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Sodium Silicate-catalyzed Multicomponent Synthesis of Pyridine Dicarbonitriles

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Pyridine dicarbonitriles have been synthesized good yields *via* a one-pot multi–component reaction of aldehyde, malononitrile, and thiol in the presence of sodium silicate as a catalyst in ethanol.

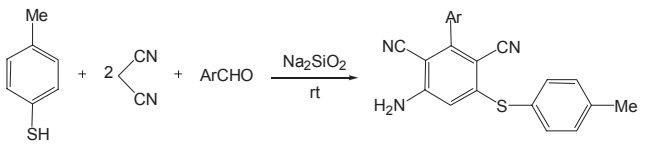
Key Words: Pyridine dicarbonitriles, Multi-component reaction, One-pot, Sodium silicate

Introduction

In recant years, multicomponent reactions (MCRs) have become important tools in modern preparative synthetic chemistry because these reactions increase the efficiency by combining several operational steps without any isolation of intermediates or change of the conditions[1,2] and MCRs have recently emerged as valuable tools in the preparation of structurally diverse chemical libraries of drug-like heterocyclic compounds.[3-5]

The pyridine nucleus is of considerable interest as this ring is the key constituent in a range of bioactive compounds, both naturally occurring and synthetic, and often of considerable complexity.[6] The pyridine dicarbonitrile substructure was therefore chosen as a basic structural scaffold for the design of a reaction-based library.[7] Thus, the synthesis of highly substituted pyridines has attracted much attention, and a number of procedures have been developed using a variety of protocols, such as hetero-Diels-Alder reaction of 3-siloxy-1-aza-1,3-butadienes with electron-deficient acetylenes[8a] three-component condensation of aldehyde, malononitrile, and thiol[8b] ruthenium-catalyzed cycloisomerization of 3-azadienynes[8c] Mannich reaction of aldehydes and iminium salts[8d] Vilsmeier-Haack reaction of *R*-hydroxyketenedithioacetals.[8e] Among these, one of the very convenient approaches which attracted our attention is the three-component condensation of aldehyde, malononitrile, and thiol to the highly substituted pyridines developed by Evdokimov *et al*.[8b] Herein, we report a mild, practical and highly efficient procedure for the preparation of the title compounds using Sodium silicate as a catalyst at room temperature (Scheme 1).

To the best of our knowledge there are no reports on the synthesis of these compounds with 4-methyl thiophenol using Sodium silicate as the catalyst.



Scheme 1

Results and Discussion

In connection with our recent interested aimed at the development of efficient protocols for the preparation of biological active heterocycles,[15-18] herein, we selected Sodium silicate as a new catalyst to synthesis of pyridine dicarbonitriles. The reaction of various aldehydes, 4-methyl thiophenol, malononitrile in the presence of Sodium silicate in ethanol afforded pyridine

Table 1. Synthesis of pyridine dicarbonitriles with deifferent aldehydes

Entry	Ar	Product	Yield (%)[a]
1	C_6H_5	4a	78
2	4-Cl-C_6H_4	4b	82
3	3-Cl-C_6H_4	4c	81
4	4-Br-C_6H_4	4d	80
5	3-Br-C_6H_4	4e	79
6	3-NO_2-C_6H_4	4f	78
7	4-NO_2-C_6H_4	4g	80
8	4-CH_3O-C_6H_4	4h	82

[a]Yields were analyzed by GC.

Table 2. Synthesis of 4a in the presence of different solvents using Sodium silicate as a catalyst

Entry	Solvent	Yield (%)[a]
1	THF	68
2	CH_3OH	72
3	CH_3CN	76
4	$CHCl_3$	70
5	C_2H_5OH	78

[a]Yields were analyzed by GC.

Table 3. Synthesis of 4a using various catalysts

Entry	Catalyst	Yield (%)[a]
1	$H_6[P_2W_{18}O_{62}]$	10
2	P-TSA	50
3	$KHSO_4$	30
4	Na_2SiO_3	80

[a]Yields were analyzed by GC.

dicarbonitriles at room temperature in good yields (Table 1).

We performed the effect of various solvents on the synthesis of 4a. This reaction was carried out in various solvents and the best results in terms of yield and time obtained in ethanol (Table 2).

In each reaction, the yield is a function of the reaction time and the best time for all reactions was completed after 1 h. The reactions proceeded well with 5 mol % of catalyst and use of an increased amount of catalyst does not make much difference.

In order to show the merit of the present work, we compared the result of the synthesis of these compounds in the presence of various catalysts but the best results obtained with Sodium silicate (Table 3).

In conclusion, we have described a highly efficient procedure for the preparation of pyridine dicarbonitriles via a condensation reaction of various aldehydes, malononitrile, and thiol using sodium silicate as a catalyst. The procedure offers several advantages including high yields, operational simplicity, cleaner reaction, minimal environmental impact, and low cost, which make it a useful and attractive process for the synthesis of these compounds

Experimental

All products were characterized by mp, IR, ^{1}H NMR and GC/MS. Melting points were measured by using the capillary tube method with an electro thermal 9200 apparatus. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DRX Avance spectrometer at 500 and 125 MHZ, respectively, with $CDCl_3$ as solvent. IR spectra were recorded from KBr disk on the FT-IR Bruker Tensor 27. GC/MS spectra were recorded on an Agilent Technologies 6890 network GC system and an Agilent 5973 network Mass selective detector. Thin layer chromatography (TLC) on commercial aluminum-backed plates of silica gel, 60 F254 was used to monitor the progress of reactions. All products were characterized by spectra and physical data.

Typical procedure for preparation of pyridine dicarbonitriles. To a magnetically stirred solution of aldehyde (1 mmol), 4-methyl thiophenol (1 mmol) and Na_2SiO_3 (5 mol %) in (5 mL) was added malononitrile (2 mmol) and stirring was continued for 1 h. The precipitate was filtered and washed with ethanol to give product.

4b: ^{1}H NMR ($CDCl_3$, 500 MHz) δ_H 2.47 (3H, s), 7.30-7.58 (9H, m, arom), 7.59 (2H, s). ^{13}C NMR ($CDCl_3$, 125 MHz) δ_C 21.85, 87.46, 96.07, 115.08, 115.49, 123.81, 129.89, 130.33, 130.62, 131.99, 136.08, 137.83, 140.85, 157.49, 159.68, 170.19.

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