

A Clean and Efficient Method for the Synthesis of 3-Aroyl-2,4,6-triaryl-4-hydroxy-1,1-cyclohexanedicarbonitriles in Water

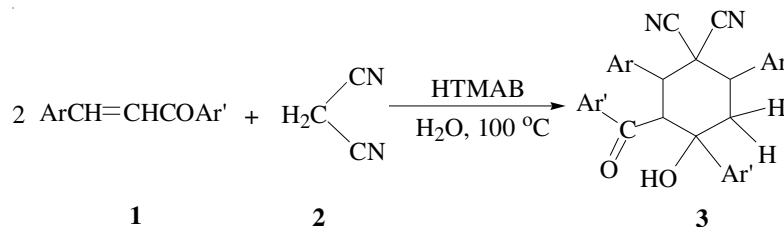
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A clean and efficient chemistry route to the synthesis of 3-aryol-2,4,6-triaryl-4-hydroxy-1,1-cyclohexanedicarbonitriles using hexadecyltrimethyl ammonium bromide (HTMAB) as the catalyst (5 mol %) in aqueous media is described. This method provides several advantages such as neutral conditions, high yields and simple work-up procedure. In addition, water was chosen as a green solvent.

Key Words: 3-Aroyl-2,4,6-triaryl-4-hydroxy-1,1-cyclohexanedicarbonitriles, Malononitrile, 1,3-Diaryl-2-propene-1-ones, Clean synthesis.

INTRODUCTION

With the increasing environmental concerns and the regulatory constraints faced by the chemical and pharmaceutical industries, development of environmentally benign organic reactions has become a crucial and demanding research area in modern organic chemical research^{1,2}. Therefore, more and more chemists involved with research in green synthesis, which means that the reagent, solvent and catalyst are environmentally friendly in the reactions. Recently organic reactions in water without use of harmful organic solvents have attracted much attention, because water is a cheap, safe and environmentally benign solvent³⁻⁷. But, water as a solvent was not frequently used until recently for several reasons such as many organic materials do not dissolve in water. So it is necessary for add some phase-transfer catalyst or surfactant. Hexadecyltrimethyl ammonium bromide (HTMAB) is a good phase transfer catalyst. As reported in previous papers⁸⁻¹³, some reactions which can take place in water were examined in our laboratory. In this manuscript, we wish to report a general and highly efficient route for the synthesis of 3-aryol-2,4,6-triaryl-4-hydroxy-1,1-cyclohexanedicarbonitriles using HTMAB as catalyst in aqueous media (**Scheme-I**). Usually these compounds are synthesized under basic conditions in organic solvent¹⁴⁻¹⁸. The usual catalysts for the preparation are sodium ethoxide, piperidine, triethylamine and diethylamine. However, the use of HTMAB as a catalyst in water for the synthesis of the 3-aryol-2,4,6-triaryl-4-hydroxy-1,1-cyclohexanedicarbonitriles has not been reported.



Scheme-I

EXPERIMENTAL

Liquid aldehydes were distilled before use. IR spectra were recorded on a Bio-Rad FTS-40 spectrometer (KBr). ^1H NMR spectra were measured on a Bruker Avance 400 (400 MHz) spectrometer using TMS as internal reference and CDCl_3 or $\text{DMSO}-d_6$ solvent. Elemental analyses were determined using Perkin-Elmer 2400 II elemental analyzer.

General procedure for the preparation of 3-aryl-2,4,6-triaryl-4-hydroxy-1,1-cyclohexanedicarbonitriles: A mixture of chalcones (**1**) (1 mmol), malononitrile (**2**) (1 mmol) and HTMAB (5 mol %) in water (20 mL) was stirred at 100°C for 3 h. The progress of the reaction was monitored by thin layer chromatograph (TLC). After completion of the reactions, the mixture was cooled to room temperature, solid was filtered off and washed with H_2O (40 mL). The crude products were purified by recrystallization by ethanol (95 %). Data of some compounds are shown below:

3a: IR (KBr, cm^{-1}): 3430, 2260, 1646, 1600. ^1H NMR (CDCl_3): δ 2.29 (dd, 1H, $J_1 = 14.6$ Hz, $J_2 = 2.8$ Hz, H_b), 2.92 (dt, 1H, $J_1 = 13.6$ Hz, $J_2 = 2.8$ Hz, H_c), 4.21 (br. d, 2H, $J = 12.0$ Hz, H_d , H_e), 4.85 (d, 1H, $J = 12.0$ Hz, H_f), 5.23 (d, 1H, $J = 2.4$ Hz, H_a), 7.14-7.60 (m, 20H, Ar-H) ppm. Anal. calcd. (%) for $\text{C}_{33}\text{H}_{26}\text{N}_2\text{O}_2$: C 82.13, H 5.43, N 5.80; Found (%) C 82.02, H 5.48, N 5.87.

