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A clean one-pot synthesis of pyrano[2,3-d]pyrimidine derivatives catalyzed by hexadecyltrimethyl ammonium bromide in aqueous media

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ABSTRACT

An efficient and convenient approach to the synthesis of pyrano[2,3-d]pyrimidine derivatives using hexadecyltrimethyl ammonium bromide (HTMAB) as catalyst 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.

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KEYWORDS

Pyrano[2,3-d]pyrimidine;
Hexadecyltrimethyl ammonium bromide;
Aqueous media;
Synthesis.

INTRODUCTION

Pyrano[2,3-d] pyrimidine and its derivatives have found their wide application in the field of pharmaceutical and agrochemical industry, they exhibit significant pharmacological activity such as antibacterial activities, antifungal activities[1-2], antitumor activity[3] and hypotensive effect[4], antipyretic, analgesic and antiphlogistic activities. They were also endowed with ant platelet, cardiotonic antibronchitic antiallergic, gastroprotective properties, and were lacking in ulcerogenicity[5].

Therefore their preparation received an increased attention to synthetic organic chemists and biologists. A number of methods have been developed for the synthesis of pyrano[2, 3-d] pyrimidine derivatives[6-14], which usually required longer time, complex synthetic pathways, expensive catalyst and often used organic solvent. Thus the pursuance of more convenient and practical synthetic methods for these compounds still remains an active research area.

Recently, for environmental and economic reasons, attention has been focused on aqueous synthesis. To date, more and more organic trasformations have been effectively carried out in water such as the Claisen rearrangement, the Aldol condensation, the Benzoin condensation, Michael addition reaction, Nucleophilic Additions, Substitution reaction, Oxidations, Reductions and Photochemistry[15-16].

Meanwhile the use of phase transfer catalyst benefit the organic materials to form a uniform dispersion in water. HTMAB has been used in a number of organic reactions as a good phase transfer catalyst[14,17]. However, the formation of Pyrano[2,3-*d*] pyrimidine derivatives catalysed by HTMAB has not been reported. In this article, we would like to report a simple one-step synthesis of pyrino [2, 3-d] pyrimidine derivatives using HTMAB as catalyst. This method which we report provides several advantages such as environment friendliness, high yields, and simple work-up procedure. In addition, water was chosen as a green solvent (TABLE 1).

EXPERIMENTAL

Apparatus

Melting points were measured using an X-4 appa-

ratus. NMR spectra were taken with a Varian 400 spectrometer using TMS as internal reference. IR spectra were obtained using NICOLET380 spectrometer instrument (KBr). Elemental analyses were carried out using Carlo Erba 1110 analyzer.

General procedure

A mixture of an aromaticaldehyde (1, 2mmol), malononitrile (2, 2.5mmol), 4,6-dihydroxylpyrimidine (3, 2 mmol), and HTMAB (10 mol %) in water (10 mL) was stirred at 80-90^{0}C. Then the mixture was cooled to room temperature; solid was filtered off and washed with H_2O and EtOH.Then the crude product was purified by recrystallization from DMF and water.

Data of the compounds are shown below

4a: ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 4.4 (s, 1H, CH), 7.16-7.22(m,5H,ArH), 8.14 (s,1H, ArH), 12.72 (s, 1H, NH); IR (KBr) ν: 3392, 3326,3215, 3025, 2190, 1650, 1597, 1390, 1210, 1388, 1272,1074, 1024, 914, 897, 787, 732, 696 cm^{-1}. Anal. calcd for $C_{14}H_{10}N_4O_2$: C 63.11, H 4.63, N 21.05; found C 63.09, H 4.60, N 21.09.

4b: ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 4.91 (s, 1H, CH), 7.18¡ «7.19 (m, 3H, ArH,NH_2), 7.24~7.28 (m, 1H, ArH), 7.38 (dd, J=7.6 Hz, J'=1.6 Hz, 1H, ArH), 8.16 (s, 1H, ArH), 11.48 (s, 1H, NH); IR (KBr) ν: 3401, 3322, 3211, 3056, 2987, 2195, 1661, 1589, 1433, 1393, 1268, 1213, 1067, 1038, 902, 794, 746, 700 cm^{-1}. Anal. calcd for $C_{14}H_9ClN_4O_2$: C 55.88, H 3.02, N 18.63; found C 55.87, H 2.99, N 18.78.

