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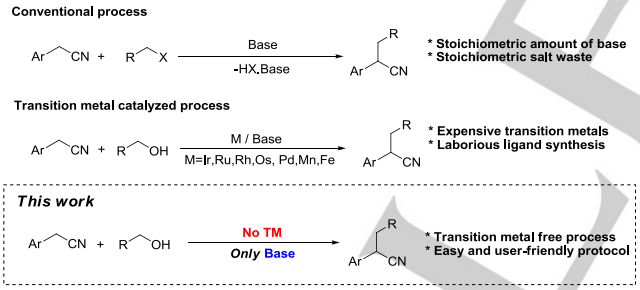
Base-Promoted α-Alkylation of Arylacetonitriles with Alcohols

Bivas Chandra Roy[†], Istikhar A. Ansari[†], Sk. Abdus Samim, and Sabuj Kundu*[a]

Abstract: A practical method to synthesize α-alkylated arylacetonitriles from arylacetonitriles and alcohols without using any expensive transition metal complexes is demonstrated here. Following this base catalysed sustainable procedure various arylacetonitriles were successfully alkylated with different alcohols. Practical applicability of this protocol was extended by one-pot synthesis of important carboxylic acids compound.

Introduction

Carbon-carbon bond forming reactions are one of the fundamental reactions in both academia as well as industry[1] and among them, alkylation of nitrile is highly significant for their use as versatile building blocks to synthesize amides, amidines, carboxylic acids, ketones and various biologically active compounds.[2] Traditionally, α-functionalized nitriles were prepared by using toxic organohalides and large amount strong bases which produced inevitable salt wastes.[3] In last decade, following the hydrogen borrowing methodology transition metal catalysed several C-C and C-N bond forming reactions were explored.[4] Inspired by this protocol, synthesis of alkylated nitrile by replacing the alkyl halides with alcohols as greener alkylating agents was explored by various groups using different precious Ir,[5] Ru,[6] Rh,[7] Pd[8] and Os[9] metal based complexes. Recently Mn catalysed α-olefination and α-alkylation of nitriles using primary alcohols were described by Milstein *et al.* and Maji *et al.* respectively.[10] Lately same reaction was also reported using phosphine based Fe(II) complex.[11]

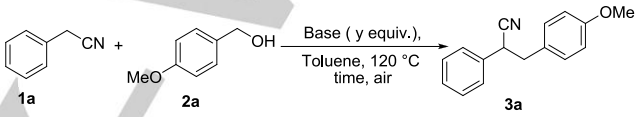


Scheme 1. α-Alkylation of Arylacetonitriles

Albeit the advantages of various metal catalysed processes, these protocols suffer from higher price of these rare metals, difficulty in synthesizing ligands and contamination of metals in the final products.[12] Recently, to overcome these drawbacks of the transition metal catalyzed systems, only base mediated β-alkylation of alcohols, α-alkylation of ketones, (*E*)-specific direct Julia-olefination of aryl alcohols, alkylation of amines and Wittig olefination of alcohols were reported by few groups.[13] Aldehyde triggered C-alkylation of methyl carbinols as well as N-alkylation of sulfonamides and amines with alcohols in presence catalytic amount of base were also disclosed by Xu group.[14] The additional advantage of these processes is that for the in situ dehydrogenation of alcohols, these protocols do not require any strong oxidants. Encouraged by these finding, herein we report transition metal free simple and practical protocol for the α-alkylation of arylacetonitriles using alcohol as an alkylating agent. To the best of our knowledge, base promoted, atom-economical coupling of arylacetonitriles and alcohols is not reported yet.