3b: IR (KBr, cm^{-1}): 3445, 2250, 1650, 1600. ^1H NMR (CDCl_3): δ 2.17 (s, 3H, CH_3), 2.25 (dd, 1H, $J_1 = 14.4$ Hz, $J_2 = 2.8$ Hz, H_b), 2.38 (s, 3H, CH_3), 2.89 (dt, 1H, $J_1 = 13.6$ Hz, $J_2 = 2.4$ Hz, H_c), 4.15 (dd, 1H, $J_1 = 12.8$ Hz, $J_2 = 2.8$ Hz, H_b), 4.17 (d, 1H, $J = 12.0$ Hz, H_e), 4.83 (d, 1H, $J = 12.0$ Hz, H_f), 5.16 (d, 1H, $J = 2.4$ Hz, H_a), 6.93-7.53 (m, 18H, Ar-H) ppm. Anal. calcd. (%) for $\text{C}_{35}\text{H}_{30}\text{N}_2\text{O}_2$: C 82.33, H 5.92, N 5.49; Found (%) C 82.41, H 5.87, N 5.57.

3c: IR (KBr, cm^{-1}): 3430, 2260, 1650, 1600. ^1H NMR (CDCl_3): δ 1.98 (dd, 1H, $J_1 = 14.4$ Hz, $J_2 = 2.8$ Hz, H_b), 3.01 (dt, 1H, $J_1 = 13.6$ Hz, $J_2 = 2.8$ Hz, H_c), 4.20 (br. d, 2H, H_d , H_e), 4.54 (d, 1H, $J = 11.6$ Hz, H_f), 5.82 (d, 1H, $J = 2.4$ Hz, H_a), 5.95 (m, 4H, $-\text{OCH}_2\text{O}-$), 6.82-7.52 (m, 16H, Ar-H) ppm. Anal. calcd. (%) for $\text{C}_{35}\text{H}_{26}\text{N}_2\text{O}_6$: C 73.67, H 4.59, N 4.91; Found (%) C 73.73, H 4.48, N 4.87.

3d: IR (KBr, cm^{-1}): 3440, 2260, 1650, 1600. ^1H NMR (CDCl_3): δ 1.94 (dd, 1H, $J_1 = 14.6$ Hz, $J_2 = 2.8$ Hz, H_b), 2.79 (s, 6H, CH_3), 2.92 (s, 6H, CH_3), 3.02 (dt, 1H, $J_1 = 13.6$ Hz, $J_2 = 2.8$ Hz, H_c), 4.21 (dd, 1H, $J_1 = 12.8$ Hz, $J_2 = 2.4$ Hz, H_d), 4.22 (d, 1H,

$J = 11.6$ Hz, H_c), 4.59 (d, 1H, $J = 12.0$ Hz, H_f), 5.58 (d, 1H, $J = 2.4$ Hz, H_a), 6.51-7.52 (m, 18H, Ar-H) ppm. Anal. calcd. (%) for $C_{37}H_{36}N_4O_2$: C 78.14, H 6.38, N 9.85; Found (%) C 78.21, H 6.26, N 9.87.

3e: IR (KBr, cm^{-1}): 3450, 2230, 1650, 1600. 1H NMR ($CDCl_3$): δ 2.19 (dd, 1H, $J_1 = 14.4$ Hz, $J_2 = 2.8$ Hz, H_b), 3.00 (dt, 1H, $J_1 = 13.6$ Hz, $J_2 = 2.4$ Hz, H_c), 4.62 (dd, 1H, $J_1 = 12.8$ Hz, $J_2 = 2.8$ Hz, H_d), 4.64 (d, 1H, $J = 11.6$ Hz, H_e), 4.90 (d, 1H, $J = 11.6$ Hz, H_f), 5.97 (d, 1H, $J = 2.4$ Hz, H_a), 7.13-8.15 (m, 18H, Ar-H) ppm. Anal. calcd. (%) for $C_{33}H_{24}N_4O_6$: C 69.22, H 4.22, N 9.79; Found (%) C 69.14, H 4.17, N 9.87.

