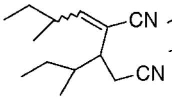

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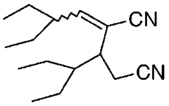

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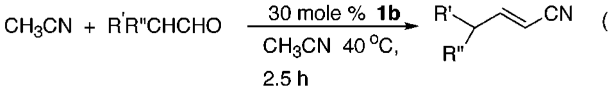

$$\mathrm{CH_3CN} + \mathrm{R'R''CHCHO} \xrightarrow[\mathrm{CH_3CN}\ 40\,^{\circ}\mathrm{C},\ 2.5\ \mathrm{h}]{30\ \text{mole \%}\ \mathbf{1b}} \mathrm{R'R''CHCH{=}CHCN} \qquad (1)$$

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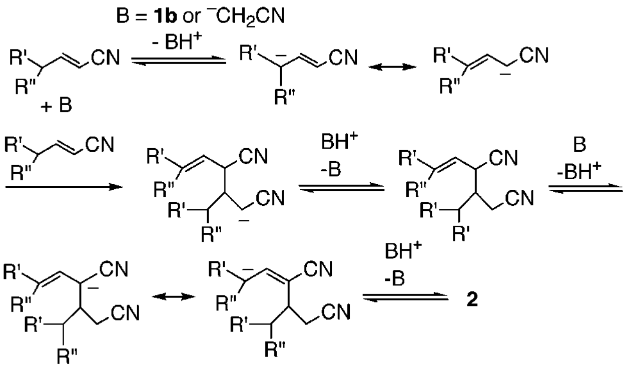
Table 1. Conditions and Yields for the Preparation of Glutaronitriles[a]

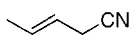
substrate	solvent	*T* (°C)	catalyst[b]	product (yield %)
3	CH_3CN	30	**1a** or **b**	**7** (98)[c]
4	CH_3CN	30	**1a** or **b**	**8** (81)[c]
5	CH_3CN	30	**1a** or **b**	**9** (85)[c]
6	CH_3CN	30	**1a** or **b**	**10** (95)[c]
11	C_6H_6	40	**1a** or **b**	**17** (98)[d]
12	C_6H_6	40	**1b**	**19** (90)[e]
12	MeOH[f]	50	**1a**	**19** (90)[e]
13	C_6H_6	30	**1b** or **1c**	**18** (94)[d]
14	C_6H_6[g,h]	40	**1a** or **1b**	0
15	C_6H_6	25	**1b**	**8** (96)
16	C_6H_6	25	**1b**	0

[a] The time was 2.5 h unless stated otherwise. [b] Present in 10 mol % concentration unless stated otherwise. [c] The amount of base used was 30 mol %. [d] The reaction time was 1 h in the presence of 10 mol % of **1a** or **1c**. [e] In addition to the glutaronitrile **19**, 10% of isomerized substrate was isolated (see text). [f] The reaction time was 10 min. [g] Several solvents were tried (MeOH, CH_3CN, THF, Et_2O). [h] The reaction was also attempted at room temperature.

Scheme 1



from substrates possessing double bonds poised to conjugate (**11**−**13**). The results of the experiments for these substrates in addition to the α,*β*-unsaturated nitriles **14**−**16** are shown in Table 1.



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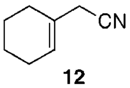

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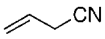

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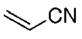

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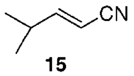

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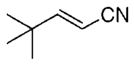

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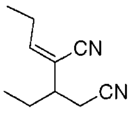

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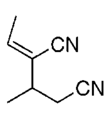

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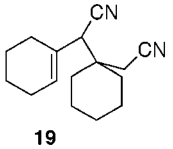

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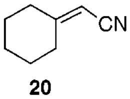

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Scheme 1 further suggests that $^-CH_2CN$ may act as a base in catalyzing the formation of the glutaronitriles. This was substantiated in reactions in which the substrates **11**−**13** were reacted separately with 10 mol % of **1b** in CD_3CN. The ^{31}P NMR of the reaction mixture revealed the existence of **1b**, **1b**H^+, and **1b**D^+. The ^{13}C NMR spectrum of the reaction mixture showed the existence of CD_3CN and a substantial amount of CD_2HCN which can be formed if the $^-CD_2CN$ produced by the deprotonation of CD_3CN deprotonates the substrate or **1b**H^+. Reactions in the presence of acetonitrile are slower, however, requiring up to 12 h to achieve yields similar to those obtained with reactions carried out in benzene that require only 1−3 h. This may be attributed to solvation of the anions in the more polar acetonitrile.

