Chem Sci Trans., 2012, **1(3),** 494-499
DOI:10.7598/cst2012.214

Chemical Science Transactions
ISSN/E-ISSN: 2278-3458/2278-3318

RESEARCH ARTICLE

Uncatalyzed Synthesis of Heteroarylidine Derivatives in Aqueous Medium and their Antibacterial Evaluation

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Received 28 May 2012 / Accepted 15 June 2012

Abstract: Knoevengal condensation of heteroaryl aldehydes with active methylene compounds in aqueous medium at room temperature is described. The products are obtained with excellent yields in short reaction times without using any catalyst. Products require no further purification. Newly synthesized compounds have shown good to excellent biological activities against *Staphylcoccus aureus, Klebsialla pneumoniae, Escherichia coli* and *Pseudomonas aeruginosa.*

Keywords: Knoevenagel condensation, Aqueous media, Antibacterial activity, Heteroarylidine

Introduction

The synthesis of electrophilic olefins from active methylene and carbonyl compounds, known as the Knoevenagel condensation[1]. Knoevenagel condensation is one of the most well known reactions in organic chemistry owing to its applicability in the preparation of various synthetic targets[2]. Many modifications have been made to this process in recent years using Lewis acid catalysis[3], ionic liquids[4], microwave irradiation[5], quaternary ammonium salts[6], heterogeneous catalysts[7], organo-base mediation[8], zeolites[9] and in aqueous media[10].

However, in many of these methods relatively harsh conditions are required, expensive reagents are involved, or a combination of several additives is employed. By keeping all these things in mind, we decided to search a new way to synthesize Knoevengal condensed products through ecofriendly, economically favorable conditions. We report here, a very simple and highly efficient method for the condensation of various 5-membered heteroaryl aldehydes with several active methylene compounds like malononitrile, ethyl cyanoacetate, and dimedone in water at room temperature. It was stimulating to observe that all the reactions occurred rapidly and were complete in a few minutes giving excellent yields of the Knoevenagel products.

Experimental

All the melting points reported are uncorrected and were taken in open capillaries. The IR spectra were recorded on Shimadzu FT-IR spectrometer using KBr (υ cm^{-1}). The ^{1}H-NMR spectra were taken on Bruker DRx-600 spectrometer using TMS (Tetra methyl silane) as internal standard and $CDCl_3$ as solvent. All chemical shift values were recorded as δ ppm. Mass spectra (FAB) were recorded on Jeol Sx-600 mass spectrometer using *m*-nitro benzyl alcohol as matrix. The purity of compounds was checked by TLC using silica gel-G adsorbent. All solvents and reagents were purchased from Aldrich and Merck with high-grade quality and used without any purification.

*General procedure for the synthesis of heteroarylidine derivatives **3(a-r)***

To a stirred solution of activemethylene compound **2a** (10 mmol) in water (10 mL) was added heteroaryl aldehyde **(1a)** in equimolar ratio, rapidly and all at once. The progress of the reaction was monitored by TLC. After few minutes, the solid produced was isolated by simple filtration and dried. The solid product **3a** (98%) was identified by spectroscopic measurements and by comparison with an authentic samples, needed no further purification. Similarly, utilizing the aldehydes **1(a-f)** and activemethylene compounds **2(a-c)**, compounds **3(a-r)** were synthesized and characterized (Table 1).

Table 1. Synthesis of heteroarylidine derivatives **3(a-r)** in aqueous media

Entry	Aldehyde	AMC*	Product[a]	Time, min	Yield, %[b]	M.P., ^{0}C	
						Found	Reported
1	1a	2a	3a	8	98	120	120-12[2a]
2	1b	2a	3b	10	96	92	91-92[7b]
3	1c	2a	3c	12	93	72	73[2a]
4	1d	2a	3d	13	95	98	98-99[7b]
5	1e	2a	3e	8	92	96	97-99
6	1f	2a	3f	9	95	101	101-102[7b]
7	1a	2b	3g	8	96	135-136	135-137[7b]
8	1b	2b	3h	7	98	105-106	105-108[7b]
9	1c	2b	3i	9	97	93	94[2a]
10	1d	2b	3j	9	98	70	-
11	1e	2b	3k	8	98	88	-
12	1f	2b	3l	9	90	104	-
13	1a	2c	3m	10	96	154	156
14	1b	2c	3n	8	95	140	140-142
15	1c	2c	3o	10	93	158	158-159
16	1d	2c	3p	12	90	152	-
17	1e	2c	3q	12	91	146	-
18	1f	2c	3r	11	92	156	-

