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An Improved Procedure for 2-amino-5-nitro-4,6-diarylcyclohex-1-ene-1,3,3-tricar Bonitriles; Carbonate on Polymer Support as Mild and Reusable Catalyst

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ABSTRACT. A new catalytic system has been developed in the synthesis of 2-amino-5-nitro-4,6-diarylcyclohex-1-ene-1,3,3-tricarbonitriles using carbonate on polymer support (Amberlyst A-26 $NaCO_3^-$). Short reaction time, simplicity of isolation, safe catalyst and high yields of product are the features.

Key words: Carbonate on polymer support (Amberlyst A-26 $NaCO_3^-$), 2-amino-5-nitro-4,6-diarylcyclohex-1-ene-1,3,3-tricarbonitriles, Nitromethane, Malanonitrile

INTRODUCTION

The popularity of multi component reaction (MCR)[1,2] methodology repose on the fact that they offer a wide range of products with minimum effort in one pot. They offer more advantages in the field of drug discovery process as opposed to the classical way of sequential synthesis. MCR strategy relies on tandem nature of constituent reactions. If the reactions happening in tandem are coupled, a successful MCR results. This is the basis of the one component reaction methodology for the synthesis of highly functionalized cyclohexenes viz 2-amino-5-nitro-4,6-diarylcyclohex-1-ene-1,3,3-tricarbonitriles developed by S.D. Samant[3] where Knovenagal-Michael reactions are coupled. Originally these compounds were synthesized using two component methodology by Texier-Boullet by the reaction of nitromethane with benzylidine malononitrile[4] using piperidine under microwave conditions. Reaction of benzylidine malononitrile with several nucleophiles has been studied extensively[5] and synthesis of these highly functionalized cyclohexenes has been done uing various catalysts like KF-Al_2O_3,[6] imidazole.[7] S.D. Samant and his group synthesised these compounds using Mg/Al: HT under solvent free conditions. They screened several classical bases as well and got the product with low to moderate yields. Most of the reported procedures suffer from long reaction hours and preparation of the catalyst poses an additional step and since the methodology gives highly functionalized cyclohexenes and very few methods are available in the literature, developing new catalytic systems which are readily available aiming at reducing time, high yields and reusability are a welcome goal. Herein we wish to describe polymer carbonate as a redily available, novel, reusable and highly efficient catalyst for the synthesis of 2-amino-5-nitro-4,6-diarylcyclohex-1-ene-1,3,3-tricarbonitriles (*Fig.* 1) from malononitrile nitromethane and aldehydes.

Polymer supported reagents (PSRs) find their application since 1960s and huge number of research articals based on PSRs indicate their wide applications in organic synthesis. The use of polymer supported materials as reagents is attractive because the reactions are often very clean and high yielding, and the workup involves simple filtration and evaporation of the solvent. This line of chemistry has resulted in the development of a number of useful polymer-supported reagents which are finding increasing utility in organic synthesis.[8]

Carbonate on polymer support (Amberlyst A-26 $NaCO_3^-$) with capacity ≈3.5 mmol/g as small beads with light red colour has been used in many organic transformations

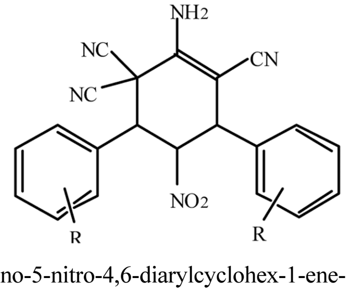


***Fig.* 1.** 2-amino-5-nitro-4,6-diarylcyclohex-1-ene-1,3,3-tricarbonitriles.

which include conversion of β-iodoamines into aziridines in high yield,[9] in combination with iodine it has been used to transform allylic amines into 5-(iodomethyl)oxazolidin-2-ones in excellent yields,[10] synthesis of cyclic hemiacetals from α-bromoketones and catechol,[11] neutralisation of ammonium salts to yield free amines in clean fashion[12] and as base in condensation reaction of benzyldihydroisoquinoline with α-nitrocinnamate derivatives to provide the corresponding 2-ethoxycarbonyl pyrroles.[13]

EXPERIMENTAL

All the chemicals used commercial grade and were used without further purification. The products were characterized by comparison of their physical, IR, ^{1}H NMR, and LC-mass spectra with those reported in the literature.