4c: ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 4.46 (s, 1H, CH), 7.17 (d, J=7.6 Hz, 1H, ArH),7.23~7.37 (m, 5H, ArH+NH_2), 8.16 (s, 1H, ArH), 11.50(s, 1H, NH);. IR (KBr) ν: 3402, 3309, 3157, 3045, 2925, 2193, 1687, 1632, 1590, 1474, 1430, 1269, 1209, 1137, 1067, 1031, 912, 841, 803, 773, 745, 690 cm^{-1}. Anal.calcd for $C_{14}H_9ClN_4O_2$: C 55.88, H 3.02, N 18.63; found C 56.01, H 3.22, N 18.55.

4d: ^{1}H NMR (DMSO-d_6, 400 MHz) δ : 4.44 (s, 1H, CH), 7.22 (d, J=8.0 Hz, 2H, ArH),7.23 (s, 2H, NH_2), 7.37 (d, J=8.0 Hz, 2H, ArH), 8.16 (s,1H, ArH), 11.50 (s, 1H, NH); IR (KBr) ν: 3399, 3326, 3215, 3025, 2197, 1681, 1602, 1491, 1434, 1388, 1269, 1063, 1014, 909, 849, 789, 754, cm^{-1}. Anal. calcd for $C_{14}H_9ClN_4O_2$: C 55.88, H 3.02, N 18.63; found C 56.03, H3.21, N 18.69.

4e : ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 4.42 (s, 1H, CH), 7.16 (d, J=8.3 Hz, 2H, ArH),7.22 (s, 2H, NH_2), 7.49 (d, J=8.3 Hz, 2H, ArH), 8.16 (s,1H, ArH),12.76 (s, 1H, NH); IR (KBr) ν: 3399, 3326, 3215, 3025, 2881, 2193, 1681, 1601, 1487, 1433, 1390, 1268, 1214, 1064, 1010, 908, 848, 834,787 cm^{-1}. Anal. calcd for $C_{14}H_9BrN_4O_2$: C 48.71, H 2.63, N 16.24; found C 48.66, H 2.72, N 16.33.

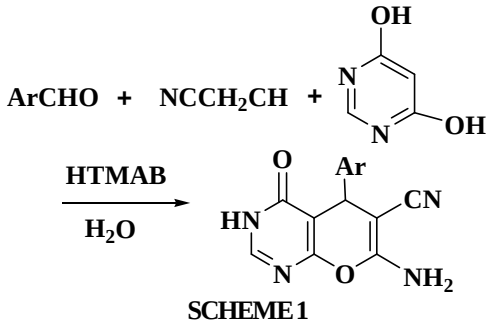
4f : ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 4.67 (s, 1H, CH), 7.34 (s, 2H, NH_2), 7.63 (t, J=8.0 Hz, 1H, ArH), 8.04~8.05 (m, 1H, ArH), 8.10~8.13(m, 1H, ArH), 8.18 (s, 1H, ArH), 11.58 (s, 1H, NH); IR (KBr) ν: 3421, 3305, 3158, 3029, 2928, 2179, 1687, 1602, 1535, 1398, 1347, 1270, 1209, 1136, 1069, 1029, 923, 827,727 cm^{-1}. Anal. calcd for $C_{14}H_9N_5O_4$: C 54.02, H 2.91, N 22.50; found C 53.89, H 3.05, N 22.62.

4g : ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 4.16 (s, 1H, CH), 7.50 (d, J=8.4 Hz, 2H, ArH),7.95 (s, 2H, NH_2),8.18 (d, J=8.4 Hz, 2H, ArH), 8.16 (s,1H, ArH), 12.81 (s, 1H, NH); IR (KBr) ν : 3421, 3315, 3160, 3024, 2924, 2190, 1690, 1597, 1569, 1390, 1347, 1272, 1210, 1134, 1062, 1029, 908, 837,702cm^{-1}. Anal. calcd for Anal. calcd for $C_{14}H_9N_5O_4$: C 54.02, H 2.91, N 22.50; found C 53.91, H 3.01, N 22.65.