*[a]All the products are characterized by mp, IR, Mass, ^{1}H,and ^{13}C NMR. [b]Isolated yields after recrystalization. *Active methylene compound*

Antibacterial evaluation

The bacterial species employed were strains of *Staphylococcus aureus, Klebsialla pneumoniae*, *Escherichia coli* and *Pseudomonas aeruginosa*. The isolates were biochemically tested[11,12]. The strains were maintained on trypticase soya agar (TSA). The bacterial inoculam were prepared from 20 mL of overnight stock culture in tryptone soya

broth (TSB) at 37±2 °C. The Muller Hinton agar (MHA) was used for sensitivity test. The compounds were tested at 2 mg/mL concentration in ethanol against all organisms. Inhibition was recorded by measuring the diameter of the inhibition zone at the end of 24 h for bacteria at 37±2 °C. All isolates of selected strains show sensitivity against synthesized molecules. The antibacterial susceptibility test of the selected strains was determined by standard disc diffusion method[13,14]. Each experiment was repeated thrice and the average of the three independent determinations was recorded. The protocols were summarized in Table 2.

Table 2. Antibacterial activities heteroarylidine derivatives (Zone of inhibition in mm)

Entry	Product	*S. aureus*	*K. pneumoniae*	*E. coli*	*P. aeruginosa*
1	3a	+	+++	++	+
2	3b	+++	+	+	+++
3	3c	+	+	+	+
4	3d	+	++	+	++
5	3e	++	+	++	+
6	3f	++	+	+	+
7	3g	+	+++	+++	++
8	3h	+++	+	+	+++
9	3i	+	+	+	+
10	3j	+	++	+	+++
11	3k	+++	+	+	+
12	3l	+	+	+	+
13	3m	+	+++	++	++
14	3n	++	++	+++	+
15	3o	+	+	++	++
16	3p	+	+	+	+
17	3q	++	++	++	++
18	3r	+	++	++	+

Zone area + =1-5 mm, ++ = 6-10 mm, +++ = 11-15 mm

Selected Spectral data

2-(1H-2-pyrrolylmethylene) malononitrile ***(3a)***

Light gray solid, m.p. 120-122 °C, IR (KBr): 3368, 2998, 2226, 589, 1511, 1393, 1322, 1123, 1045, 927, 868, 769, 700, 583. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 6.40(dd, J = 2.5, 3.4 Hz, 1H), 7.20 (d, J = 2.5Hz, 1H), 7.40(d, J = 3.4 Hz, 1H), 7.65(s, 1 H), 11.5(br. s, 1 H NH)ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ =69.5, 113.2, 114.5, 115.5, 125.2, 126.6, 130.2, 149.9 ppm. EI-MS: *m/z* (%) = 143(100)[M+], 116(25), 92(67), 39 (24), 28(38), $C_8H_5N_3$ (143.15): calcd. C 67.13, H 3.52, N 29.35 found C 67.19, H 3.45, N 29.41.

2-(2-Furylmethylene) malononitrile ***(3c)***

Pale yellow solid, m.p. 67-68 °C, IR (KBr) : 3415, 3041, 2221, 1596, 1525, 1456, 1391, 1299, 1149, 1024, 923, 765, 582 ^{1}H NMR (200 MHz, $CDCl_3$) δ: 6.75(dd, J = 3.9, 1.8 Hz, 1H), 7.40 (d, J = 3.9Hz, 1H), 7.55(d, J = 1.8 Hz, 1H), 7.8(s, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ =77.2, 112.5, 113.7, 114.3, 123.5, 143.0, 147.9, 149.5 ppm. EI-MS: *m/z* (%) = 144(100) [M+], 141(90), 115(35), 89 (20), 69(14), 62(13), 43(18). $C_8H_4N_2O$ (144.13): calcd. C 66.67, H 2.80, N 19.44 found C 66.62, H 2.84, N 19.51.