As shown in Table 1, both **1a** and **1b** function as catalysts for these Michael addition reactions. Likewise, **1c** catalyzes reactions of **3** and **4** with acetonitrile to produce the corresponding glutaronitriles **7** and **8** in 97 and 93% conversions, respectively (estimated by ^1H NMR integration), in 2.5 h. As postulated in Scheme 1, the *γ*- rather than the α-hydrogen is deprotonated by nonionic bases at the α,*β*-unsaturated nitrile stage of these Michael additions. This assumption receives support from the lack of reaction in Table 1 of substrates **14** and **16**, which both lack a *γ*-hydrogen. Substrate **15**[15] on the other hand produces the dimer in excellent yield. The reaction of the methylene interrupted unsaturated nitrile **12** in the presence of catalytic amounts of **1a** or **1b** produces the dimer **19** in 90% yield in addition to the isomerized monomer **20** in 10% yield. Evidence for the isomerization of the *β*,*γ*-unsaturated glutaronitrile produced in the penultimate step of Scheme 1 to the more stable α,*β*-unsaturated isomeric final product is therefore provided by the formation of product **19**. The failure of **19** to undergo conjugation may be due to the sterically hindered environment of the α-hydrogen owing to the presence of the two six-membered rings. The formation of compound **19** also serves as evidence for the postulated reaction pathway shown in Scheme 1. The isolation of product **20** on the other hand supports our previous observation that **1b** is capable of isomerizing double bonds. In a similar way, the production of the glutaronitriles **17** and **18** from the substrates **11** and **13**, respectively, using **1a**, **1b**, or **1c** as bases indicate that all these bases are capable of isomerizing double bonds.

Although further experiments along the above lines are underway, we have thus far recovered only starting materials in attempted dimerizations of methylene-interrupted *β*,*γ*-unsaturated esters or ketones. Diphenyl acetaldehyde and 2-phenylpronionaldehyde have so far also failed to give the glutaronitriles under the reaction conditions used here for secondary aldehydes. Primary aldehydes undergo aldol condensation as we previously reported.[13]

Experimental Section

The aldehydes and nitriles (Aldrich Chemical Co.) were used as received. Acetonitrile was distilled from calcium hydride and stored over 4 Å molecular sieves. All reactions were carried out under nitrogen. The bases **1a**,[10] **1b**,[11] and **1c**[12] were prepared according to our previously reported procedures,[10−12] although **1a** is commercially available (Strem).

General Procedure for the Preparation of Glutaronitriles from Aldehydes. In a typical experiment, 30 mg (0.12 mmol) of **1b** was weighed under nitrogen in a 10 mL round-bottomed flask containing a magnetic stirring bar. Dry acetonitrile (2 mL) was then added, and the solution was warmed to 40 °C in an oil bath. The aldehyde (0.40 mmol) was added in one portion, and the reaction mixture was stirred for 2.5 h. After the volatiles were removed under vacuum, the glutaronitriles were eluted on a silica gel column with Et_2O in hexane. The ratio of Et_2O was gradually increased from 0 to 60% in 5% increments. The dinitriles eluted with 40% Et_2O in hexane to afford a mixture of diastereomers in 98, 81, 85, and 95% yield

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for **7**−**10**, respectively.[16] Attempts to isolate the E-isomer from the mixture by column chromatography failed.

General Procedure for the Preparation of Glutaronitriles from Nitriles. This reaction was carried out by weighing 25 mg (0.12 mmol) of **1a** or 30 mg of **1b** (0.12 mmol) under nitrogen in a 10 mL round-bottomed flask containing a magnetic stirring bar. To this was added 2 mL of the solvent, and the resulting solution was warmed to the required temperature (Table 1). The nitrile was then added (1.2 mmol), and the mixture was stirred for the time shown in Table 1. Removal of the volatiles under vacuum followed by column chromatography using ether and hexane as mentioned above afforded the coresopnding glutaronitriles as products.[16]

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Supporting Information Available: Text and tables of ^{1}H and ^{13}C NMR data and mass spectral molecular weights figures of NMR spectra (23 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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[16] See Supporting Information for spectral data recorded for these compounds.