Results and Discussion

Table 1. Optimization Table for α-Alkylation of Arylacetonitriles.[a]



Entry	**2a** (equiv.)	Base (equiv.)	Time (h)	Yield of **3a** (%)[b]
1	5	KO^{t}Bu (1)	12	>99
2	3	KO^{t}Bu (1)	12	>99
3	3	KOH (1)	12	90
4	3	NaOH (1)	12	52
5	3	K_3PO_4 (1)	12	10
6	3	Cs_2CO_3 (1)	12	18
7	3	LiO^{t}Bu (1)	12	14
8	3	K_2CO_3 (1)	12	-
9	3	KO^{t}Bu (0.8)	12	96
10	3	KO^{t}Bu (0.8)	10	95
11[c]	3	KO^{t}Bu (0.8)	10	90
12[d]	3	KO^{t}Bu (0.8)	10	92

[a] Reaction conditions: phenylacetonitrile (0.087 mmol), 4-methoxybenzyl alcohol (x equiv.), base (y equiv.) and toluene (2 mL) were refluxed at 120 °C under closed air condition. [b] Determined by GC using mesitylene as an internal standard. [c] Dioxane as a solvent. [d] Phenylacetonitrile (0.435 mmol), 4-methoxybenzyl alcohol (1.30 mmol), base (0.348 mmol.) and toluene (10 mL).

We commenced our study by treating phenylacetonitrile with excess of 4-methoxybenzyl alcohol (5 equiv.) and KO^{t}Bu (1 equiv.) in toluene (2 mL) at 120 °C under air atmosphere which resulted formation of 3-(4-methoxyphenyl)-2-phenylpropanenitrile (**3a**) in >99% yield after 12 h of heating (Table 1, entry 1). To minimize the amount of alcohol, we further carried out the reaction with 3 equiv. of 4-methoxybenzyl alcohol which also showed >99% yield of **3a** after 12 h using same amount of KO^{t}Bu under

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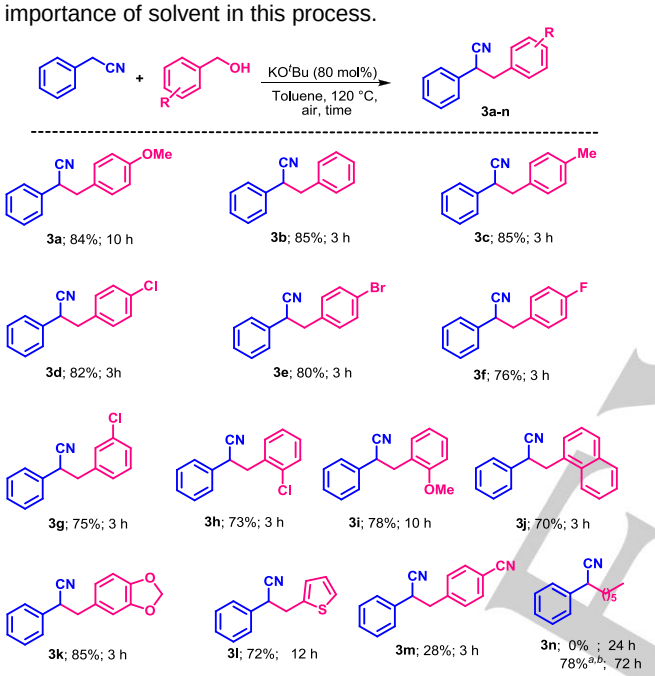
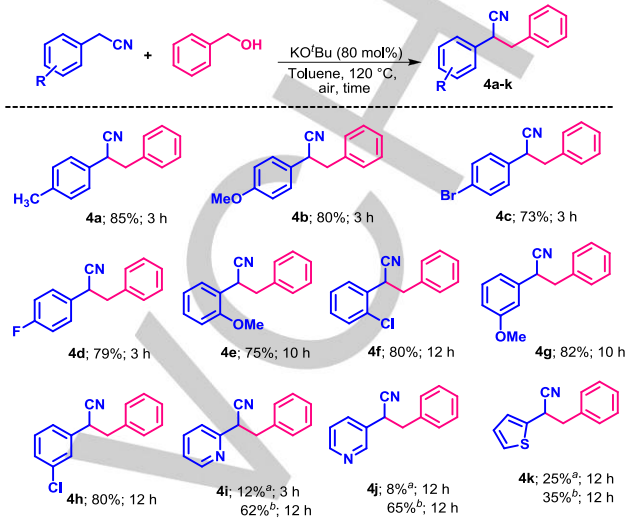
air (Table 1, entry 2). Afterward, KOH was used as a base which gave 90% of **3a** under similar conditions (Table 1, entry 3). Other bases were also examined but they behaved poorly (Table 1, entries 4-8). The yield of **3a** was slightly lower in 1,4-dioxne compared to toluene (Table 1, entry 11). Further, both lower base and time were tried (Table 1, entry 9-10) and 0.8 equiv. of KO^{t}Bu was found to be optimal to afford the desired product (**3a**) after 10 hour (Table 1, entry 10). The attempts to use of fewer than three equivalents of benzyl alcohol and lower amounts of KO^{t}Bu were unsuccessful (see *SI,* Table 1). Next, to scale up the reaction, 0.435 mmol of phenylacetonitrile was reacted with 4-methoxybenzyl alcohol and the reaction proceeded smoothly. However, proportionate amount of toluene (10 mL) was required (Table 1, entry 12). Additionally, under the neat condition the yield of **3a** was low (see *SI,* Table 3) which also indicated the importance of solvent in this process.



