One-pot easy conversion of Baylis-Hillman adducts into arylpyrazoles under ultrasound irradiation

Manouchehr Mamaghani* and Sahar Dastmard

Chemistry Department, Faculty of Sciences, Islamic Azad University, Rasht Branch, Rasht, Iran

E-mail: m-chem41@guilan.ac.ir

Abstract

Baylis-Hillman adducts were used in a regioselective reaction for the synthesis of new 1,5-diarylpyrazoles under ultrasound irradiation (45 KHz, 60 ^{o}C) in excellent yields (80-90%).

Keywords: Baylis-Hillman, arylpyrazole, ultrasound

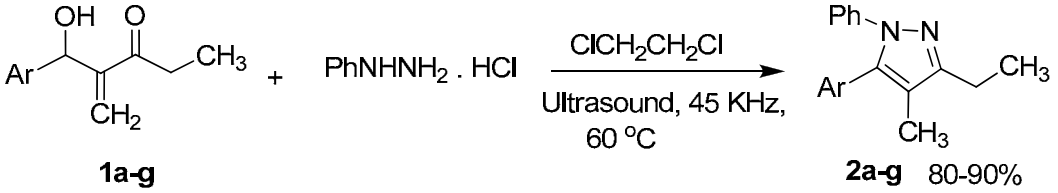
Introduction

Arylpyrazoles play an important role in the pharmaceutical and agrochemical industries.[1,2] A number of compounds containing the pyrazole moiety are being developed in a wide range of therapeutic areas including CNS, metabolic diseases, oncology, selective Cox-2 inhibitor, CCK_1 receptor antagonist, nonstereoidal anti-inflammatory agent[3-8] and blockbuster drugs such as celecoxib (Celebrex) and sidennafil (Viagra).[9,10] In recent years extensive studies have been devoted to the synthesis of arylpyrazoles.[11-13] Usually they can be prepared from the venerable Konor reaction involving condensation of hydrazine derivatives with 1,3-dicarbonyls,[12,14a] 1,3-dipolar cycloaddition of diazoalkanes or nitrile imines with olefins or alkynes,[14b] use of Baylis-Hillman adducts,[6] palladium catalyzed arylation of hydrazones, solid-phase combinatorial approaches, zinc-catalyzed synthesis via hydrohydrazination and condensation of α,β-unsaturated ketones with phenylhydrazine.[9,15-17] However most of these syntheses suffer from multi-step reactions, low yields of products and low regioselectivity, and there is still a lack of general and efficient method for the synthesis of arylpyrazoles.

On the other hand, a literature survey shows that various organic reactions could be accelerated by ultrasonic irradiation with a higher yield, shorter reaction time and milder conditions.[18-22] Therefore, in continuation of our recent interests in the synthesis and chemistry of heterocyclic compounds,[23] an ultrasound-assisted method was developed for the synthesis of new series of 1,5-diarylpyrazoles.

Results and Discussion

At the outset of this study, the required Baylis-Hillman adducts were prepared by the reaction of ethyl vinyl ketone, arylaldehydes in the presence of imidazole and L-proline as catalysts.[24] To convert these products to the related 1,5-diarylpyrazoles under ultrasound condition (45 KHz), the reaction of Baylis-Hillman adduct (**1a)**, phenylhydrazine hydrochloride in 1,2-dicloroethane was used (Scheme 1). This reaction was examined at various temperatures. The optimum condition based on the yield and reaction time was achieved at 60 ^{o}C. Therefore preparation of all the 1,5-diarylpyrazoles described in this paper, under ultrasound condition (45 KHz), was carried out at 60 ^{o}C which afforded the desired products in excellent yields (80-90%) and reasonable reaction times (1.5-3 h) (Table 1). The reaction condition in classical method was also optimized by carrying out the reaction at different temperatures and using substrates **1a** and **1d**. The best results were obtained at 80 ^{o}C. The reaction under classical condition produced the products in lower yields (60-75%) and longer reaction times (6-9 h) (Table 1).



