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Selective oligomerization of nitriles having α-hydrogen catalyzed by alkali

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Abstract

Highly selective cyclotrimerization of acetonitrile was achieved in the presence of a catalytic amount of alkali under mild conditions to produce 4-amino-2,6-dimethylpyrimidine in satisfactory yields. Among different base catalysts sodium hydride has the highest activity in this reaction. This catalytic system is also efficient for reactions of other nitriles having α-hydrogen. Linear dimers, linear- or cyclo-trimers can be obtained selectively.

Keywords: Nitriles; Oligomerization; 4-Aminopyrimidine; Alkali; Catalysis

1. Introduction

The oligomers of nitriles are versatile materials in organic synthesis. As an example dimeric β-enaminonitriles are valuable tools in the synthesis of a large variety of unique heterocyclic systems such as pharmaceuticals, fungicides, and solvatochromatic dyes. Their preparation and use were reviewed in several papers and books [1]. The corresponding trimers, for example, 4-aminopyrimidines, not only have important biological activity [2], but also constitute intermediates for some pharmaceuticals [3]. 4-Aminopyrimidines can be prepared by cyclotrimerization of nitriles having α-hydrogen. Meyer found that acetonitrile can be cyclotrimerized to 4-amino-2,6-dimethylpyrimidine (A, R = H) in the presence of sodium [4]. Acetonitrile also give this product in the presence of an excess amount of sodium methoxide or potassium methoxide in a sealed equipment at 140 °C for 5 h in yields of 70–80% [5,6]. In addition, Grignard reagents, active magnesium and fused sodium-lead can also be used to transform nitriles to the corresponding products (A, R = H, CH_3, C_4H_9) [7–9]. Unfortunately all these reactions require an excess amount of alkali and have to be carried out under severe reaction conditions. $Fe(CO)_5$ (10 mol%) has been used to catalyze the cyclotrimerization of acetonitrile, but the conditions were not mild (at 220 °C for 24 h), and the yield was only 33.3% [10]. Recently, Takaya et al. used 10 mol% of an iridium hydride complex $IrH(CO)(PPh_3)_3$ to catalyze the cyclotrimerization of nitriles. Here, the yield was 37% for acetonitrile (A, R = H) and 87% for benzyl cyanide (A, R = Ph), respectively [11].

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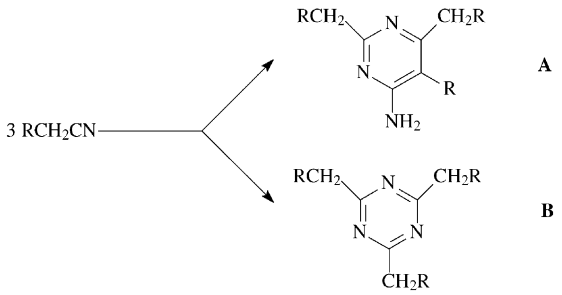


On the other hand, 2,4,6-alkyl-1,3,5-triazine (B, R = alkyl) can also be obtained by the cyclotrimerization of nitriles. In 1995, Liao et al. found that acetonitrile reacted with three equivalent of nano-particle-size NaH to produce trimethyltriazine (B, R = H) in 22% yield [12,13]. In the presence of 1 mol% $Ln(OTf)_3$ the cyclotrimerization of nitriles produced trialkyltriazine, but 4-aminopyrimidine was obtained when the reaction time was prolonged [14].

Here, we report a highly selective oligomerization of nitriles having α-hydrogen applying catalytic amount of base under mild conditions to produce dimer-, linear- or cyclo-trimer in satisfactory yields. The reaction conditions and mechanism are discussed.