Scheme 2. α-Alkylation of phenylacetonitrile with different substituted benzyl alcohols; Reaction conditions: Phenylacetonitrile (0.435 mmol), alcohol (1.30 mmol), KO^{t}Bu (0.348 mmol) and toluene (10 mL) were heated at 120 °C under closed air condition for different time; isolated yield. [a] GC yield using mesitylene as an internal standard. [b] 20 mol% 1-hexanal; heated at 150 °C for 3 days.

Afterward, α-alkylation of phenylacetonitrile with various alcohols was explored to magnify the scope of the present protocol which is summarized in Scheme 2. The reaction of phenylacetonitrile with electron donating groups (-Me and -OMe) substituted benzyl alcohols and simple benzyl alcohol progressed smoothly and afforded the desired products in good yields (**3a-3c** & **3i**). Different halide containing benzyl alcohols were successful alkylated to α-position of phenylacetonitrile with good to moderate yields within 3 h (**3d**-**3h**). However, the reaction of 4-cyanobenzyl alcohol with phenylacetonitrile yielded only 28% of desired product (**3m**). Following this protocol 3-(naphthalen-1-yl)-2-phenylpropanenitrile (**3j**) and 3-(benzo[*d*][1,3]dioxol-5-yl)-2-phenylpropanenitrile (**3k**) were synthesized in good yields. With thiophen-2-ylmethanol the yield of the desired product (**3l**) was good within 12 h. The reaction with long chain alcohol, initially did not prosper under the standard conditions or heating for prolonged time. However, addition of 20 mol% corresponding aldehyde afforded the desired product **3n** in good yield after heating at 150 °C for 72 hour.[13b, 14a]



Scheme 3. α-Alkylation of substituted phenylacetonitriles with benzyl alcohol; Reaction conditions: arylacetonitriles (0.435 mmol), benzyl alcohol (1.30 mmol), KO^{t}Bu (0.348 mmol) and toluene (10 mL) at 120 °C under closed air condition for specified time; isolated yields. [a] GC yield using mesitylene as an internal standard. [b] 20 mol% benzaldehyde was added.

After that, α-alkylation of a wide range of substituted phenylacetonitriles with benzyl alcohol was conducted to explore the generality of the present protocol which is summarized in Scheme 3. The reaction of benzyl alcohol with electron donating groups (-Me and -OMe) substituted phenylacetonitriles progressed smoothly and afforded the desired products in good yields within 3 h (**4a**-**4b**). However, the yield of the corresponding α-alkylated products was moderate with the electron withdrawing groups (-Br and -F) substituted phenylacetonitriles (**4c**-**4d**). Coupling of *ortho*-(-OMe and -Cl) and *meta*-(-OMe and -Cl) substituted phenylacetonitriles with benzyl alcohol required longer heating (10-12 h) to achieve good yields (**4e**-**4h**). However, the result was not satisfactory with heteroatom containing arylacetonitriles even after longer period of heating. Hence, inspired by the Xu group's report of aldehyde promoted β-alkylation of secondary alcohols with primary alcohols, the same reactions were carried out in presence of 20 mol% benzaldehyde which afforded the corresponding α-alkylated nitriles in moderate yield (**4i**-**4k**).[14a]