Ar = 2-$NO_2C_6H_4$, 3-$NO_2C_6H_4$, 4-$NO_2C_6H_4$, 3-ClC_6H_4, 4-ClC_6H_4, 2,4-$Cl_2C_6H_3$, 3-BrC_6H_4

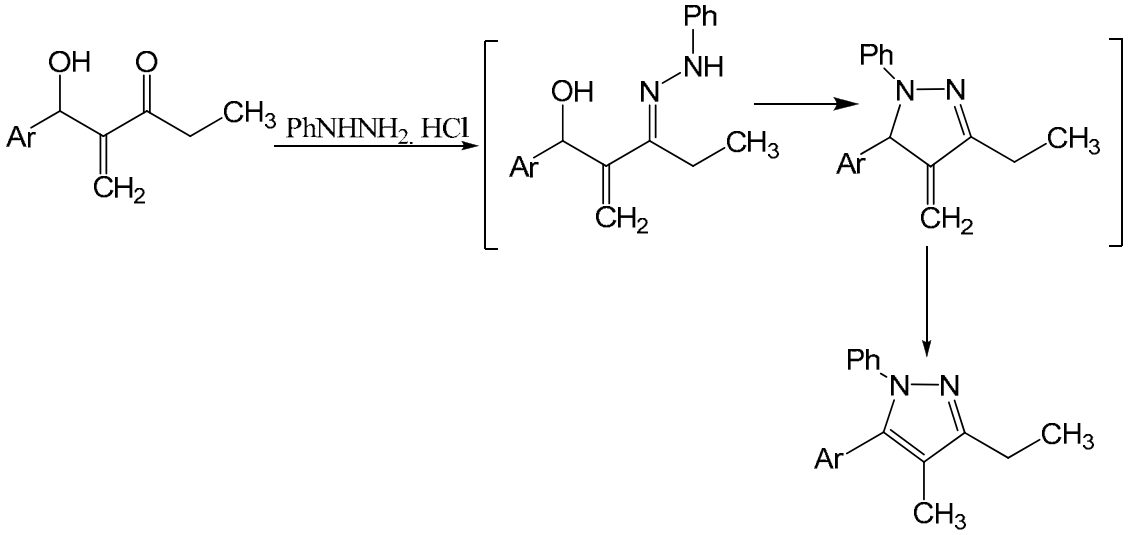
Scheme 1

Table 1. Synthesis of 1,5-diarylpyrazoles (**2**) under classical and ultrasound conditions

Entry	Ar	Classical		Ultrasound	
		Time (h)	Yield (%)	Time (h)	Yield (%)[a,b]
a	2-$NO_2C_6H_4$	6	70	1	85
b	3-$NO_2C_6H_4$	6	75	1	90
c	4-$NO_2C_6H_4$	6	60	1.5	80
d	3-ClC_6H_4	9	75	2	85
e	4-ClC_6H_4	9	70	2.5	86
f	2,4-Cl_2 C_6H_3	9	75	3	85
g	3-BrC_6H_4	9	70	3	80

[a]Isolated yields. [b]Identified by spectroscopic analysis (IR, ^{1}H NMR, ^{13}C NMR).

Mechanistically, the reaction of the Baylis-Hillman adducts with phenyl hydrazine hydrochloride afforded 1,5-diarylpyrazoles by successive hydrazone formation, cyclization and double bond isomerization (Scheme 2).



Scheme 2

In conclusion this protocol provides an easy and efficient method for the synthesis of 1,5-diarylpyrazoles from Baylis–Hillman adducts under ultrasound irradiation.

Experimental Section

General Procedures. All chemicals were purchased from Merck and Fluka. For the ultrasound reactions, ultrasound apparatus Astra 3D from TECNO-GAZ was used. IR spectra were determined on a Shimadzo IR-8900 spectrometer. NMR spectra were recorded on a 500 MHz Bruker DRX-500 using $CDCl_3$ as the solvent. ^1H and ^{13}C chemical shifts (δ) are reported in ppm relative to TMS as internal standard. Mass spectra were obtained from a GC MS-QP 1100EX Shimadzu instrument. Elemental analyses were done on a Carlo-Erba EA1110CNNO-S analyzer and agreed with the calculated values. Preparative thin layer chromatography was prepared from Merck silica gel 60 H, F_{254}, Art No 7730. For column chromatography, Merck silica gel 60, Art No 107733 was employed. All solvents used were dried and distilled according to standard procedures.

General procedure for the synthesis of 1,5-diarypyrazoles under ultrasound irradiation (2a-g)

In a small flask a mixture of Baylis-Hillman adduct (**1a-g**) (0.45 mmol) and phenyl hydrazine hydrochloride (0.57 mmol) in 1,2-dichloroethane (4 mL) was irradiated by ultrasound (45 KHz

frequency) in water bath (60 ^{o}C) for the required reaction time (Table 1). The mixture was diluted with $CHCl_3$ and washed with water and the organic layer was dried ($MgSO_4$). Evaporation of the solvent under vacuum provided a residue which was purified by column chromatography (petroleum ether / ethyl acetate of 6/1) to afford the desired pyrazoles (**2a-g)** (Table 1).

