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Synthesis of N-Substituted 1,3,5-Triazacyclohexanes Catalyzed by Starch Sulfuric Acid

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N-substituted 1,3,5-triazacyclohexanes were simply synthesized from the reaction of aromatic or fatty amines and formaldehyde catalyzed by recyclable starch sulfuric acid with good yields at room temperature.

Key Words: Azacyclohexanes, Synthesis, Starch sulfuric acid.

INTRODUCTION

During the last 10 years, N-substituted 1,3,5-triazacyclohexane (R_3TAC) is causing more and more interest due to their use in coordination chemistry and catalysis[1], systems switchable under the action of light or redox transformations[2,3], metal-template effects in the redox formation of crown ethers[2], allosteric effects in multicontour crown systems[4], as well as in recognition, extraction, detection and other applications requiring molecular selectivity[5]. It's products have also attained prominence to meet the requirements of increased stability and insensitivity coupled with high performance or a favourable compromise[6].

This series of compounds is easily accessible and highly variable due to its simple preparation from primary amines and formaldehyde[7]. However, many of those methods were carried out under toxic organic solvent or expensive catalysts with moderate yield.

In our previous work[8], starch sulfuric acid (SSA) was synthesized and successfully used as catalyst to promote some interesting reaction. We reported herein full details of a convenient procedure for the preparation of N-substituted 1,3,5-triazacyclohexane from the one-pot reaction of formaldehyde and aromatic or fatty amines also catalyzed by starch sulfuric acid at room temperature (**Scheme-I**).

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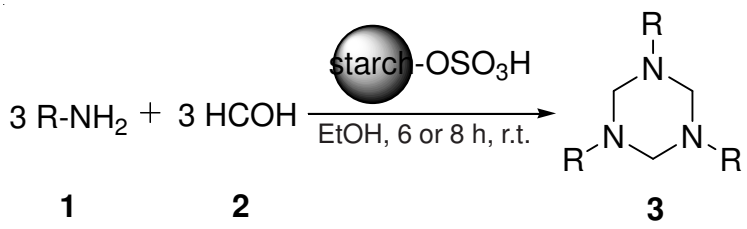

Scheme-I

EXPERIMENTAL

All reagents were purchased from commercial sources and used without further purification. TLC analysis was performed with glass backed plates precoated with silica gel and examined under UV (254 nm). NMR spectra were measured in $CDCl_3$ with Me_4Si as the internal standards on a Bruker Advance DPX- 400 at room temperature. IR spectra were recorded on Brucker FT-IR spectrometer, absorbencies are reported in cm^{-1}. Elemental analyses were performed on a Perkin-Elmer-2400 elemental analyzer.

General procedure for the synthesis of compound 3: In a 50 mL reaction flask, a mixture of amines (2.0 mmol), formaldehyde (2.0 mmol) and starch sulfuric acid (0.08 g) were stirred in EtOH (2.0 mL) at room temperature for 6-8 h. The solution was extracted with ethyl acetate and the organic phase was dried with anhydrous Na_2SO_4 and condensation under vacuum. The products were obtained by recrystalized the crude mixtures with EtOH (95 %) and DMF. In addition, the residue which containing catalyst was rinsed with ethyl acetate and dried under a vacuum to give recycled catalyst.

Spectral data

1,3,5-*Tris*(4-fluorophenyl)-1,3,5-triazinane (3a): IR (KBr, ν_{max}, cm^{-1}): 3051, 2967, 1610, 1507, 1225, 815. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.07-7.10 (m, 6H, m-Ar-H), 6.96-7.01 (t, 6H, *J* = 8.0 Hz, *o*-Ar-H), 4.80 (s, 6H, CH_2). Anal. calcd. (%) for $C_{21}H_{18}N_3F_3$: C, 68.23; H, 4.91; N, 11.38. Found (%): C, 68.15; H, 4.72; N, 11.49.

