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A FACILE AND EFFICIENT ULTRASOUND-ASSISTED SYNTHESIS OF 1,3,5-TRIS-ARYLHEXAHYDRO-1,3,5-TRIAZINE THROUGH MANNICH REACTION

Xiaoxing Zhong and Guolan Dou*

School of Safety Engineering, China University of Mining &Technology, Xuzhou 221116, China. e-mail: gldou@yahoo.cn

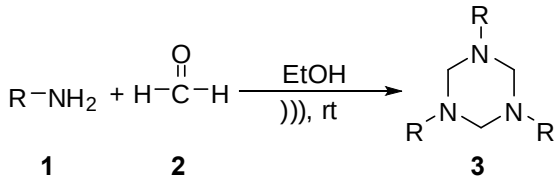
Abstract – In this paper, we report a facile and efficient method for the synthesis of 1,3,5-tris-arylhexahydro-1,3,5-triazines by reaction of formaldehyde and aromatic amines catalyzed by triethylamine (Et_3N) and assisted by ultrasound at rt. This method has the advantages of short reaction times, good.

It is well-known that heterocycles are abundant in nature and are of great significance to life. N-Substituted 1,3,5-triazacyclohexanes are an important class of heterocyclic compounds due to their use in coordination chemistry and systems switchable under the action of light or redox transformations,[1-3] catalysis,[4] metal-template effects in the redox formation of crown ethers,[1] allosteric effects in multicontour crown systems,[5] as well as in recognition, extraction, detection and other applications requiring molecular selectivity.[6] Moreover, 1,3,5-tris-arylhexahydro-1,3,5-triazines are frequently used as precursors to imines, starting materials for further synthesis. For example, several novel Schiff base macrocyclic compounds of 1,3,5-triazine were synthesized.[7] For these reasons, much attention has been paid to the synthesis and stereodynamics of N-substituted 1,3,5-triazacyclohexanes.

The synthesis of 1,3,5-trisubstituted-1,3,5-triazines is effected by condensation of formaldehyde and amines in the classical Mannich reaction.[8-13] However, many of those methods suffer from some disadvantages such as drastic conditions, unsatisfactory yields, and long-reaction time. Rivera and coworkers reported a facile and efficient procedure for the synthesis of 1,3,5-tris-arylhexahydro-1,3,5-triazines,[14] but the use of 1,3,6,8-tetrazatricyclo[4.4.1.$1^{3.8}$]dodecane (TATD) is less than ideal because the commercial availability of TATD is very limited, and we also found that only four products were synthesized using this method. Therefore, the development of an efficient, rapid, and clean synthetic route of such compounds is of great importance to synthetic chemists.

Ultrasonic irradiation,[15-19] as a powerful tool in modern chemistry, has been widely applied in organic

synthesis. It accelerates a variety of advantages such as convenient operation, mild reaction conditions, short reaction time and high efficiency.[20,21] In this work, we report a facile and efficient synthesis of 1,3,5-tris-arylhexahydro-1,3,5-triazines using formaldehyde and aromatic amines promoted by ultrasound at rt (Scheme 1).



Scheme 1

Initially we studied the synthesis of 1,3,5-triazines using 37% aqueous formaldehyde and *p*-toluidine as model substrates under both stirring (Method A) and ultrasound irradiation (Method B) conditions. The results are shown in Table 1.

Table 1. Optimization of catalyst in the synthesis of **3a** under classical stirring and ultrasound irradiation.

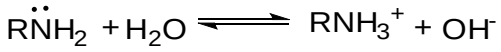
Entry	Catalyst	Method A (without US[a])		Method B (with US[b])	
		Time	Isolated yield (%)	Time	Isolated yield (%)
1	No	24 h	36	12 h	73
2	H_2SO_4 (10%)	8 h	76	6 h	85
3	pyridine (10%)	8 h	63	6 h	70
4	Et_3N (10%)	6 h	85	15 min	96

[a] Reaction under stirring.

[b] Reaction under ultrasonic (US) waves at rt and the ultrasonic power 250 W, irradiation frequency 40 kHz.

