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Microwave assisted one-pot regioselective synthesis of 3,5-arylated pyrazoles from 2,3-dibromo-1,3-diarylpropan-1-ones using amberlite IR-120

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ABSTRACT

An efficient and direct protocol for the preparation of 3,5-disubstituted pyrazoles, one-pot regioselective condensation reaction of 2,3-dibromo-1,3-diarylpropan-1-ones with hydrazine derivatives via useful intermediate 4-bromo- 1,3- aryl 4,5-dihydro-1H-pyrazole in the presence of amberlite IR-120 under thermal and microwave conditions in EtOH as solvent is described. In this method, several types of aromatic diarylpropan, containing electron-withdrawing groups as well as electron-donating groups, were rapidly converted to the corresponding pyrazoles in good to excellent yields. The thermal solvent-free and microwave green procedures offer advantages such as shorter reaction times, simple work-up, excellent yield, recovery and reusability of catalyst.

KEYWORDS

3,5-Arylated pyrazoles;
One-pot regioselective synthesis;
2,3-Dibromo-1,3-diarylpropan-1-ones;
4-bromo- 1,3- aryl- 4,5-dihydro-1H-pyrazole;
Amberlite IR-120.

INTRODUCTION

Pyrazoles are an important class of bio-active drug targets in the pharmaceutical industry, as they are the core structure of numerous biologically active compounds[1], including blockbuster drugs such as Celebrex[2] and Viagra[3]. They also possess important biological properties such as antitumor cyclin-dependent kinase (CDK) inhibitors[4], monoamine oxidase-B (MAO-B) inhibitors and anti-inflammatory agents[5]. Recently, they have also emerged as potential atypical antipsychotics[6]. Several syntheses of pyrazoles have been developed and by far the most prevalent method of choice is the reaction of 1,3-diketones with hydrazines[7]. Other methods for the synthesis of pyrazoles that do not require 1,3-diketones have been reported[8]. Recently, a few efficient methods have been developed[9], however, most of these utilize a circuitous route, require longer reaction time, and are often carried out in organic solvents. Compared with the reactions in organic solvents, solventless reactions are often rapid, regio- or chemoselective, occur in high yields and have environmental and economic advantages[10,11].

However, many of the reported methods are associated with one or more of the following drawbacks: (i) low yield, (ii) long reaction time, (iii) harsh reaction conditions, (iv) the use of toxic, corrosive, expensive, or non-reusable catalysts, (v) the use of large amount of

catalyst, (vi) application of large amount of acetamide (as reactant), and (vii) because of the use of acidic catalysts in most of the reported methods, application of aldehydes bearing basic groups or acid-sensitive aldehydes in the reaction is not possible.

EXPERIMENTAL

All the reactions were carried out using a conventional (unmodified) household microwave oven (LG, 230 V, ~50 Hz). Reactions were monitored on TLC by comparison with the samples prepared by known procedures. The IR spectra were recorded using a Shimadzu UV-2100 spectrophotometer (KBr pellets) and the NMR spectra were obtained in using a Bruker Avance 500-MHz spectrometer. All melting points were determined on a Büchi 530 melting point apparatus and are reported uncorrected.

General procedure for the synthesis of 4-bromo-1,3- arylphenyl- 4,5-dihydro-pyrazoles (Method A)

In the first step the 2,3-dibromo-1,3-diarylropan-1-one 2a-t are prepared according to a standard procedure[14]. A mixture of 2,3-dibromo-1,3-diarylropan-1-one (1 mmol) dissolving in 14 mL 96% ethanol, hydrazine reagent (1.2 mmol) and amberlite IR-120 (0.16 g) was stirred at thermal condition. The completion of the reaction was monitored through TLC (ethyl acetate/cyclohexane, 1:3), after the reaction was completed, EtOH (10 mL) was added and the product was filtered and then recrystallized from hot ethyl alcohol. The desired pure products were characterized by comparison of their physical data with those of known amidoalkyl naphthols.

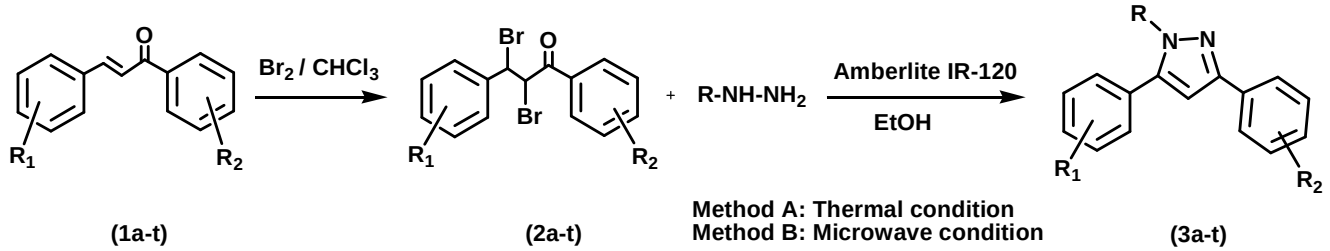
General procedure for the synthesis of 4-bromo-1,3- arylphenyl- 4,5-dihydro-pyrazoles (Method B)