1,3,5-*Tris*(4-chlorophenyl)-1,3,5-triazinane (3b): IR (KBr, ν_{max}, cm^{-1}): 2938, 2849, 1594, 1494, 1449, 816. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.20 (d, 6H, *J* = 8.0 Hz, m-Ar-H), 7.07 (d, 6H, *J* = 8.0 Hz, *o*-Ar-H), 4.91 (s, 6H, CH_2). Anal. calcd. (%) for $C_{21}H_{18}N_3Cl_3$: C, 60.23; H, 4.33; N, 10.03. Found (%): C, 60.26; H, 4.27; N, 10.13.

1,3,5-*Tris*(4-bromophenyl)-1,3,5-triazinane (3c): IR (KBr, ν_{max}, cm^{-1}): 2977, 1667, 1610, 1521, 1426, 1260, 1043, 804. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.51 (d, 6H, *J* = 8.4 Hz, m-Ar-H), 6.48 (d, 6H, *J* = 8.4 Hz, *o*-Ar-H), 5.41 (s, 6H, CH_2). Anal. calcd. (%) for $C_{21}H_{18}N_3Br_3$: C, 45.68; H, 3.29; N, 7.61. Found (%): C, 45.73; H, 3.21; N, 7.53.

1,3,5-*Tris*(4-nitrophenyl)-1,3,5-triazinane (3d): IR (KBr, ν_{max}, cm^{-1}): 2981, 1671, 1610, 1537, 1430, 1269, 1033, 813. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.12 (d, 6H, *J* = 8.4 Hz, m-Ar-H), 6.93 (d, 6H, *J* = 8.4 Hz, *o*-Ar-H), 5.43 (s, 6H, CH_2). Anal. calcd. (%) for $C_{21}H_{18}N_6O_6$: C, 56.00; H, 4.03; N, 21.31. Found (%): C, 55.78; H, 4.21; N, 21.18.

1,3,5-Triphenyl-1,3,5-triazinane (3h): IR (KBr, ν_{max}, cm^{-1}): 2865, 1662, 1518, 1225, 809, 623. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.21 (m, 9H, *o*, *p*-Ar-H), 7.08 (m, 6H, m, Ar-H), 4.92 (s, 6H, CH_2). Anal. calcd. (%) for $C_{21}H_{21}N_3$: C, 79.97; H, 6.71; N, 13.32. Found (%): C, 79.82; H, 6.80; N, 13.26.

1,3,5-Tri-*p*-tolyl-1,3,5-triazinane (3i): IR (KBr, ν_{max}, cm^{-1}): 2878, 2604, 1576, 1499, 1170, 1025. ^1H NMR (400 MHz, $CDCl_3$): δ = 6.97-6.71 (m, 12H, Ar-H), 4.76 (s, 6H, CH_2), 2.18 (s, 9H, CH_3). Anal. calcd. (%) for $C_{24}H_{27}N_3$: C, 80.63; H, 7.61; N, 11.75. Found (%): C, 80.51; H, 7.86; N, 11.70.

1,3,5-*Tris*(4-methoxyphenyl)-1,3,5-triazinane (3j): IR (KBr, ν_{max}, cm^{-1}): 2977, 1601, 1520, 1260, 1043, 737. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.02 (d, 6H, m-Ar-H), 6.78 (d, 6H, *o*-Ar-H), 4.66 (s, 6H, CH_2), 3.67 (s, 9H, OCH_3). Anal. calcd. (%) for $C_{24}H_{27}N_3O_3$: C, 71.09; H, 6.71; N, 11.84. Found (%): C, 71.01; H, 6.61; N, 11.76.

1,3,5-Trimethyl-1,3,5-triazinane (3m): ^1H NMR (400 MHz, $CDCl_3$): δ = 3.39 (s, 6H, CH_2), 2.09 (s, 9H, CH_3). Anal. calcd. (%) for $C_6H_{15}N_3$: C, 55.78; H, 11.70; N, 32.52. Found (%): C, 55.67; H, 11.58; N, 32.41.

1,3,5-Triethyl-1,3,5-triazinane (3n): ^1H NMR (400 MHz, $CDCl_3$): δ = 3.32 (s, 6H, CH_2), 2.31 (q, 6H, CH_2), 0.98 (t, *J* = 7.2 Hz, 9H, CH_3). Anal. calcd. (%) for $C_9H_{21}N_3$: C, 63.11; H, 12.36; N, 24.53. Found (%): C, 63.23; H, 12.29; N, 24.41.