It can be seen from the Table 1 that the reaction performed under classical stirring condition afforded comparatively lower yields at long reaction time. Then we have studied the sonochemical effect on model reaction. In all cases, the experimental results show that the reaction times are shorter and the yields of the products are higher under sonication. To improve the yields, some catalysts such as H_2SO_4, pyridine and Et_3N were examined (Table 1, entries 2-4), With the exception of the reaction, it is notable that Et_3N is identified as the optimal catalyst, with **3a** being isolated in 96% yield (Table 1, entry 4). Then we evaluated the amount of Et_3N required for this reaction (Table 2). It was found that when increasing the amount of Et_3N from 5 to 10%, the yields increased from 92 to 96%. Using 10% mol Et_3N is sufficient to push this reaction forward. More amounts of the catalysts did not improve the yields (Table 2, entry 3). Thus, 10% Et_3N is the choice for this reaction under ultrasound irradiation. This reaction is a Mannich

reaction, so we conclude that the reason of Et_3N promoted the reaction is that the following reaction (Scheme 2) moved to left so that increasing the nucleophilic activity of amine.



Scheme 2

Table 2. Optimization of amount of Et_3N required for the reaction

Entry	catalyst	time	Yield/%
1	Et_3N (10%)	15 min	96%
2	Et_3N (5%)	15 min	92%
3	Et_3N (20%)	15 min	95%

In order to demonstrate the scope of this synthetic methodology, we investigated a variety of commercially available amines with formaldehyde assisted by ultrasound, using Et_3N as Brønsted bases. The results are summarized in Table 3.

Table 3. Synthesis of 1,3,5-tris-arylhexahydro-1,3,5-triazines from amines and formaldehyde

Entry	Product	R	Time	Isolated yield (%)
1	**3a**	4-MeC_6H_4	15 min	96
2	**3b**	3,4-$Me_2C_6H_3$	30 min	86
3	**3c**	3-MeC_6H_4	20 min	85
4	**3d**	3-Cl-4-MeC_6H_3	30 min	80
5	**3e**	4-$MeOC_6H_4$	15 min	88
6	**3f**	C_6H_5	15 min	98
7	**3g**	4-ClC_6H_4	5 h	Nr[a]
8	**3h**	4-BrC_6H_4	1 h	<10
9	**3i**	2,4-$Cl_2C_6H_3$	5 h	Nr[a]

[a] No reaction

The scope of the reaction of various aromatic amines and formaldehyde catalyzed by Et_3N and promoted by ultrasound at rt was evaluated. As shown in Table 3, we found that the method can be applied not only to the aromatic amines, but also to heteroaromatic amines. However, the electronic effect of substituted

group in aromatic amine have serious influence on the yields. Aromatic amines bearing electron-donating groups (Table 3, entries 1-6) have better results than that bearing electron-withdrawing groups (entries 8-10). As steric hindrance of the aryl amine increased and nucleophilicity decreased, the reaction was also impeded by severe steric hindrance. For example, no desired product was obtained when 2,4-dichloroaniline was used (entry 9).

The structures of all the products **3** were established by IR and ^{1}H NMR, and new synthesized products were established by HRMS spectroscopy. Furthermore, the structure of product **3a** has been confirmed by X-ray analysis. The molecular structure of the product **3a** is shown in Figure 1.[22]

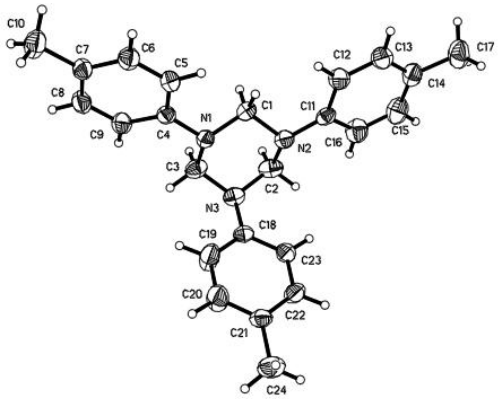


Figure 1. Molecular structure of product **3a**

From Figure 1, we found that the ring of heterocyclohexane adopts the chair conformation. With the use of Density Function Theory (DFT) and the computer programme, B3LYP/6-31G, a geometrical optimization of the product **3a** was obtained. The optimized geometry of **3a** was shown in Figure 2. From Figure 2, we found the ring adopts chair conformation too.