2. Experimental

All the reactions were carried out under an atmosphere of dry argon. Solvents were purified by conventional methods and distilled under argon. Nitriles were distilled under reduced pressure. Sodium hydride (60%) was washed with petroleum ether and dried. Products were purified by TLC using silica GF254 (10–40 μ mesh), and identified by ^{1}H NMR and ^{13}C NMR spectral data obtained from a Variant GRMINI 300 MHz and an ADVANCE 500 MHz NMR spectrometer using tetramethylsilane as internal standard. Melting points were obtained in open capillary tubes and uncorrected.

2.1. The reaction of acetonitrile with NaH in toluene

To a suspension of sodium hydride (0.03 g, 1.25 mmol) in toluene (2 ml), dry acetonitrile (1.025 g, 25 mmol) was added in a Schlenk flask under argon, and this reaction was carried out at 80 °C for 24 h. The reaction mixture was cooled down to room temperature, then unreacted acetonitrile and solvent were removed under reduced pressure. The residue was purified by preparative TLC with a solvent system of petroleum ether/ethyl acetate. Three compounds were obtained: 3-aminocrotononitrile (**2a**) yield: 0.112 g, 11%; mp 51–52 °C (ref. [15] mp 52–53 °C). 4-Amino-2,6-dimethylpyrimidine (**3a**) yield: 0.410 g, 40%; mp 180–182 °C (ref. [16] mp 182 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.33 (s, 3H), 2.50 (s, 3H), 4.80 (br, 2H), 6.13 (s, 1H); ^{13}C NMR (300 MHz, CF_3COOH) δ: 20.14, 21.79, 106.44, 159.06, 166.57, 166.68; MS (*m*/*z*): 123 (M^+). *N*-(2,6-dimethyl-4-pyrimidyl)-acetamidine (**4a**) yield: 0.123 g, 12%; mp 184–186 °C (ref. [16] mp 148–149 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.93 (br, 1H), 2.21 (s, 3H), 2.48 (s, 3H), 2.57 (s, 3H), 7.82 (s, 1H), 8.00 (br, 1H); ^{13}C NMR (300 MHz, $CDCl_3$) δ: 24.42, 24.80, 25.62, 105.85, 156.93, 167.01, 168.98, 169.28; MS (*m*/*z*): 165 ($M^+ + 1$), 123 (M^+-CH_3CN).

2.2. 4-Amino-2,6-dimethylpyrimidine (*3a*)

A mixture of dry acetonitrile (4.10 g, 100 mmol), sodium hydride (0.12 g, 5 mmol) in a Schlenk flask under argon was heated at 80 °C for 24 h. Then, it was cooled down to room temperature and unreacted acetonitrile was removed under reduced pressure. The residue was washed with 2 ml × 3 ml water and 3 ml × 10 ml ether, then dried, and the pale yellow solid 4-amino-2,6-dimethylpyrimidine (**3a**, yield: 3.28 g, 80%) was obtained.

2.3. 4-Amino-5-ethyl-2,6-dipropylpyrimidine (*3b*)

According to the above procedure starting from propionitrile, (**3b** yield: 70%) was obtained. mp 186–188 °C (ref. [17] mp 188–189 °C); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.22 (t, J = 7.6 Hz, 3H), 1.29 (t, J = 7.6 Hz, 3H), 2.05 (s, 3H), 2.71 (t, J = 7.6 Hz, 2H), 2.73 (t, J = 7.6 Hz, 2H), 4.90 (br, 2H).

2.4. 4-Amino-5-phenyl-2,6-dibenzylpyrimidine (*3c*)

According to the above method starting from benzylcyanide, (**3c** yield: 93%) was obtained. mp 102–103 °C (ref. [17] mp 106–107 °C); ^{1}H NMR

(500 MHz, $CDCl_3$) δ: 3.78 (s, 2H), 4.11 (s, 2H), 4.74 (br, 2H), 6.97–7.42 (m, 15H).

