Green synthesis of pyrazole systems under solvent-free conditions

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ABSTRACT
In this paper, we offered a green, environment-friendly, novel and inexpensive method for the synthesis of a series of pyrazole derivatives. The reaction took place in the presence of tetrabutylammonium bromide, a commercially available organic ionic salt, at room temperature under solvent-free conditions. All products were confirmed by infrared radiation, nuclear magnetic resonance and elemental analysis. Yields of products were 75–86%.

Introduction
The development of simple synthetic methods for widely used organic compounds from readily available starting materials is one of the major challenges in organic synthesis (1). Nitrogen-containing heterocyclic compounds are widespread in nature, and their applications to biologically active pharmaceuticals, agrochemicals and functional materials are becoming more and more important (2–6). Thus, the development of new and efficient synthetic methods for N-heterocycles with structural diversity is one of the major interests of modern synthetic organic chemists (7–9). The interest in five-membered systems with two adjacent nitrogen atoms stems from the occurrence of saturated and partially saturated pyrazoles in biologically active compounds and natural products (10, 11). Some are used in supramolecular and polymer chemistry, pharmaceuticals, agrochemicals, food, cosmetic coloring, complexing agents for the synthesis of hydrogenation catalysts, and UV stabilizers, while some have liquid crystal properties (11–17).

Various methods have been developed for the synthesis of pyrazole ring systems (18–21). In most of these methods, diverse organic solvents such as ethanol, toluene, CH₂Cl₂, acetone and acetonitrile have been used (22–31). The obtained product yields of most of these reactions are significant, but the solvents used are not compatible with the environment or cost savings. For these reasons, the development of efficient and operationally simple procedures for the synthesis of pyrazole ring systems under environment-friendly conditions is highly appreciated. Due to the harmful effects of organic solvents on the environment and humans, solvent-free reactions have received a widespread attention. Furthermore, solvent-free reactions have several benefits compared with solvents’ technique reaction, such as faster reaction rate, reduce reaction time, less energy usage, easy separation, formation of product with fewer impurities and high yields.

Due to the reasons mentioned above, to continue our previous studies in this field (32–35), we have reported...
the synthesis of highly functionalized pyrazoles by a simple and efficient one-pot three-component protocol with good yields via the reaction of isocyanides, the dialkyl acetylenedicarboxylates in the presence of 1,2-dibenzoylhydrazines, using environment-friendly organic ionic salt tetrabutylammonium bromide (TBAB) as a high polar reaction medium at room temperature under solvent-free conditions (Scheme 1).

Experimental section
1,2-dibenzoylhydrazines 1 were synthesized according to the literature procedures (36). Isocyanides, and dialkyl acetylenedicarboxylates and 4-phenylurazole were purchased from Merck and used without further purification. Liquid starting materials were transferred via syringe. Organic solvents were removed under reduced pressure by a rotary evaporator. Reactions were monitored by thin-layer chromatography (TLC) carried out on silica-gel plates (SILG/UV 254, Merk) using UV light as the visualizing agent. Chromatography was performed on Merk 60 silica gel (230–240 mesh) with n-hexane and ethyl acetate mixtures as eluent. Fourier transform infrared radiation spectra were recorded on a Perkin-Elmer RX-1 instrument. Mass spectra were recorded on a Shimadzu GC-MS-QP 1000PX. Elemental analysis for C, H and N was performed using a Heraeus CHN-O-Rapid analyzer. 1H nuclear magnetic resonance (NMR) and 13C NMR spectra were recorded mostly on a Bruker 400 MHz instrument. The melting points were determined in open capillaries with a Stuart Melting Point Apparatus and are uncorrected.

General procedure for the synthesis of pyrazole systems in the presence of TBAB
To a well ground mixture of 4-phenylurazole or 1,2-dibenzoylhydrazines (1.0 mmol) and TBAB (1.0 mmol), dialkyl acetylenedicarboxylates (1.0 mmol) and then isocyanides (1.0 mmol) were added and mixed thoroughly with a glass rod. The resulting mixture was kept at room temperature. After a few minutes, a brown thick solution was formed. The reaction flask was kept at this temperature for stipulated time (Table 1), and the reaction was completed as monitored by TLC. Then chloroform (15 mL) was added and the solution was stirred to dissolve all of the crude mixture. TBAB was recovered by the addition of water (3 × 20 mL) to this solution, then collected and dried under vacuum. The chloroform layer was washed with water (3 × 15 mL). After dried with sodium sulfate and removal of the organic solvent, the residue was purified on short silica-gel column with n-hexane/ethyl acetate (9:1) as the eluent.