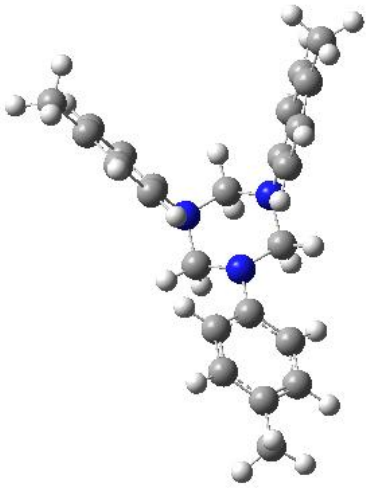


Figure 2. Optimized geometry of **3a**

In conclusion, it is found that the preparation of 1,3,5-tris-arylhexahydro-1,3,5-triazines from amines and formaldehyde can be efficiently catalyzed by Et_3N under sonochemical conditions at rt. Because of the advantages of ultrasonic irradiation of mild reaction conditions, short reaction time, mild reaction conditions, convenient disposition and high efficiency, it is quite valuable to develop the 1,3,5-tris-arylhexahydro-1,3,5-triazines under this conditions.

EXPERIMENTAL

All reagents were purchased from commercial sources and used without further purification. Melting points are uncorrected. IR spectra were recorded on a Nicolet 6700 spectrometer in KBr with absorptions in cm^{-1}. ^1H NMR were determined in a Bruker Advance DPX- 400 MHz spectrometer in DMSO-d_6 and $CDCl_3$ solution. *J* values are in Hz. Chemical shifts are expressed in ppm downfield from internal standard TMS. HRMS data were obtained using TOF–MS microma GCT-TOF instrument. X-Ray diffractions were recorded on a Siemens P4 diffractometer. Elemental analyses were performed on a Perkin-Elmer-2400 elemental analyzer. Sonication was performed in a SY5200DH-T ultrasound cleaner with a frequency of 40 kHz and an output power of 250 W. The reaction flask was located at the maximum energy area.

General procedure for the synthesis of compound **3** under sonochemical conditions

A dry 50 mL flask was charged with 37% aqueous formaldehyde (1.0 mmol), amines (1.0 mmol) and Et_3N (0.1 mmol) and EtOH (10 mL). The mixture was sonicated in the water bath of an ultrasonic cleaner under air condition at 25 °C (monitored by TLC). After completion of the reaction, the solvent was removed under vacuum. The resulting crude products were purified by recrystallization from EtOH.

1,3,5-Tri-*p*-tolyl-1,3,5-triazinane (**3a**): mp 125-126 °C (lit.,[23,24] 126-127 °C), IR (KBr): 3029, 2917, 2863, 2734, 1613, 1573, 1517, 1470, 1416, 1325, 1240, 1208, 1175, 1014, 960, 886, 804. ^1H NMR (DMSO-d_6, δ): 2.10 (s, 9H, 3 × CH_3), 4.68 (s, 6H, 3 × CH_2), 6.87-6.89 (m, 6H, ArH), 6.92-6.94 (m, 6H, ArH).

1,3,5-Tris(3,4-dimethylphenyl)-1,3,5-triazinane (**3b**): mp 134-135 °C, IR (KBr): 3013, 2964, 2919, 2857, 1612, 1568, 1510, 1339, 1262, 1190, 1176, 1125, 1004, 973, 890, 846, 801. ^1H NMR ($CDCl_3$, δ): 2.16 (s, 9H, 3 × CH_3), 2.19 (s, 9H, 3 × CH_3), 4.71 (s, 6H, 3 × CH_2), 6.76-6.80 (m, 6H, ArH), 6.98-6.99 (m, 3H, ArH). HRMS [Found: *m/z* 399.2907 (M^+), calcd for $C_{27}H_{33}N_3$: M, 399.2674]. Anal. Calcd for $C_{27}H_{33}N_3$: C, 81.16; H, 8.32; N, 10.52. Found: C, 81.01; H, 8.41; N, 10.46.