3f: IR (KBr, cm^{-1}): 3450, 2230, 1650, 1600. 1H NMR ($CDCl_3$): δ 2.28 (dd, 1H, $J_1 = 14.4$ Hz, $J_2 = 2.8$ Hz, H_b), 2.95 (dt, 1H, $J_1 = 13.6$ Hz, $J_2 = 2.8$ Hz, H_c), 4.50 (dd, 1H, $J_1 = 12.8$ Hz, $J_2 = 2.4$ Hz, H_d), 4.52 (d, 1H, $J = 12.0$ Hz, H_e), 4.96 (d, 1H, $J = 12.0$ Hz, H_f), 5.28 (d, 1H, $J = 2.4$ Hz, H_a), 7.13-8.15 (m, 18H, Ar-H) ppm. Anal. calcd. (%) for $C_{33}H_{24}N_4O_6$: C 69.22, H 4.22, N 9.79; Found (%) C 69.16, H 4.13, N 9.85.

3g: IR (KBr, cm^{-1}): 3458, 2255, 1650, 1602. 1H NMR ($CDCl_3$): δ 2.18 (dd, 1H, $J_1 = 14.6$ Hz, $J_2 = 2.8$ Hz, H_b), 2.98 (dt, 1H, $J_1 = 13.6$ Hz, $J_2 = 2.8$ Hz, H_c), 4.28 (dd, 1H, $J_1 = 12.6$ Hz, $J_2 = 2.4$ Hz, H_d), 4.30 (d, 1H, $J = 12.0$ Hz, H_e), 4.78 (d, 1H, $J = 12.0$ Hz, H_f), 5.46 (d, 1H, $J = 2.4$ Hz, H_a), 6.96-7.56 (m, 18H, Ar-H) ppm. Anal. calcd. (%) for $C_{33}H_{24}N_2O_2Cl_2$: C 71.87, H 4.39, N 5.08; Found (%) C 71.92, H 4.33, N 5.15.

3h: IR (KBr, cm^{-1}): 3446, 2250, 1650, 1605. 1H NMR ($CDCl_3$): δ 2.15 (s, 3H, CH_3), 2.22 (dd, 1H, $J_1 = 14.4$ Hz, $J_2 = 2.8$ Hz, H_b), 2.34 (s, 3H, CH_3), 2.93 (dt, 1H, $J_1 = 13.6$ Hz, $J_2 = 2.4$ Hz, H_c), 4.17 (dd, 1H, $J_1 = 12.8$ Hz, $J_2 = 2.8$ Hz, H_d), 4.18 (d, 1H, $J = 12.0$ Hz, H_e), 4.83 (d, 1H, $J = 12.0$ Hz, H_f), 5.18 (d, 1H, $J = 2.4$ Hz, H_a), 6.95-7.58 (m, 18H, Ar-H) ppm. Anal. calcd. (%) for $C_{35}H_{30}N_2O_2$: C 82.33, H 5.92, N 5.49; Found (%) C 82.26, H 5.98, N 5.54.

3i: IR (KBr, cm^{-1}): 3430, 2246, 1650, 1600. 1H NMR ($DMSO-d_6$): δ 1.98 (dd, 1H, $J_1 = 14.4$ Hz, $J_2 = 2.4$ Hz, H_b), 3.01 (br. t, 1H, $J = 13.6$ Hz, H_c), 4.24 (d, 1H, $J_1 = 12.8$ Hz, $J_2 = 2.4$ Hz, H_d), 4.25 (d, 1H, $J = 11.6$ Hz, H_e), 4.54 (d, 1H, $J = 12.0$ Hz, H_f), 5.82 (br. s, 1H, H_a), 5.95 (m, 4H, $-OCH_2O-$), 7.11-7.73 (m, 14H, Ar-H) ppm. Anal. calcd. (%) for $C_{35}H_{24}N_2O_6Cl_2$: C 65.74, H 3.78, N 4.38; Found (%) C 65.78, H 3.75, N 4.45.

3j: IR (KBr, cm^{-1}): 3440, 2250, 1650, 1600. 1H NMR ($DMSO-d_6$): δ 2.11 (dd, 1H, $J_1 = 14.4$ Hz, $J_2 = 2.8$ Hz, H_b), 2.18 (s, 3H, CH_3), 2.36 (s, 3H, CH_3), 3.15 (br. t, 1H, $J = 13.6$ Hz, H_c), 4.52 (dd, 1H, $J_1 = 12.8$ Hz, $J_2 = 2.0$ Hz, H_d), 4.54 (d, 1H, $J = 12.0$ Hz, H_e), 4.89 (d, 1H, $J = 12.0$ Hz, H_f), 6.08 (br. s, 1H, H_a), 7.15-8.49 (m, 16H, Ar-H) ppm. Anal. calcd. (%) for $C_{35}H_{28}N_4O_6$: C 69.99, H 4.70, N 9.33; Found (%) C 70.06, H 4.63, N 9.37.