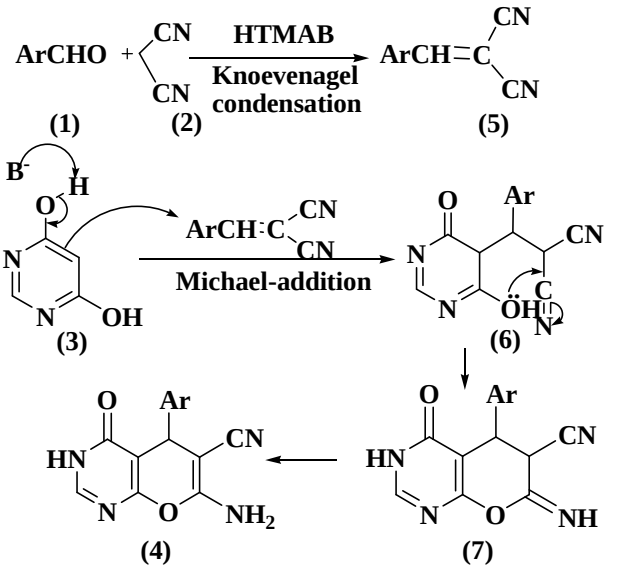
4h : ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 4.90 (s, 1H, CH), 7.23 (s, 2H, NH_2), 7.24 (d, J=8.4 Hz, 1H, ArH), 7.44 (dd, J,8.4 Hz, J'=2.4 Hz, 1H,ArH), 7.55 (d, J=2.4 Hz, 1H, ArH), 8.17 (s, 1H, ArH), 11.60 (s, 1H, NH); IR (KBr) ν : 3396, 3298, 3157, 2885, 2187, 1691, 1600, 1534, 1469, 1378, 1269, 1133, 1064,901, 841, 746, 699 cm^{-1}.Anal. calcd for $C_{14}H_8Cl_2N_4O_2$: C 50.17, H 2.41, N 16.72; found C 50.22, H 2.55, N 16.78.

4i : ^{1}H NMR (DMSO-d_6, 400 MHz) δ : 4.35 (s, 1H, CH), 7.06 (d, J=8.1Hz, 2H, ArH),7.13 (s, 2H, NH_2),7.10 (d, J=8.1 Hz, 2H, ArH), 7.13 (s,1H, ArH),2.25(s,1H,ArH), 12.70 (s, 1H, NH); IR (KBr) ν : 3425, 3320, 3161, 3012, 2870, 2190, 1660, 1592, 1487, 1390, 1272, 1210, 1140, 1095, 1013, 901, 837,721 cm^{-1}. $C_{15}H_{12}N_4O_2$: C 64.25, H 4.318, N 20.00; found C 64.21, H 4.32, N 19.92.

4g : ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 4.50(s, 1H, CH), 7.20 (dd, 1H, J=8.4Hz, J'=2.4Hz, ArH), 7.29 (s, 2H, NH_2), 7.47 (d, 1H, J=2.4Hz, ArH), 7.58 (s,1H, J=8.4Hz,ArH), 8.17(s,1H,ArH), 11.52 (s, 1H, NH);



SCHEME 1



SCHEME 2

TABLE 1: Reaction times and yields of the products (4)

Compd.	Ar	Time/h	Yields/%	Mp(℃)	
				Found	Report
(4a)	C_6H_5	5.5	71	258-260	-
(4b)	2-Cl C_6H_4	6	85	251-253	265-267
(4c)	3-Cl C_6H_4	6.5	90	269-271	273-275
(4d)	4- Cl C_6H_4	6.5	87	258-260	252-254
(4e)	4-Br C_6H_4	8	74	253-255	247-249
(4f)	3-NO_2 C_6H_4	5	88	271-272	275-276
(4g)	4-NO_2 C_6H_4	6.25	76	261-263	-
(4h)	2,4-$Cl_2C_6H_3$	5.5	91	255-256	254-256
(4i)	4-$CH_3C_6H_4$	9.5	63	249-251	-
(4j)	3,4-$Cl_2C_6H_3$	6	93	272-273	281-283

IR (KBr) ν : 3403, 3325, 3171, 2092, 1683, 837,804 cm^{-1}. $C_{15}H_{12}N_4O_2$: C 64.21, H 4.309, N 20.01; found C 64.19, H 4.35, N 19.90.

RESULT AND DISCUSSION

As shown in TABLE 1, we can find a series of aromatic aldehyde 1 were reacted with **(2)** and **(3)** in the presence of HTMAB in water at 80-90^{0}C, the reaction proceed smoothly to afford the corresponding products **(4)** in good yields. In general, when R represented the electron with drawing groups such as chloro (TABLE 1, entries **(4b-4d)**) and nitro groups (TABLE 1, entries **(4f-4g)**), the yield of the product were obviously better and few reaction time was required, but when R with electron-donating groups such as methyl(TABLE 1,entries **(4i)**) the yield was worse and long time was required.