1,3,5-Tri-isopropyl-1,3,5-triazinane (3o): ^1H NMR (400 MHz, $CDCl_3$): δ = 3.43 (s, 6H, CH_2), 2.89 (m, 3H, CH), 1.02 (d, *J* = 6.8 Hz, 18H, CH_3). Anal. calcd. (%) for $C_{12}H_{27}N_3$: C, 67.55; H, 12.75; N, 19.69. Found (%): C, 67.49; H, 12.68; N, 19.81.

RESULTS AND DISCUSSION

At the beginning, three acids were tested in the reaction of *p*-fluoroaniline and formaldehyde. The reaction was carried out at room temperature in EtOH for 8 h. No product was detected in the control reaction (Table-1, entry 1). Interestingly, we found that HCl and H_2SO_4 did not catalyze this reaction (entries 2-3). When starch sulfuric acid was used, the results seemed to be better, it promoted this reaction to afford desired product with 88 % yield at room temperature (Table-1, entry 4). The efficient catalystic activity of starch sulfuric acid was not only from its Brønsted acidity but also from its surfactancy. This colloidal dispersion increases solubility of three organic reagents in solvent. In addition, compared with other classic solvents and water (Table-1, entries 4-9), the best results were observed in EtOH (Table-1, entry 4). The optimum amount of catalyst was determined from corresponding experiments (Table-1, entries 10-13). Finally, reaction time screening (Table-1, entries 14-17) revealed that the reaction performed in 8 h afforded the best result.

TABLE-1
TESTING OF DIFFERENT REACTION CONDITIONS
BASED ON THE MODEL REACTION

Entry	Solvent	Catalyst (g)	Time (h)	Yield* (%)
1	EtOH	-	8	Nr**
2	EtOH	HCl (0.08)	8	Nr**
3	EtOH	H_2SO_4 (0.08)	8	Nr**
4	EtOH	SSA (0.08)	8	88
5	CH_3CN	SSA (0.08)	8	75
6	CH_2Cl_2	SSA (0.08)	8	63
7	Ethyl acetate	SSA (0.08)	8	58
8	H_2O	SSA (0.08)	8	Nr**
9	MeOH	SSA (0.08)	8	76
10	EtOH	SSA (0.02)	8	78
11	EtOH	SSA (0.04)	8	75
12	EtOH	SSA (0.06)	8	63
13	EtOH	SSA (0.10)	8	40
14	EtOH	SSA (0.08)	2	53
15	EtOH	SSA (0.08)	4	69
16	EtOH	SSA (0.08)	6	84
17	EtOH	SSA (0.08)	10	87

*Isolated yields; **No reaction; SSA = Starch sulfuric acid.

The scope of the reaction of various aromatic amines and formaldehyde in the presence of starch sulfuric acid was evaluated first. As shown in Table-2, the electronic effect and steric effect of substituted group in aromatic amine have serious influence on the yields. Aromatic aldehydes bearing electron-donoring group gave better results than that bearing electron-withdrawing group, especially the electron-withdrawing group at the *ortho*- or *meta*-position (Table-2, entries 5-7 and 11-12).

Subsequently, the reactions of aliphatic amines such as methanamine, ethanamine, *n*-propanamine (Table-2, entries 13-15) and formaldehyde were also studied. Comparing with aromatic amines, all of them gave excellent yields except cyclohexanamine due to their stronger basicity and nucleophility. This result indicate the extended scope of starch sulfuric acid as catalyst. The crystal of product (**3j**) were afforded by recrystallized the crude mixtures with EtOH (95 %) and DMF[9] (Fig. 1).

One of the main aims of using catalyst was to study the possibility of its recycle and reuse, for the same as well as different types of reaction. We found that the recycling of starch sulfuric acid is viable and recycled for the reaction of *p*-fluoroaniline and formaldehyde. The reaction was carried out five times in consecutive runs with only a slight decrease in isolated yields (Table-3).