To increase the effectiveness of this method, one-pot synthesis of acid from arylitrile and alcohol was carried out. Using this simple alkylation protocol followed by acidic and basic hydrolysis, compounds **5a** and **5b** were synthesized smoothly in one-pot manner. These molecules could act as an intermediate for the production of biologically active compounds, for example, inhibitors of transient receptor potential canonical (TRPC) channel activity (Scheme 4).[15]

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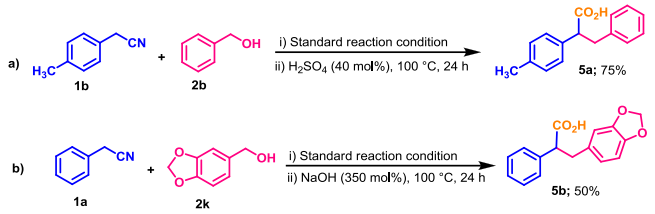
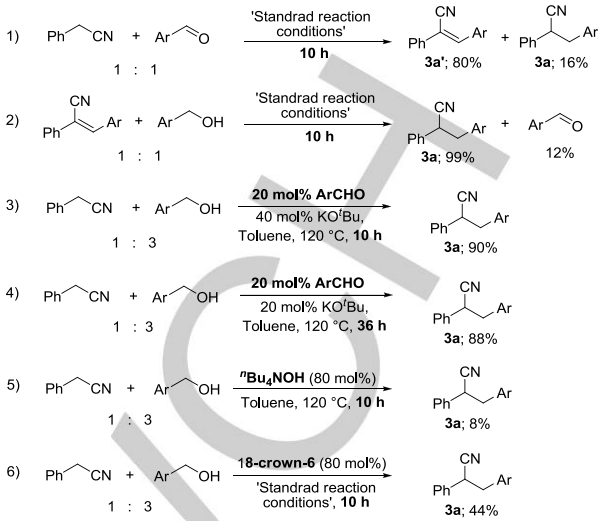


Scheme 4. Synthesis of intermediate acids of biologically active compounds: a) Synthesis of **5a**: Reaction conditions: i) **1b** (0.435 mmol), **2b** (1.30 mmol), KO^{t}Bu (0.348 mmol), toluene (10 mL), 120 °C, 3h. ii) H_2SO_4 (0.174 mmol, 50%), 100 °C, 24 h. b) Synthesis of **5b**: Reaction conditions: i) **1a** (0.435 mmol), **2k** (1.30 mmol), KO^{t}Bu (0.348 mmol), toluene (10 mL), 120 °C, 3 h. ii) NaOH (1.53 mmol), 100 °C for 24 h.