1,3,5-Tri-*m*-tolyl-1,3,5-triazinane (**3c**): mp 120-121 °C, IR (KBr): 3040, 2917, 2883, 1600, 1580, 1537, 1496, 1455, 1416, 1397, 1315, 1268, 1211, 1194, 1169, 1002, 968, 874, 839, 776, 769, 691. ^1H NMR ($CDCl_3$, δ,): 2.27 (s, 9H, 3 × CH_3), 4.82 (s, 6H, 3 × CH_2), 6.69 (d, J = 7.2 Hz, 3H, ArH), 6.80-6.82 (m, 6H, ArH), 7.09-7.13 (m, 3H, ArH). HRMS [Found: *m/z* 357.2430 (M^+), calcd for $C_{24}H_{27}N_3$: M, 357.2205]. Anal. Calcd for $C_{24}H_{27}N_3$: C, 80.63; H, 7.61; N, 11.75. Found: C, 80.41; H, 7.79; N, 11.62.

1,3,5-Tris(3-chloro-4-methylphenyl)-1,3,5-triazinane (**3d**): mp 137-138 °C, IR (KBr): 3027, 2944, 2882, 2853, 1609, 1580, 1562, 1537, 1504, 1497, 1471, 1463, 1365, 1250, 1271, 1043, 1002, 967, 891, 873, 856, 847, 802. ^{1}H NMR ($CDCl_3$, δ): 2.26 (s, 9H, 3 × CH_3), 4.74 (s, 6H, 3 × CH_2), 6.79 (dd, J_1 = 2.4 Hz, J_1 = 8.4 Hz, 3H, ArH), 6.96 (d, J = 2.4 Hz, 3H, ArH), 7.05 (d, J = 8.0 Hz, 3H, ArH). HRMS [Found: *m/z* 459.1263 (M^+), calcd for $C_{24}H_{24}Cl_3N_3$: M, 459.1036]. Anal. Calcd for $C_{24}H_{24}Cl_3N_3$: C, 62.55; H, 5.25; N, 9.12. Found: C, 62.69; H, 5.19; N, 9.23.

1,3,5-Tris(4-methoxyphenyl)-1,3,5-triazinane (**3e**): mp 132-133 °C (lit.,[23,24] 131-132 °C), IR (KBr): 2995, 2955, 2930, 2912, 1513, 1463, 1451, 1274, 1245, 1189, 1160, 1034, 983, 833, 827, 820, 804. ^{1}H NMR ($CDCl_3$, δ): 3.74 (s, 9H, 3 × CH_3O), 4.67 (s, 6H, 3 × CH_2), 6.77-6.79 (m, 6H, ArH), 6.99-7.02 (m, 6H, ArH).

1,3,5-Triphenyl-1,3,5-triazinane (**3f**): mp 140-141 °C (lit.,[23,24] 145 °C), IR (KBr): 3092, 3066, 2941, 2847, 1597, 1557, 1537, 1504, 1468, 1375, 1228, 1192, 1163, 1022, 991, 971, 934, 920, 882, 838, 752, 691. ^{1}H NMR ($CDCl_3$, δ): 4.88 (s, 6H, 3 × CH_2), 6.86 (t, J = 7.2 Hz, 3H, ArH), 6.99-7.02 (m, 6H, ArH), 7.19-7.22 (m, 6H, ArH).

1,3,5-Tris(4-bromophenyl)-1,3,5-triazinane (**3h**): mp 170-172 °C (lit.,[23] 169-170 °C), IR (KBr): 3050, 2977, 2880, 1667, 1610, 1521, 1426, 1260, 1170, 1043, 970, 864, 804, 775. ^{1}H NMR ($CDCl_3$, δ): 4.82 (s, 6H, 3 × CH_2), 7.32-7.34 (m, 12H, ArH).

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22. Crystal data for **3a**: $C_{24}H_{27}N_3$; M = 357.49, colorless block crystal, 0.45×0.28×0.22 mm, monoclinic, space group P2(1)/c, a = 11.5493(11), b = 5.8979(8), c = 29.320(2) Å, α = 90, β = 98.3780(10), γ = 90 º, V = 1975.9(4) Å^3, Z = 4, Dc = 1.202 g.cm^{-3}, F(000) = 768, $\mu(M_oK_\alpha)$ = 0.071 mm^{-1}. Intensity data were collected on a Smart-1000 diffractometer with graphite monochromated M_oK_α radiation (λ = 0.71073 Å) using the ω scan mode with 2.42º<θ<25.52º. 3475 unique reflections were measured and reflections with $I > 2\ \sigma\ (I)$ were used in the Fourier techniques. The final refinement was converged to R = 0.0670 and wR = 0.1644.
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