A mixture of 2,3-dibromo-1,3-diarylropan-1-one (1 mmol) dissolving in 14 mL 96% ethanol, hydrazine reagent (1.2 mmol) and amberlite IR-120 (0.16 g) was taken in a 100ml conical flask. The mixture was mixed well and then irradiated in a domestic microwave oven at 160 W for appropriate time (see TABLE 1). After completion of reaction, mass was cooled to 25 °C, then the solid residue was solved in boiling EtOH and the mixture stirred for 5 min. The catalyst was recovered. Then solution was cooled to room temperature, the solid so obtained was filtered and recrystallized from aqueous EtOH (15%).

The products were characterized on the basis of their physical and spectral analysis and by direct comparison with literature data[8,9,13].

RESULTS AND DISCUSSION

In continuation of our work on the development of simple and environmentally friendly experimental procedures using readily available reagents and catalysts for the synthesis of biologically active molecules and heterocyclic compounds[15-19]. We, in this article, are reporting the use of amberlite IR- 120[H^+] resin[20] as a highly efûcient and homogeneous organic catalyst for the exclusive synthesis of 3,5-disubstituted pyrazoles derivatives 3a-t from one-pot regioselective reaction of 2,3-dibromo-1,3-diarylpropan-1-ones 1a-t with hydrazine derivatives 2a-t under thermal condition and microwave irradiation in $CHCl_3$ as solvent. (Scheme 1)



Scheme 1 : The synthesis of pyrazoles

In a typical general experimental procedure under conventional method (Method A), one equivalent of 2,3-dibromo-1,3-diarylpropan-1-one and catalytic amounts of amberlite IR-120 was strided with various hydrazines at thermal condition for 24-37 min to afford the 3,5-disubstituted pyrazoles derivatives in 91–96%. In microwave irradiation method (Method B) one equivalent of 2,3-dibromo-1,3-diarylpropan-1-ones, catalytic amounts of amberlite IR-120 and one equivalent of various hydrazines were heated in a domestic

microwave oven at 160 w for 3–7 min to yield the 3,5-disubstituted pyrazoles derivatives in 89–95 % yield. After completion of the reaction (in both the Methods A and B) as indicated by TLC, the reaction mixture was cooled to 15 °C and triturated with hot ethanol, the resulting precipitate was ûltered to give analytically pure 3,5-disubstituted pyrazoles derivatives in good to high yields. The highlighting feature of this protocol is: (i) the method is highly efûcient and selective; (ii) the catalyst is recyclable; (iii) gives excellent yield of the products; and (iv) all the reactions go to completion within minimum time when compared with other reported methods. (TABLE 1)

For optimizing the reaction, it was examined under two different conditions: (i) thermal condition, and (ii) under microwave irradiation in acetonitrile. Firstly, 2,3-dibromo-1,3-diphenylpropan-1-one 1a (1 mmol) and phenyl hydrazine (1.2 mmol) were taken, and 0.16 g of amberlite IR-120 was added and the mixture was heated under room temperature for 32 min in acetonitrile to get 94% of product 3a [the progress of the reaction was monitored on TLC], continuation of the reaction did not improve the yield of the product. When the same reaction was carried out under the inûuence of microwave irradiation in acetonitrile, the reaction proceeded effectively affording the product in 92% yield in 4 min. According to this data, the optimum amount of catalyst was 0.16 g. Further increasing the amount of catalyst did not improve the yield and the reaction time. After optimizing these conditions using 2,3-dibromo-1,3-diphenylpropan-1-one as a model, the reactions were performed with various other 2,3-dibromo-1,3-diarylpropan-1-ones, and the results of this study are presented in TABLE 1.