General procedure for the synthesis of 1,5-diarypyrazoles under classical condition[6] (2a-2g) In a two necked small flask, equipped with a condenser and thermometer, a mixture of the Baylis-Hillman adduct (**1a-g**) (0.45 mmol) and phenyl hydrazine hydrochloride (0.57 mmol) was heated in 1,2-dichloroetane (4 mL) at 80 ^{o}C and the progress of the reaction was monitored by TLC(petroleum ether / ethyl acetate of 6/1). After completion of the reaction (Table 1, 6-9 h) the work-up of the products was carried out as the reaction under ultrasound irradiation.

3-Ethyl-4-methyl-5-(*o*-nitrophenyl)-1-phenylpyrazole (2a). Orange oil; IR(neat): (ν_{max}/cm^{-1}): 3050, 2971, 2962, 2910, 1600, 1548, 1490, 1350, 1450, 900, 748; ^{1}H NMR (500 MHz, $CDCl_3$): 1.36 (t, *J* = 7.6 Hz, 3H), 1.94 (s, 3H), 2.75 (q, *J* = 7.6 Hz, 2H), 7.21-7.26 (m, 5H), 7.34 (dd, *J* = 7.6, 1.4 Hz, 1H), 7.55 (dt, *J* = 8.1, 1.4 Hz, 1H), 7.62 (dt, *J* = 7.5, 1.30 Hz, 1H), 7.98 (dd, *J* = 8.1, 1.2 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): 154.4, 149.6, 140.2, 136.1, 133.5, 133.4, 130.0, 129.3, 127.2, 126.7, 125.0, 124.5, 115.3, 20.6, 13.8, 8.5 ppm. GC-MS *m*/ *z* 307 (M^+). Anal. Calcd. For $C_{18}H_{17}N_3O_2$: C, 70.35; H, 5.54; N, 13.68. Found: C, 70.21; H, 5.46; N, 13.49.

3-Ethyl-4-methyl-5-(*m*-nitrophenyl)-1-phenylpyrazole (2b). Yellow viscous oil; IR (neat): (ν_{max}/ cm^{-1}): 3050, 2914, 2850, 1600, 1500, 1450, 1531, 1346, 870, 730, 694; ^{1}H NMR (500 MHz, $CDCl_3$): 1.38 (t, *J* = 7.6 Hz, 3H), 2.13 (s, 3H), 2.79 (q, *J* = 7.6 Hz, 2H), 7.21-7.33 (m, 5H), 7.46 (d, *J* = 7.7 Hz, 1H), 7.53 (t, *J* = 8.0 Hz, 1H), 8.14 (t, *J* = 1.7 Hz, 1H), 8.21 (ddd, *J* = 8.1, 2.0, 0.9 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): 154.8, 148.7, 140.1, 138.2, 136.2, 133.2, 129.8, 129.4, 127.5, 125.3, 124.8, 123.1, 115.3, 20.6, 13.9, 9.0 ppm. GC-MS *m*/ *z* 307 (M^+). Anal. Calcd. For $C_{18}H_{17}N_3O_2$: C, 70.35; H, 5.54; N, 13.68. Found: C, 70.15; H, 5.44; N, 13.51.

3-Ethyl-4-methyl-5-(*p*-nitrophenyl)-1-phenylpyrazole (2c). Orange oil; IR(neat): (ν_{max}/cm^{-1}): 3050, 2972, 2923, 2820, 1593, 1450, 1515, 1344, 758; ^{1}H NMR (500 MHz, $CDCl_3$): 1.38 (t, *J* = 7.6 Hz, 3H), 2.13 (s, 3H), 2.77 (q, *J* = 7.6 Hz, 2H), 7.22 (dd, *J* = 8.7, 1.3 Hz, 2H), 7.28-7.35 (m, 3H), 7.38 (d, *J* = 8.7 Hz, 2H), 8.23 (d, *J* = 8.7 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): 154.9, 147.5, 140.2, 138.1, 130.9, 129.5, 127.6, 125.7, 125.6, 124.1, 115.6, 20.6, 13.8, 9.1 ppm. GC-MS *m*/ *z* 307 (M^+). Anal. Calcd. For $C_{18}H_{17}N_3O_2$: C, 70.35; H, 5.54; N, 13.68. Found: C, 70.13; H, 5.39; N, 13.61.