Ethyl (E)-2-cyano-3-(2-thienyl)-2-propionate ***(3h)***

Pale yellow solid, m.p. 105-108 °C, IR (KBr): 3083, 2223, 1717, 1608, 1465, 1334, 1244, 1207, 1083, 1005, 758. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.40 (t, J = 6.9 Hz, 3H), 4.38 (q, J = 6.9Hz, 2H), 7.20-7.28 (m, J = 1H), 7.78(d, J =4.5Hz, 1H), 7.85(d, J = 2.1 Hz, 1H), 8.30(s, 1H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ =14.1, 62.4, 99.2, 115.6, 128.5, 130.0, 135.9, 137.1, 146.6, 162.5 ppm. EI-MS: *m/z* (%) = 207(100) [M+], 179(52), 162(95), 134 (72), 108(34), 90 (30), 45(35). $C_{10}H_9NO_2S$ (207.25): calcd. C 58.12, H 4.38, N 6.76, S 15.47 found C 58.14, H 4.41, N 6.86, S 15.43.

Ethyl (E)-2-cyano-3-(2-furyl-2-propionate ***(3i)***

Coloureless solid, m.p. 89-91 °C, IR (KBr) : 3034, 2216, 1760, 1618, 1530, 1462, 1382, 1217, 1091, 923, 758. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.38(t, J = 7.1 Hz, 3H), 4.35 (q, J = 7.1Hz, 2H), 6.65(dd, J = 1.9, 4.0 Hz, 1H), 7.40(d, J =4.0Hz, 1H),7.55(d, J = 1.9 Hz, 1H), 8.0(s, 1H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ =13.9, 62.3, 98.3, 113.7, 115.1, 121.6, 139.2, 148.1, 148.5, 162.3 ppm. EI-MS: *m/z* (%) = 191(100) [M+], 163(18), 146(14), 63 (20). $C_{10}H_9NO_3$ (191.18): calcd. C 62.82, H 4.74, N 7.33 found C 62.87, H 4.81, N 7.42.

5,5-Dimethyl-2-((5-methylfuran-2-yl)methylene)cyclohexane-1,3-dione ***(3p)***

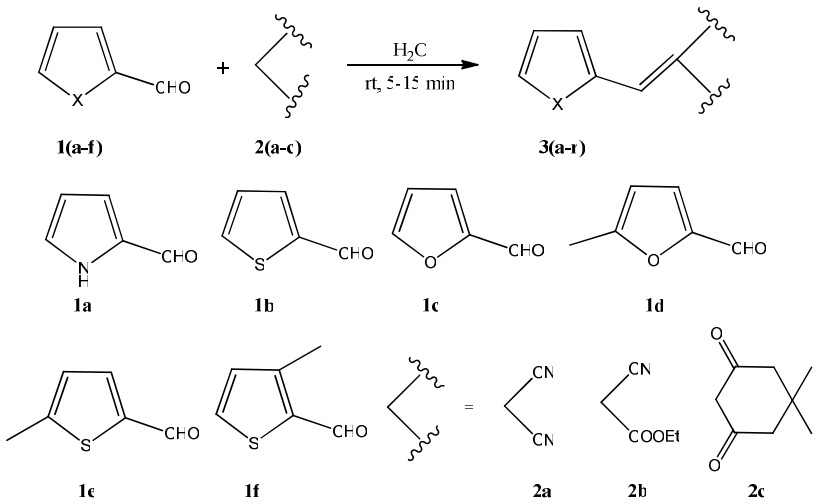
Light yellow solid, 152-156 °C, IR (KBr): 3083, 1745, 1608, 1465, 1244, 1207, 1083, 1005, 758. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.11 (s, 6H), 2.29 (s, 4H), 7.21-7.27(m, J = 1H), 7.72(d, J =4.6Hz, 1H), 7.83(d, J = 2.0 Hz, 1H), 8.21(s, 1H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ =14.3, 26.8, 30.0, 52.3, 109.6, 112.4, 145.2, 146.4, 149.7, 154.8, 185.4 ppm. EI-MS: *m/z* (%) = 232 [M+], 217(100), 201(95), 150(72), 81(34). $C_{14}H_{16}O_3$ (232.27): calcd. C=72.39, H=6.94. Found C=72.35, H=6.96.