2.5. 2-Amino-1,1,3-tricyanopropene (**2d**) and 2,4-diamino-1,1,3,5-tetracyano-1,4-pentadi-ene (**3′d**)

A mixture of malononitrile (1.49 g, 22.6 mmol) and sodium hydride (0.027 g, 1.13 mmol) in a Schlenk flask was heated slowly under argon. When the temperature of the reaction was reaching 37 °C, malononitrile began to melt and reacted with sodium hydride violently. Then, the temperature was raised to 80 °C and kept for 24 h. The reaction mixture was cooled down to room temperature and triturated to powder. The powder was washed with 2 ml × 3 ml toluene to remove the unreacted malononitrile. The residue was purified by preparative TLC with a solvent system of petroleum ether/ethyl acetate. Two compounds were obtained: 2-amino-1,1,3-tricyanopropene (**2d**) yield: 0.267 g, 18%; mp 166–168 °C (ref. [18] mp 168–169 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.76 (s, 2H), 8.81 (br, 1H), 8.92 (br, 1H). 2,4-Diamino-1,1,3,5-tetracyano-1,4-pentadiene (**3′d**) yield: 1.144 g, 77%; mp 199–200 °C (ref. [19] mp 200 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.63 (s, 1H), 3.76 (s, 2H), 7.5 (br, 2H) [19].

2.6. 2-Amino-1,1,3-tricyanopropene (**2d**)

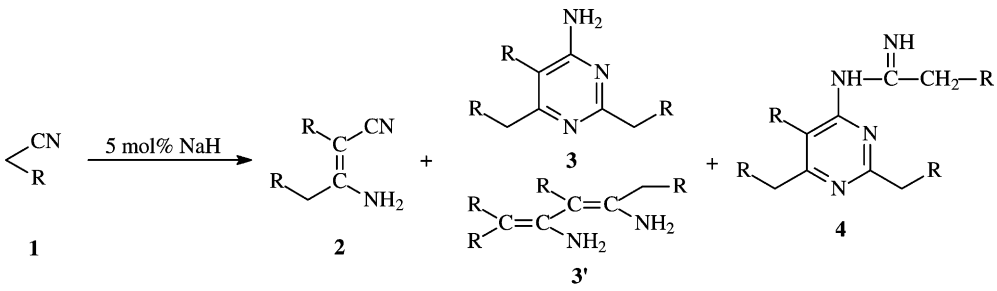
When the above reaction was run at 65 °C for 2 h, **2d** (yield: 51%) was the only product obtained.

2.7. 2-Amino-1-cyano-1,3-diethoxycarbonyl-1-propene (**2e**)

A mixture of dry ethyl cyanoacetate (1.13 g, 10 mmol) and sodium hydride (0.012 g, 0.5 mmol) in a Schlenk flask under argon was heated at 80 °C for 24 h. The reaction mixture was cooled down to room temperature, then purified by preparative TLC with a solvent system of petroleum ether/ethyl acetate. A white solid was obtained: 2-amino-1-cyano-1,3-diethoxycarbonyl-1-propene (**2e**) yield: 0.114 g, 10%; mp 54–55 °C (ref. [18] mp 55–56 °C); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.31 (t, J = 7.0 Hz, 6H), 3.57 (s, 2H), 4.2 (q, J = 7.0 Hz, 2H), 4.23 (q, J = 7.0 Hz, 2H), 7.45 (br, 1H), 9.23 (br, 1H).

2.8. 4-Amino-2-benzyl-6-methylpyrimidine (**3f**)

A mixture of dry benzylcyanide (1.17 g, 10 mmol), 3-aminocrotononitrile (0.82 g, 10 mmol) which was prepared according to a reported method [15]), and sodium hydride (0.024 g, 1 mmol) in a Schlenk flask under argon was heated at 80 °C for 24 h. Then, the mixture was cooled down to room temperature and triturated to powder. The powder was washed with 2 ml × 3 ml toluene, and the residue were purified by preparative TLC with solvent system of petroleum ether/ethyl acetate. A white solid was obtained: 4-amino-2-benzyl-6-methylpyrimidine (**3f**) yield: 1.77 g, 89%; mp 148–150 °C; ^{1}H NMR (300 MHz,



Scheme 1. Oligomerization of nitriles in the presence of base.