General procedure for the synthesis of 2-amino-5-nitro-4, 6-diarylcyclohex-1-ene-1, 3, 3-tricarbonitrile

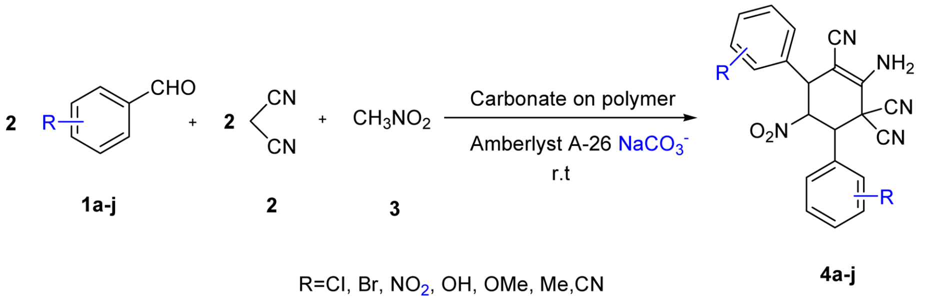
In a 50 ml round bottom flask, benzaldehyde (5 mmole), malononitrile (5 mmole) and carbonate on polymer support (Amberlyst A-26 $NaCO_3$) (0.05 gm) were taken in dry MDC (5 ml) and stirred at room temperature till consumption of aldehyde (TLC). Nitromethane (2.5 mmole) was added and the reaction mixture was stirred at room temperature (29 °C) until completion of the reaction (TLC). The reaction mixture was filtered and the catalyst was washed with MDC.The filterate was concentrated and the residue was purified by column chromatography on silica gel with 10% ethyl acetate in pet ether.

Representative Compound data

Compound 4a: White solid, IR (KBr): 3433, 3341, 3220, 2203, 1645, 1565, 1366, 670 cm^{-1}. ^{1}H NMR (DMSO, 400 MHz) δ_H; 4.11 (d, 1H, *J* 12Hz), 4.33 (d, 1H, *J* 10Hz), 5.18 (s, 2H), 5.33 (dd, IH, J_1 12Hz, J_2 10Hz), 7.20-7.45 (m, 10H) ppm. MS: *m/z* = 370 (M$^+$). Anal. Calcd for $C_{21}H_{15}N_5O_2$: C, 68.28: H, 4.09: N, 18.96: Found C, 67.10: H, 3.99: N, 18.01. **Compound 4b**: White solid, IR (KBr): 3462, 3361, 3221, 2206, 1649, 1521, 1369,1279cm^{-1}.^{1}H NMR (DMSO, 400 MHz) δ_H; 3.77 (s, 3H), 3.79 (s, 1H), 4.19 (d, 1H, *J* 10 Hz), 4.70 (d, 1H *J*=12 Hz), 5.26 (dd, 1H, J_1 12 Hz, J_2 10 Hz), 6.66-6.99 (m, 8H) ppm. MS: *m/z* = 462 (M$^+$). Anal. Calcd for $C_{23}H_{19}N_5O_6$: C, 59.87: H, 4.15: N, 15.18: Found C, 59.84: H, 4.17: N, 15.17. **Compound 4c**: White solid, IR (KBr): 3446, 3347, 3217, 2206, 1649, 1556, 1364, 1279 cm^{-1}. ^{1}H NMR (DMSO, 400 MHz) δ_H; 4.33 (d, 1H, *J* 10Hz),4.95 (d, 1H *J* = 12 Hz), 6.04 (br s, 1H), 7.33-7.71 (m, 10H) ppm. MS: *m/z* = 420(M$^+$). Anal. Calcd for $C_{23}H_{13}N_7O_2$: C, 65.87: H, 3.12: N, 23.38: Found C, 65.84: H, 3.15: N, 23.33. **Compound 4f**: White solid, IR (KBr): 3432, 3361, 3221, 2206, 1649, 1561, 1369, 830 cm^{-1}. ^{1}H NMR (DMSO, 400 MHz) δ_H; 3.77 (s, 6H), 4.22 (d, 1H, *J* 11Hz), 4.89 (d, 1H, *J* 10Hz), 5.58 (t, 1H J_1 = 12Hz, J_2 = 10Hz), 6.97-7.45 (m, 10H) ppm. MS: *m/z* = 430 (M$^+$). Anal. Calcd for $C_{23}H_{19}N_5O_4$: C, 64.33: H, 4.46: N, 16.31: Found C, 65.10: H, 4.99: N, 16.01. **Compound 4j**: Cremish solid, IR (KBr): 3429, 3361, 3221, 2206, 1649, 1561, 1369, 830 cm^{-1}. ^{1}H NMR (DMSO, 400 MHz) δ_H; 4.67 (d, 1H, J 10 Hz), 5.22 (d, 1H, *J* 11Hz), 6.50 (br s, 1H), 7.77-7.90 (m, 10H) ppm. MS: *m/z* = 460 (M$^+$). Anal. Calcd for $C_{21}H_{13}N_7O_6$: C, 54.91: H, 2.85: N, 21.34: Found C, 54.99: H, 2.81: N, 21.32.