3k: IR (KBr, cm^{-1}): 3446, 2250, 1648, 1600. 1H NMR ($DMSO-d_6$): δ 2.13 (dd, 1H, $J_1 = 14.4$ Hz, $J_2 = 2.4$ Hz, H_b), 3.19 (br. t, 1H, $J = 13.6$ Hz, H_c), 4.60 (dd, 1H, $J_1 = 12.8$ Hz, $J_2 = 2.0$ Hz, H_d), 4.62 (d, 1H, $J = 12.0$ Hz, H_e), 4.87 (d, 1H, $J = 12.0$ Hz, H_f), 6.00 (br. s, 1H, H_a), 7.13-8.52 (m, 16H, Ar-H) ppm. Anal. calcd. for $C_{33}H_{22}N_4O_6Cl_2$: C 61.79, H 3.46, N 8.73; Found (%) C 61.73, H 3.41, N 8.82.

3l: IR (KBr, cm^{-1}): 3460, 2260, 1650 1604. ^1H NMR (DMSO- d_6): δ 2.05 (dd, 1H, $J_1 = 14.4$ Hz, $J_2 = 2.4$ Hz, H_b), 3.13 (br. t, 1H, $J = 13.6$ Hz, H_c), 4.42 (dd, 1H, $J_1 = 12.8$ Hz, $J_2 = 2.4$ Hz, H_d), 4.44 (d, 1H, $J = 12.0$ Hz, H_e) 4.67 (d, 1H, $J = 12.0$ Hz, H_f), 5.90 (br. s, 1H, H_a), 7.11-7.73 (m, 16H, Ar-H) ppm. Anal. calcd. (%) for $\text{C}_{33}\text{H}_{22}\text{N}_2\text{O}_2\text{Cl}_4$: C 63.89, H 3.57, N 4.52; Found (%) C 63.83, H 3.48, N 4.61.

RESULTS AND DISCUSSION

In a typical general experimental procedure, a solution of 1,3-diaryl-2-propene-1-ones (**1**) and malononitrile (**2**) in water was heated in presence of a catalytic amount of HTMAB, the corresponding 3-aroyle-2,4,6-triaryl-4-hydroxy-1,1-cyclohexanedicarbonitriles (**3**) were obtained in good to excellent yields. The results are summarized in Table-1.

TABLE-1
SYNTHESIS OF 3-AROYL-2,4,6-TRIARYL-4-HYDROXY-1,1-CYCLOHEXANEDICARBONITRILES IN WATER

Entry	Ar	Ar'	Product	Yield (%)	m.p. ($^{\circ}\text{C}$)
1	C_6H_5	C_6H_5	3a	90	236-238
2	4- $\text{CH}_3\text{C}_6\text{H}_4$	C_6H_5	3b	80	218-220
3	3,4- $\text{OCH}_2\text{OC}_6\text{H}_3$	C_6H_5	3c	76	256-257
4	4- $\text{Me}_2\text{NC}_6\text{H}_4$	C_6H_5	3d	77	225-227
5	3- $\text{NO}_2\text{C}_6\text{H}_4$	C_6H_5	3e	91	236-238
6	4- $\text{NO}_2\text{C}_6\text{H}_4$	C_6H_5	3f	92	217-219
7	C_6H_5	4- ClC_6H_4	3g	78	198-200
8	C_6H_5	4- $\text{CH}_3\text{C}_6\text{H}_4$	3h	82	238-240
9	3,4- $\text{OCH}_2\text{OC}_6\text{H}_3$	4- ClC_6H_4	3i	80	252-254
10	3- $\text{NO}_2\text{C}_6\text{H}_4$	4- $\text{CH}_3\text{C}_6\text{H}_4$	3j	86	245-247
11	3- $\text{NO}_2\text{C}_6\text{H}_4$	4- ClC_6H_4	3k	88	248-250
12	3- ClC_6H_4	4- ClC_6H_4	3l	87	260-262

According to the results, the effect of electron deficiency and the nature of the substituents on the aromatic rings (Ar not Ar') (Table-1) showed some effect on this conversion. The reaction gave higher yields of 3-aroyle-2,4,6-triaryl-4-hydroxy-1,1-cyclohexanedicarbonitriles when the aromatic rings (Ar) bear an electron-withdrawing substituents (Table-1), probably because the Michael addition is easier.