TABLE 1 : Amberlite IR-120 catalyzed synthesis of pyrazoles derivatives

Entry	Product[a]	R	R_1	R_2	Method A Time/Yields (%)[b]	Method B Time/Yields (%)[b]	M.p., °C (Lit.)[c]
1	3a	Ph	H	H	(32 min/94)	(4 min/92)	154-156(152-154)
2	3b	Ph	H	4-Me	(35 min/96)	(5min/94)	193-195 (190-192)
3	3c	Ph	H	3-Me	(37 min/95)	(6 min/93)	181-184 (183-185)
4	3d	Ph	H	4-OMe	(31 min/93)	(4 min/90)	187-189 (190-192)
5	3e	Ph	H	3-OMe	(33 min/96)	(5 min/95)	160-162 (161-163)
6	3f	Ph	H	4-NO_2	(32 min/91)	(7 min/89)	238-240 (135-237)
7	3g	Ph	H	3-NO_2	(34 min/92)	(5 min/93)	219-221 (218-220)
8	3h	Ph	H	4-Cl	(26 min/91)	(3 min/92)	248-250 (247-250)
9	3i	Ph	4-Cl	H	(28 min/92)	(4 min/90)	214-216 (211-213)
10	3j	Ph	4-Cl	4-Me	(30 min/93)	(5 min/94)	178-180 (177-179)
11	3k	Ph	4-Cl	4-NO_2	(27 min/95)	(4 min/94)	220-222 (223-225)
12	3l	Ph	4-Cl	4-Cl	(30 min/94)	(5 min/90)	211-213 (212-215)
13	3m	H	4-Cl	H	(27 min/93)	(4 min/94)	188-190 (189-191)
14	3n	H	4-Cl	4-Me	(27 min/96)	(3 min/95)	196-197 (198-200)
15	3o	H	4-Cl	3-Me	(24 min/94)	(4 min/95)	183-185 (183-184)
16	3p	H	4-Cl	4-OMe	(30 min/94)	(5 min/90)	196-198 (194-196)
17	3q	H	4-Cl	3-OMe	(27 min/93)	(4 min/94)	228-230 (227-229)
18	3r	H	4-Cl	4-NO_2	(27 min/96)	(3 min/95)	202-203 (203-205)
19	3s	H	4-Cl	3-NO_2	(24 min/94)	(4 min/95)	199-201 (198-199)
20	3t	H	4-Cl	4-Cl	(30 min/94)	(5 min/90)	197-198 (194-196)

[a]Isolated yields. [b]All the products are known, characterized by IR, NMR spectral analysis and compared with the authentic samples. [c]Melting points of compounds are consistent with reported values[8,9,13]

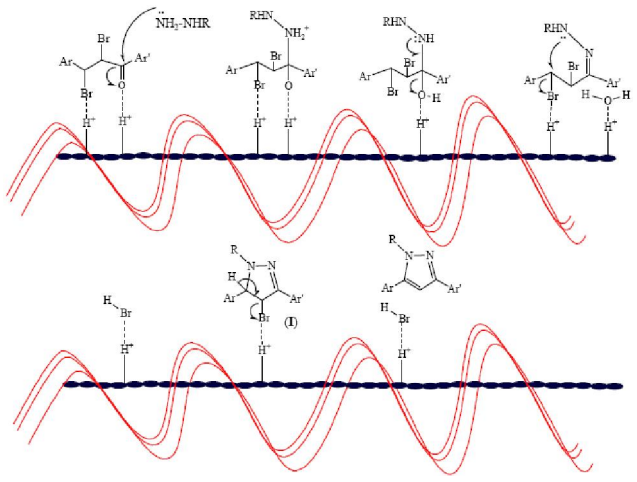
In order to evaluate the effect of solvent, we examined different solvents under room temperature for the above model reaction (TABLE 2). The outstanding feature of data that can be elicited from TABLE 2 is the role of the hydrophobic property of ethanol in this reaction.

TABLE 2 : The effect of amount of amberlite IR-120 and solvent different for product 3a

Entry	Amount Catalyst (g)	Solvent	Time (min)	Yield[a] (%)
1	0.05	H_2O	70	53
2	0.16	H_2O	70	54
3	0.05	CH_3CN	70	78
4	0.16	CH_3CN	70	80
5	0.05	EtOH	70	85
6	0.16	EtOH	32	94
7	0.2	EtOH	70	94
8	0.0	EtOH	100	0.0

[a]Yields refer to the pure isolated products.

A possible mechanism of this one pot reaction under both conditions is expected to include the '*in situ*' formation of intermediate 4-bromo- 1,3- arylphenyl-4,5-dihydro-1*H*-pyrazole (I) in the presence of amberlite IR-120. It is assumed that, due to the collapse of the cavitations bubbles near the surface of the catalyst, the oxygen of the carbonyl group in step 1 may easily influence [H^+] of the catalyst amberlite IR-120[H^+] to give the activated chalcone which may attack hydrazine derivatives to give 4-bromo- 1,3-arylphenyl- 4,5-dihydro-1*H*-pyrazole (I). Further, the intermediate (I) may undergo influence [H^+] of the catalyst to give corresponding pyrazoles as shown in. (Scheme 2)



Scheme 2 : A possible mechanism for the synthesis of pyrazoles

CONCLUSIONS

The present methodology shows that amberlite IR-120 is an efficient catalyst in the one-pot synthesis of pyrazoles derivatives. The main advantages of the presented protocol are efficient, mild, green, clean and environmentally benign reaction conditions, as well as the high yields. Furthermore, this protocol provides very fast and low cost procedure for the synthesis of these products.

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