$CDCl_3$) δ: 2.34 (s, 3H), 4.04 (s, 2H), 4.81 (s, 2H), 6.10 (s, 1H), 7.27 (m, 5H).

3. Results and discussion

In our investigation of the effect of solvents and base on the coupling reaction of nucleophilic reagents and aryl halides catalyzed by transition metals [20], NaH was found to be a highly selective catalyst for the cyclotrimerization of acetonitrile under mild conditions to produce 4-amino-2,6-dimethylpyrimidine (**3a**).

However, when 5 mol% NaH was mixed with acetonitrile and heated in toluene, three compounds were obtained (Scheme 1). Two of them, dimer (**2a**) and trimer (**3a**), were identified by ^{1}H NMR and their melting points were compared with reported data [15]. The last one, tetramer (**4a**), was identified by ^{1}H NMR, ^{13}C NMR, and the two-dimensional NMR (HMBC, HMQC, and NOESY), but its melting point differs from reported data [21].

By comparing catalytic reactions in the presence of additional solvent, we observed that added solvent decreased not only the selectivity of the reaction but also the conversion rate.

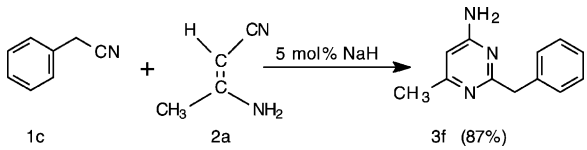
3.1. The effect of alkali

After further studying the reaction, we observed that various bases such as ^{t}BuONa (Table 1, entries 1 and 2), $NaNH_2$ (Table 1, entry 6) also catalyze this reaction in good yields [22]. Table 1 gives a summary of the results of the cyclotrimerization of acetonitrile under various conditions. It can be seen that the greater the molar ratio of alkali/CH_3CN, the higher the yield, but when the amount of base is greater than 5 mol% there is no noticeable effect on the yield (Table 1, entries 3–5).

Table 1
Alkali-catalyzed cyclotrimerization of acetonitrile to produce **3a**

Entry	Alkali	Alkali/CH_3CN (mol%)	Yield (%)
1	^{t}BuONa	3	43
2	^{t}BuONa	5	80
3	NaH	3	42
4	NaH	5	80
5	NaH	10	82
6	$NaNH_2$	5	75
7	MeONa	5	10
8	AcONa	10	Trace
9	Na_2CO_3	10	Trace
10	NaOH	10	Trace

Reaction conditions: acetonitrile (100 mmol); alkalis (3–10 mmol) at reflux for 24 h under argon.

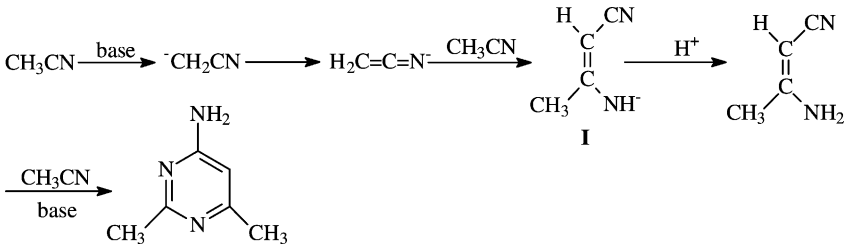


Scheme 3. Reaction of benzylcyanide and **2a**.