In conclusion, it is found that the preparation for 1,3,5-triazacyclohexanes from amines and formaldehyde can be efficiently catalyzed by starch sulfuric acid at room temperature. The significant features of this procedure include: (1) a novel and efficient catalyst; (2) high yields; (3) mild condition. In addition, this series of 1,3,5-triazacyclohexanes may prove new classes of biological active compound for biomedical screening, which is in progress in our laboratories.

TABLE-2
SYNTHESIS OF 1,3,5-TRIAZACYCLOHEXANES
FROM AMINES AND FORMALDEHYDE*

Entry	Product	R	Time (h)	Yield** (%)
1	**3a**	4-FC_6H_4	6	88
2	**3b**	4-ClC_6H_4	6	83
3	**3c**	4-BrC_6H_4	6	79
4	**3d**	4-$NO_2C_6H_4$	8	76
5	**3e**	2-ClC_6H_4	8	<10
6	**3f**	2-BrC_6H_4	8	<10
7	**3g**	3-$NO_2C_6H_4$	8	Nr***
8	**3h**	C_6H_5	6	83
9	**3i**	4-Me C_6H_4	8	76
10	**3j**	4-$OMeC_6H_4$	8	78
11	**3k**	2-Me C_6H_4	8	<10
12	**3l**	2-OMe C_6H_4	8	<10
13	**3m**	-CH_3	6	87
14	**3n**	-C_2H_5	6	86
15	**3o**	-iso-C_3H_7	6	83
16	**3p**	Cyclohexan-	8	Nr***

*Reaction conditions: amines (2.0 mmol), formaldehyde (2.0 mmol) and catalyst (0.08 g);
**Isolated yield; ***No reaction.

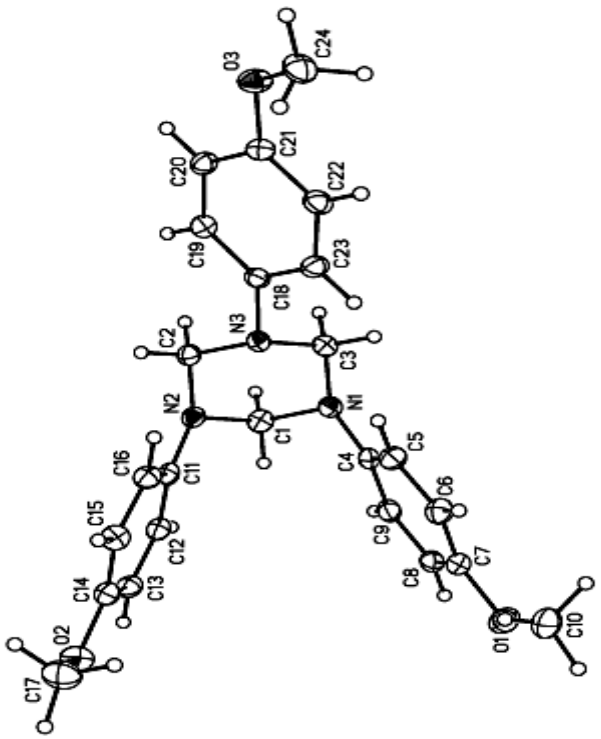

Fig. 1. X-ray structure of compound **3j**

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9. The single crystal growth was carried out in EtOH and DMF at room temperature. Crystal data for **3j**: empirical formula: $C_{24}H_{27}N_3O_3$, colourless, crystal dimension: 0.38 × 0.26 × 0.20 mm, monoclinic, space group: C2/c, a = 26.913(4) Å, b = 11.0868(14) Å, c = 14.088(2) Å, $\alpha = 90^\circ$, $\beta = 100.124(4)^\circ$, $\gamma = 90^\circ$, V = 4137.9(10) $Å^{-3}$, Mr = 405.49, Z = 8, Dc = 1.302 Mg/m^{-3}, λ = 0.71070 Å, $\mu(MoK\alpha)$ = 0.087 mm^{-1}, F(000) = 1728, R1 = 0.0694, wR_2 = 0.1305, number of reflections collected and number of unique reflections is 19831 and 3798 respectively. Crystallographic data for the structure of **3j** reported in this letter have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication No. CCDC-714677.

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