5-(*m*-Chlorophenyl)-3-ethyl-4-methyl-1-phenylpyrazole (2d). Orange oil; IR (neat): (ν_{max}/cm^{-1}): 3050, 2962, 2850, 1596, 1560, 1492, 1050, 950, 880, 758, 696; ^{1}H NMR (500 MHz, $CDCl_3$): 1.38 (t, *J* = 7.6 Hz, 3H), 2.1 (s, 3H), 2.7 (q, *J* = 7.6 Hz, 2H), 7.0 (dt, *J* = 7.5, 1.2 Hz, 1H), 7.22-7.34 (m, 8H); ^{13}C NMR (125 MHz, $CDCl_3$): 154.5, 140.4, 139.2, 134.7, 133.7, 133.4, 130.1, 129.2, 128.5, 128.5, 127.1, 125.0, 114.8, 20.7, 13.9, 9.0 ppm. GC-MS *m*/ *z* 296 (M^+). Anal. Calcd. For $C_{18}H_{17}ClN_2$: C, 72.97; H, 5.74; N, 9.46. Found: C, 72.76; H, 5.65; N, 9.28.

5-(*p*-Chlorophenyl)-3-ethyl-4-methyl-1-phenylpyrazole (2e). Orange oil; IR (neat): (ν_{max}/cm^{-1}): 3050, 2966, 2925, 2862, 1598, 1500, 1450, 1726, 756; ^{1}H NMR (500 MHz, $CDCl_3$): 1.32 (t, *J* = 7.5 Hz, 3H), 2.04 (s, 3H), 2.74 (q, *J* = 7.5 Hz, 2H), 7.10 (d, *J* = 7.0 Hz, 2H), 7.18-7.20 (m, 3H), 7.26 (m, 2H), 7.30 (d, *J* = 7.0 Hz, 2H); ^{13}C NMR (500 MHz, $CDCl_3$): 154.9, 147.5, 142.1, 136.1, 130.9, 128.5, 126.6, 125.7, 124.3, 124.1, 115.5, 20.4, 13.8, 9.1 ppm. GC-MS *m*/ *z* 296 (M^+). Anal. Calcd. For $C_{18}H_{17}ClN_2$: C, 72.97; H, 5.74; N, 9.46. Found: C, 72.85; H, 5.57; N, 9.32.

5-(2,4-Dichlorophenyl)-3-ethyl-4-methyl-1-phenylpyrazole (2f). Orange oil; IR (neat): (ν_{max}/cm^{-1}): 3050, 2972, 2933, 2880, 1593, 1502, 1450, 910, 820, 727, 660; ^{1}H NMR (500 MHz, $CDCl_3$): 1.38 (t, *J* = 7.5 Hz, 3H), 1.97 (s, 1H), 2.79 (q, *J* = 7.5 Hz, 2H), 7.15 (d, *J* = 8.2 Hz, 1H), 7.20-7.30 (m, 6H), 7.49 (d, *J* = 1.9 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): 154.2, 140.5, 137.0, 135.9, 135.8, 133.6, 130.2, 129.7, 129.2, 127.7, 126.9, 124.1, 116.1, 20.7, 13.8, 8.2 ppm. GC-MS *m*/ *z* 330 (M^+). Anal. Calcd. For $C_{18}H_{16}Cl_2N_2$: C, 65.45; H, 4.85; N, 8.48. Found: C, 65.37; H, 4.76; N, 8.35.

5-(*m*-Bromophenyl)-3-ethyl-4-methyl-1-phenylpyrazole (2g). Yellow oil; IR (neat): (ν_{max}/cm^{-1}): 3047, 2972, 2933, 2850, 1593, 1550, 1492, 1446, 1080, 910, 790, 731, 700; ^{1}H NMR (500 MHz, $CDCl_3$): 1.38 (t, *J* = 7.5 Hz, 3H), 2.1 (s, 1H), 2.79 (q, *J* = 7.5 Hz, 2H), 7.1 (d, *J* = 7.8 Hz, 1H), 7.21 (t, *J* = 7.8 Hz, 1H), 7.24-7.32 (m, 5H), 7.43 (t, *J* = 1.6 Hz, 1H), 7.48 (dm, *J* = 8.7, 0.8 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): 154.5, 140.4, 139.1, 133.6, 133.0, 131.4, 130.3, 129.2, 129.0, 127.1, 125.1, 122.8, 114.8, 20.7, 13.9, 9.0 ppm. GC-MS *m*/ *z* 340 (M^+). Anal. Calcd. For $C_{18}H_{17}BrN_2$: C, 63.53; H, 5.0; N, 8.23. Found: C, 63.27; H, 5.15; N, 8.14.

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