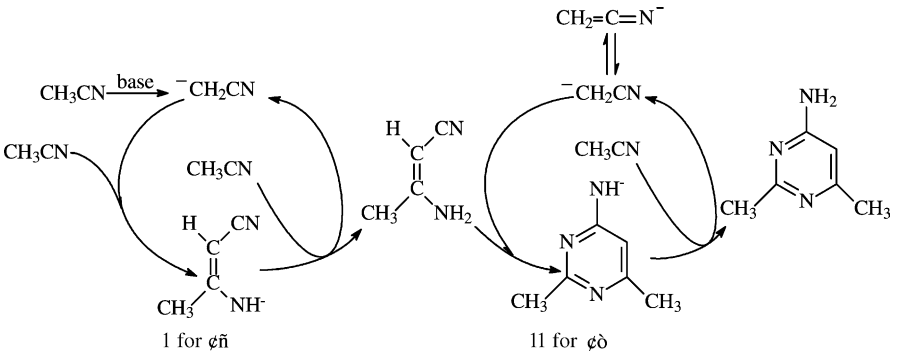
The stronger the base, the higher the conversion rate (Table 1, entries 2, 4, 6, and 7). MeONa is less effective in this reaction (Table 1, entry 7), probably due to its poor basicity. Simple alkali salts are ineffective for this reaction (Table 1, entries 8–10) due to their low basicity and insolubility.

3.2. Oligomerization of nitriles catalyzed by NaH

Next, we investigated the oligomerization of other nitriles catalyzed by 5 mol% NaH. The results are presented in Table 2.



Scheme 2. Mechanism of base-catalyzed oligomerization of acetonitrile.



Scheme 4. Mechanism of base-catalyzed oligomerization of acetonitrile.

Alkyl-substituted nitriles (R = H, CH_3, Ph) produce the corresponding 4-aminopyrimidines as the only product in good yield (Table 2, entries 1–3). The order of activity decreases: Ph > H > CH_3, which is similar to the order of the acidity of the α-H atom. Hence, benzyl cyanide provides the best yield (93%).

Oligomers of malononitrile are important intermediates for organic synthesis, dyes and pigments and medicines [1b,c]. Thus, it is interesting to note that malononitrile can also be oligomerized using a simple base catalyst (Table 2, entries 4 and 5). Although 95% of malononitrile can be converted, a mixture of dimer and trimer is obtained and the main product is trimer. When the reaction time and temperature are decreased, the dimer is the only product, but the conversion rate decreases to 51% (Table 2, entry 5). Ethyl cyanoacetate can be oligomerized by NaH, but the yield is low (10%) and could not be increased through the change of reaction conditions.

Table 2
Sodium hydride-catalyzed oligomerization of nitriles

Entry	R	Reaction condition		Yield (%)	Product
		T (°C)	*t* (h)		
1	H	80	24	82	**3a**
2	CH_3	80	24	70	**3b**
3	Ph	80	24	93	**3c**
4	CN	80	24	95	**2d** (1) **3d** (4)
5	CN	65	2	51	**2d**
6	COOEt	80	24	10	**2e**

Reaction conditions: nitriles (100 mmol); NaH (5 mmol) under argon.

3.3. Discussion of cyclotrimerization mechanism

The reaction mechanism may be similar to that for the Claisen and Dieckmann reaction [1e].

From the above process, it can be seen that an imine anion (**I**) should be formed (Scheme 2). We suppose that it may act as a base to catalyze the reaction. The same kind of imine anion may also be formed in the process of the reaction of dimer with another molecule of acetonitrile anion. In order to prove this, the following experiment was done (Scheme 3): a mixture of dimer of acetonitrile (**2a**), benzyl cyanide (**1c**), and 5 mol% NaH was heated. Indeed, 4-amino-2-benzyl-6-methylpyrimidine (**3f**), the anticipated product, was obtained.

Based on this observation we suggest the following mechanism of this reaction (Scheme 4). Initiation of the reaction is achieved via elimination of the α-proton of acetonitrile, followed by the formation of the anion **I**. After protonation the dimer reacts with another molecule of acetonitrile anion to give the imine anion **II**, which is protonated.

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