5,5-Dimethyl-2-[(5-methyl-2-thienyl)methylene]cyclohexane-1,3-dione ***(3q)***

Yellow solid, 140 °C, IR (KBr): 3055, 1738, 1608, 1465, 1244, 1207, 1083, 1005, 758. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.10 (s, 6H), 2.27 (s, 4H), 7.24-7.30(m, J = 1H), 7.78(d, J =4.4Hz, 1H), 7.84(d, J = 2.3 Hz, 1H), 8.24(s, 1H), 2.34 (s, 3H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ =14.8, 26.9, 30.4, 52.6, 127.9, 130.4, 135.9, 142.9, 145.5, 148.2, 149.7, 184.8 ppm. EI-MS: *m/z* (%) = 248 (100) [M+], 203(52), 178(46) 162(95), 123 (72). $C_{14}H_{16}O_2S$ (248.34): calcd. C=67.71, H=6.49, S=12.91 found C=67.71, H=6.49, S=12.95.

Results and Discussion

In this report, we wish to highlight our findings on uncatalyzed condensation of heteroaryl aldehyde with activemethylene compounds and their biological activities. Water itself has been employed as an efficient catalyst for this reaction. In all the cases, the reaction proceeds smoothly with same reaction conditions. The reaction is highly stereoselective affording *α, β*- unsaturated compounds in excellent yields with an *E*-geometry. Furthermore, the treatment of aldehydes with malononitrile and dimedone also gave trisubstituted olefinic products under similar reaction conditions. The use of 5-membered heterocyclic aldehydes and their derivatives **1(a-f)** gave comparatively higher yields than previously reported aliphatic or aryl aldehydes (Scheme 1). In general, the reactions are clean and free from the formation of side products. In addition the use of water as a medium helps to avoid the use of environmentally unfavorable organic solvents.



Scheme 1

From the screening results, molecules **3h, 3b** and **3k** displayed broad-spectrum antimicrobial activity against *S. aureus,* **3a, 3g** and **3m** against *K. pneumoniae*, **3g** and **3n** against *E. coli* and **3b, 3h** and **3j** against *P. aeruginosa,* remaining products shown moderate activity.

Conclusion

In conclusion, we have demonstrated a very simple and highly efficient method for the condensation of heteroaromatic aldehydes with various activemethylene compounds to give Knoevenagel products in excellent yields. The attractive features of this procedure are operational simplicity and cleaner reaction profile. Replacement of organic solvents by water is the desirable factor for the preparation of trisubstituted olefins. Reaction completes in few minutes and no further purification is required to obtain pure product. The products obtained are suitable starting materials for the synthesis of densely substituted molecules of pharmaceutical interest. The further work is in progress on Knoevenagel condensed products in our laboratory. We suggest that the present method may displace all other methods that use various organic solvents, catalysts, MW irradiation and that are performed at high temperatures.

Acknowledgement

Authors are thankful to Deputy Director and Head, SAIF, Central Drug Research Institute (CDRI), Lucknow for providing spectral data, Department of Chemistry, Vikram University, Ujjain for extending laboratory facilities and IR data. The authors are also thankful to Mr. Kapilesh Jadhav, Lok Manya Tilak Sc. & Comm. College, Ujjain for providing microbiological facilities

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