RESULTS AND DISCUSSION

Benzaldehyde (**1a**), malononitrile (**2**), and nitromethane (**3**) were selected as model substrates to carry out the reaction. Since theoretically to get the required product 2 moles each of benzaldehyde and malononitrile are required for each mole of nitromethane, molar ratio of 1:1:0.5 was selected for aldehyde, malononitrile and nitromethane respectively. Initially 10% w/w of the catalyst was used with dichloromethane (MDC) as solvent. Benzaldehyde, malononitrile and catalyst stirred in MDC until benzylidine malononitrile was formed and nitromethane was introduced and the course of the reaction was monitored by Thin Layer Chromatography (TLC). Interestingly the required product (**4a**) formed within 30 min in 95% as indicated by LCMS analysis.Isolation of the product on column chromatography gave 93% of the same as white solid. Heating the reaction mixture to 50 °C did not improve the conversion beyond 93%. Optimisation of the reaction condition was done by carrying out the reaction with different solvents including water and varied amounts of catalyst loading.The results are summerised in *Table* 1 and *Table* 2. The best condition comes out to be the one with MDC as solvent and 10 wt% of catalyst at room temperature. With the conditions optimized we checked the generality of the methodology by subjecting various aldehydes to get the product. Aldehydes (**1a-j**) containing electron donating and electron withdrawing groups on the benzene ring gave the required products (**4a-j**) in excellent yields (*Table* 2). It is interesting to note that in case of phenolic aldehydes the yield was as high as 81%. (*Table* 2, entry 2) which makes the new catalyst system better than Mg/Al: HT system[2] where the yield claimed is only 30%.



***Scheme* 1.**

***Table* 1.** Optimization of reaction conditions for the synthesis of **4a**[a,b] using carbonate on polymer support (Amberlyst A-26 $NaCO_3$)

Entry	Quantity (Wt%)	Solvent	Time (minutes)	Yields (%)[c]
1	5	DCM	60	62
2	10	DCM	30	93
3	15	DCM	30	90
4	10	CH_3OH	60	60
5	10	CH_3CN	60	55
6	10	DMF	60	60
7	10	THF	60	65
8	10	Water	60	25

[a]Reagents: **1a** (1 mmol), **2** (1 mmol), **3** (0.5 mmol), solvent (20 volume). [b]Reactions were carried out at room temperature condition. [c]Yield refers to isolated product

***Table* 2.** Synthesis of 2-amino-5-nitro-4,6-diarylcyclohex-1-ene-1,3,3-tricarbonitriles

Entry	Ar	Product	Time (min)	Yield (%)[a]	Mp (°C)/(lit.)
1.	C_6H_5	4a	30	93	210-213 (207-210)[2]
2.	3-OH, 4-MeO C_6H_3	4b	30	81	219-223 (225226)[2]
3.	4-CN C_6H_4	4c	30	92	235-237 (230234)[2]
4.	4-Br C_6H_4	4d	30	93	220-225 (225227)[2]
5.	2-Br C_6H_4	4e	30	82	130-135 (128131)[2]
6.	4-MeO C_6H_4	4f	30	88	246-249 (243244)[2]
7.	4-Cl C_6H_4	4g	30	86	230-235 (228230)[2]
8.	3-$CH_3OC_6H_4$	4h	30	87	230-235 (230231)[6]
9.	3, 4-$(CH_3O)_2C_6H_3$	4i	30	83	166-169 (168170)[6]
10.	3-NO_2 C_6H_4	4j	30	87	190-191 (188-190)[2]

[a]Yields are related to isolated pure products

Reusability of the catalyst

Reusability of the catalyst was examined employing the reaction between **1a**, **2** and **3** to obtain **4a** under identical reaction conditions. The catalyst was easily recovered from the mixture by filteration. The catalyst was washed with MDC and dried under vaccum at 100 °C for 10 hrs and used for the reaction in the same way. The recycled catalyst was used five times to obtain 2-amino-5-nitro-4, 6-diarylcyclohex-1-ene-1, and 3,3-tricarbonitriles without appreciable decrease in the yield 93, 91, 87, 85 and 82% respectively for 1-4 cycles. After every reaction, the catalyst was recovered from the reaction mixture by filteration and regenerated as described above.

CONCLUSION

In conclusion carbonate on polymer support (AmberlystA-26 $NaCO_3^-$) finds to be efficient, mild, safe, ecofriendly and reusable catalyst for the preparation of widely substituted, highly functionalised cyclohexenes viz 2-amino-5-nitro-4,6-diarylcyclohex-1-ene-1,3,3-tricarbonitrile. The methodology successfully exploits the advantages of polymer supported reagents for the synthesis of various organic compounds.

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