Apparently, the reaction between compounds **(1, 2,** and **3)** follows SCHEME 2.One molecule of aromatic aldehyde **(1)** was first condensed with malononitrile **(2)** to afford a-cyanocinnamonitrile derivative **(5)**. The step (1 + 2→5) can be regarded as a fast knoevenagel addition. The active methylene of 3 by reaction with the electrophilic C=C double bond cyclized by the nucleophilic attack of OH group on the cyano (CN) moiety and gave the intermediate **(7)**. Finally the expected products **(4)** were afforded by isomerization of water (7→4). In this process, HTMAB could promote these reactions as an emulsifier.

Take **(4d)** as the example, the products have been identified by ^{1}H NMR, and IR analyses, and found to be comparable in all respects to the authentic sample. Sharp bands at 3215 cm^{-1} (NH_2) and 2197 cm^{-1} (CN) were observed in the IR spectrum of the compound. The ^{1}H NMR spectrum showed the presence of an aromatic proton at δ= 8.16 as a singlet.

In conclusion, we have developed a novel and efficient method for the synthesis of pyrano [2, 3-d] pyrimidine derivatives from aromaticaldehyde, malononitrile and **(4)**, 6-dihydroxylpyrimidin using hexadecyltrimethyl ammonium bromide (HTMAB) as catalyst in water. The attractive features of this procedure are the mild reaction conditions,high conversions, green reaction profiles, inexpensive and environmentally friendly catalyst, all of which make it a useful and attractive strategy for the preparation of various pyrano[2,3-d]pyrimidine derivatives simply by changing different substrates.

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REFERENCES

[1] A.M.El-Agrody, M.H.El-Hakim, M.S.Abd El-Latif, A.H.Fakery, E.S.M.El-Sayed, K.A.El-Ghareab; Acta Pharm., **50**, 111 **(2000)**.
[2] J.Zamocka, E.Misikova, J.Durinda; Cesk-Farm Ceska a Slovenska Farmacie, **41**, 170 **(1992)**.
[3] D.Broom, Jaewon L.Shim, L.Gary; J.Org.Chem., **41**, 1095 **(1976)**.
[4] V.K.Tandon, M.Vaish, S.Jain, D.S.Bhakuni, R.C. Srimal; Indian J.Pharm.Sci., **53**, 22 **(1991)**.
[5] O.Bruno, C.Brullo, A.Ranise, S.Schenone, F. Bondavalli, E.Barocelli, V.Ballabeni, M.Chiavarini, M.Tognolinib, M.Impicciatoreb; Med.Chem.Lett., **11**, 1397 **(2001)**.
[6] J.Yu, H.Q.Wang; Synth.Commun., **35**, 3133 **(2005)**.
[7] Ipsita Devi, Harsha N.Borah, Pulak J.Bhuyan; Tetrahedron Lett., **44**, 8307 **(2003)**.
[8] Ipsita Devi; Harsha N.Borah; Pulak J.Bhuyan. Tetrahedron Lett., **45**, 2405 **(2004)**.
[9] Y.Gao, S.J.Tu, T.J.Li, X.J.Zhang, S.L.Zhu, F.Fang, D.Q.Shi; Synth.Commun., **34**, 1295 **(2004)**.
[10] Ipsita Devi, Pulak J.Bhuyan; Synth.Lett., **2**, 283 **(2004)**.
[11] A.A.Shestopalov, L.A.Rodinovskaya, A.M. Shestopalov, V.P.Litvinov; 2 Russ Chem.Bull.Int. Ed., **53**, 2342 **(2004)**.
[12] X.S.Wang, Z.S.Zeng, D.Q.Shi, S.J.Tu, X.Y.Wei; Org.Chem., **26**, 256 **(2006)**.
[13] Y.L.Li, B.X.Du, X.S.Wang, D.Q.Shi, S.J.Tu; J. Chem.Res., **3**,157 **(2006)**.
[14] T.S.Jin, A.Q.Wang, Z.L.Cheng, J.S.Zhang, T.S.Li; Synth.Lett., **5**, 871 **(2004)**.
[15] T.S.Jin, A.Q.Wang, Z.L.Cheng, J.S.Zhang, T.S.Li; Synth.Commun., **35**, 137 **(2005)**.
[16] T.S.Jin, A.Q.Wang, Z.L.Cheng, J.S.Zhang, T.S.Li; Synth.Lett., **5**, 866 **(2004)**.
[17] T.S.Jin, A.Q.Wang, Z.L.Cheng, J.S.Zhang, T.S.Li; J.Org.Chem., **7**, 457 **(2004)**.