The catalyst plays a crucial role in the success of the reaction in terms of the rate and the yields. To test the catalysts, the reaction of 1,3-diphenyl-2-propene-1-one and malononitrile in water was selected as a model reaction. Among the catalysts tested, HTMAB was found to be the most efficient catalyst. We examined several experiments and found that the amount of the catalyst also showed crucial effect on these conversions. For example, 1,3-diphenyl-2-propene-1-one reacted with malononitrile in presence of 1 mol % HTMAB to give the product **3a** in quantitative yield (68 %) at refluxing water after 3 h of reaction time. Increasing of the catalyst to 3, 5 and 6 mol % results in accelerating the reaction yields to 84, 90 and 90 %, respectively.

respectively. Use of just 5 mol % HTMAB in 100 °C water is sufficient to push the reaction forward. Higher amounts of the catalyst did not improve the results to a greater extent. Therefore, 5 mol % HTMAB was chosen as a quantitative catalyst for the reactions.

In summary, a novel and efficient procedure for the synthesis of 3-aryol-2,4,6-triaryl-4-hydroxy-1,1-cyclohexanedicarbonitriles through the reaction of 1,3-diaryl-2-propene-1-ones and malononitrile using a catalytic amount of HTMAB as catalyst is reported. In addition, these reactions confirm the unique property of water as a reaction medium. This procedure offers several advantages including mild reaction conditions, cleaner reaction, high yields of products as well as a simple experimental and isolated procedure which makes it a useful and attractive process for the synthesis of these compounds. Mostly important, water has been chosen as a green solvent for these reactions.

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REFERENCES

1. P. Anastas and T. Williamson, *Green Chemistry, Frontiers in Benign Chemical Synthesis and Procedures*, Oxford Science Publications (1998).
2. B. Cornils and W.A. Herrmann, *Aqueous-Phase Organometallic Chemistry-Concepts and Applications*, Wiley-VCH, Weinheim (1998).
3. C.J. Li, *Chem. Rev.*, **105**, 3095 (2005).
4. P.A. Grieco, *Organic Synthesis in Water*, Blackie, London (1998).
5. C.J. Li and T.H. Chan, *Organic Reactions in Aqueous Media*, Wiley, New York (1997).
6. (a) H.A. Stefani, C.M.P. Pereira, F.A. Dorr and R. Cell, *Arkivoc*, **6**, 19 (2005); (b) X.S. Wang, M.M. Zhang, Z.S. Zeng, D.Q. Shi, S.J. Tu, X.Y. Wei and Z.M. Zong, *Arkivoc*, **7**, 117 (2006).
7. D.Q. Shi, *Chin. J. Xuzhou Normal Univ.*, **23**, 1 (2005).
8. (a) T.S. Jin, R.Q. Zhao and T.S. Li, *Arkivoc*, **7**, 176 (2006); (b) T.S. Jin, R.Q. Zhao, L.B. Liu, Y. Zhao and T.S. Li, *Arkivoc*, **7**, 53 (2006).
9. (a) T.S. Jin, J.S. Zhang, J.C. Xiao, A.Q. Wang and T.S. Li, *Synlett*, 866 (2004); (b) T.S. Jin, A.Q. Wang, X. Wang, J.S. Zhang and T.S. Li, *Synlett*, 871 (2004).
10. T.S. Jin, J.S. Zhang, T.T. Guo, A.Q. Wang and T.S. Li, *Synthesis*, **12**, 2001 (2004).
11. T.S. Jin, J.S. Zhang, A.Q. Wang and T.S. Li, *Ultrason. Sonochem.*, **13**, 220 (2006).
12. (a) T.S. Jin, J.S. Zhang, L.B. Liu, A.Q. Wang and T.S. Li, *Synth. Commun.*, **36**, 2009 (2006); (b) T.S. Jin, L.B. Liu, Y. Zhao and T.S. Li, *Synth. Commun.*, **35**, 1859 (2005).
13. T.S. Jin, X. Wang, L.B. Liu and T.S. Li, *J. Chem. Res(s)*, 346 (2006).
14. A.I. Darwish, *Egypt. J. Chem.*, **44**, 373 (2001).
15. M.M. Al-Arab, H.D. Tabba, B.S. Ghanem and M.M. Olmstead, *Synthesis*, 1157 (1990).
16. S.K. El-sadany, S.M. Sharaf and A.I. Darwish, *Indian J. Chem.*, **30B**, 567 (1991).
17. P. Vicctory, J.I. Borrell, A. Vidal-Ferran, C. Aeoane and J.L. Soto, *Tetrahedron Lett.*, **32**, 5375 (1991).
18. J.L. Soto, C. Seoane and J.A. Ciller, *An. Quim.*, **76**, 281 (1980).