In 2010, Crabtree *et al.* reported base-mediated coupling of 1-phenylethanol and benzyl alcohol under aerobic conditions which was proposed to be operated via Oppenauer oxidation and MPV reduction routes.[13a] In recent times, for the transition metal free base promoted alcohol oxidations reactions, few groups also suggested similar type of mechanism.[13b, 14] Based on these literature reports, we hypothesized that for α-alkylation of arylacetonitrile using alcohols probably similar type of mechanism also was operating. For better understanding the mechanism several control experiments were carried out which are summarized in Scheme 5. Under the standard reaction conditions, 4-methoxybenzaldehyde underwent base catalyzed aldol condensation to afford 3-(4-methoxyphenyl)-2-phenylacrylonitrile (**3a'**) with 80% yield along with minor amount of **3a** (Scheme 5, equation 1). The reaction of 3-(4-methoxyphenyl)-2-phenylacrylonitrile (**3a'**) with 4-methoxybenzyl alcohol under standard reaction conditions yielded 99% of 3-(4-methoxyphenyl)-2-phenylpropanenitrile (**3a**) along with small amount of 4-methoxybenzaldehyde which indicated that MPV-O type mechanism was probably operating here (Scheme 5, equation 2). The lower yields of **3a** and 4-methoxybenzaldehyde in equations 1 and 2 respectively indicated depletion of aldehyde via cannizzaro reaction. 4-methoxybenzyl alcohol produced via Cannizzaro reaction probably acted as a hydrogen donor for the formation of **3a** (Scheme 5, equation 1). As in MPV-O type mechanism, aldehyde plays a crucial role, we performed two reactions for 10 and 36 hour, employing 20 mol% 4-methoxybenzaldehyde with less amount of KO^{t}Bu (40 mol% and 20 mol%) which afforded 90% and 88% yield of **3a** respectively (Scheme 5, equations 3 & 4). Additionally, when ^{n}Bu$_4$NOH was used instead of KO^{t}Bu as base, the yield of **3a** was dropped significantly (Scheme 5, equation 5). This data indirectly suggested certain role of the cation although, possibility of the hemiaminal model can not be ruled out.[13b-d, 14a] The yield of **3a** under the standard conditions did not alter considerably when KO^{t}Bu from three different manufacturers as well as from four different laboratories were tested. To check the role of potassium cation in the reaction, the coupling of 4-methoxybenzyl alcohol with phenylacetonitrile was carried out in the presence of 18-crown-6 (80 mol%) which lowered the yield **3a**; this advocated the importance of the potassium ion in this reaction (Scheme 5, equation 6).



Scheme 5. Control experiments. (Ar is used to indicate 4-methoxylbenzyl group).

Conclusions

In summary, a simple, economical, and transition metal free synthesis of α-alkylated of arylacetonitriles using alcohol as a green alkylating agent is developed. Using this sustainable protocol a wide range of arylacetonitriles are successfully alkylated. The synthetic benefits of this process was also established by one-pot synthesis of few acid derivatives which are intermediates for the manufacture of biologically active compounds. In addition, several mechanistic investigations were carried out to understand the mechanism this reaction. Furthermore, absence of any expensive transition metal complexes makes this methodology highly attractive for the direct synthesis of α-alkylated arylacetonitriles.

Experimental Section

General Procedure for α-Alkylation of Arylacetonitriles: A Schlenk flask was charged with KO^{t}Bu (0.348 mmol), arylacetonitrile (0.435 mmol), alcohol (1.30 mmol) and toluene (10 mL) under open air condition. Then it was sealed and dipped in a preheated oil bath at 120 °C and heated for the appropriate time. After the reaction, the flask was cooled at room temperature and the reaction mixture was passed through a small pad of silica and small amount of this solution was directly injected for GC analysis. Afterward, the solvent was evaporated under reduced pressure and the desired product was isolated by column chromatography using silica gel and hexane-ethyl acetate as eluent.

Acknowledgements

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Keywords: Transition metal free; Base catalysed; α-Alkylation of arylacetonitriles; C-C bond formation.

Conflicts of interest

There are no conflicts to declare.

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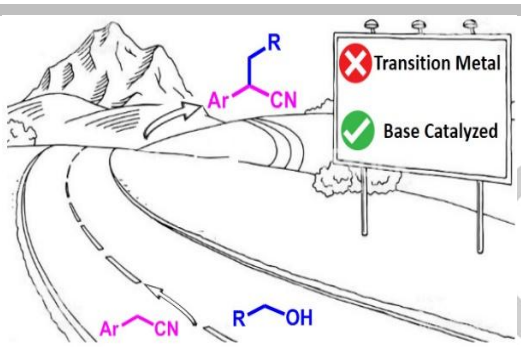
α-Alkylation of arylacetonitriles using alcohols was reported using only less than stoichiometric amount of KO^{t}Bu.



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