Physical and spectroscopic data of isolated products

**Dimethyl 1,2-dibenzoyl-5-(cyclohexylamino)-2,3-dihydro-1H-pyrazole-3,4-dicarboxylate (4a).** White solid, mp 133–134°C; 1H NMR (400 MHz, CDCl3): δ ppm 1.24–2.35 (m, 11H), 3.62 (s, 3H), 3.72 (s, 3H), 3.76–3.85 (m, 1H), 4.39 (s, 1H), 7.15–7.77 (m, 10H); 13C NMR (100 MHz, CDCl3): 23.3, 23.5, 24.4, 28.2, 49.7, 51.5, 53.8, 64.6, 68.4, 126.7, 126.9, 127.8, 127.9, 130.7, 131.9, 133.2, 168.4, 173.6; infrared radiation (IR) (KBr, cm⁻¹): 3303, 3062, 2931, 1747, 1706, 1622, 1471, 1275, 1107, 704; Anal. Calcd. for C27H29N3O6: C, 65.97; H, 5.95; N, 8.55. Found: C, 66.32; H, 6.12; N, 8.17.

**Diethyl 1,2-dibenzoyl-5-(cyclohexylamino)-2,3-dihydro-1H-pyrazole-3,4-dicarboxylate (4b).** White solid, mp 138–139°C; 1H NMR (400 MHz, CDCl3): δ ppm 1.16–1.31 (m, 6H), 1.31–2.35 (m, 11H), 3.70 (s, 1H), 3.97–4.11 (m, 2H), 4.13–4.22 (m, 2H), 4.90 (s, 1H), 7.32–7.79 (m, 10H); 13C NMR (100 MHz, CDCl3): 13.0, 13.5, 23.3, 24.4, 31.5, 33.2, 53.6, 58.2, 60.5, 64.7, 126.8, 126.9, 127.8, 128.0, 130.6, 131.8, 133.2; IR (KBr, cm⁻¹): 3265, 3068, 2973, 1742, 1708, 1618, 1450, 1275, 1118, 703; Anal. Calcd. for C29H33N3O6: C, 67.04; H, 6.40; N, 8.09. Found: C, 66.87; H, 6.73; N, 7.69.

**Dimethyl 5-(cyclohexylamino)-1,2-bis(4-nitrobenzoyl)-2,3-dihydro-1H-pyrazole-3,4-dicarboxylate (4e).** Chartreuse solid, mp 201–202°C; 1H NMR (400 MHz, CDCl3): δ ppm 1.24–2.13 (m, 11H), 3.64 (s, 3H), 3.77 (s, 3H),
Table 1. One-pot three-component addition reaction for the production of pyrazole systems 4a–4f under solvent-free conditions.

| Entry | R   | R1          | R2       | Timea (h) | Timeb (h) | Yieldsa (%) | Yieldsb (%) |
|-------|-----|-------------|----------|-----------|-----------|-------------|-------------|
| 1     | H   | CH3         | Cyclohexyl | 72        | 0.5       | 4a (75)     | 4a (82)     |
| 2     | H   | CH3CH2      | Cyclohexyl | 72        | 0.5       | 4b (78)     | 4b (86)     |
| 3     | H   | CH2(CH3)C   | Cyclohexyl | 120       | 12        | 4c (--)     | 4c (--)     |
| 4     | H   | CH3CH2      | Cyclohexyl | 90        | 0.5       | 4e (73)     | 4e (80)     |
| 5     | NO2 | CH3         | Cyclohexyl | 90        | 0.5       | 4f (67)     | 4f (75)     |
| 6     | NO2 | CH3CH2      | Cyclohexyl | 90        | 0.5       | 4f (67)     | 4f (75)     |

*Acetone solvent (10 mL), r.t.

*Organic salt TBAB (1.0 mmol), r.t.

4.22–4.27 (m, 1H), 4.88 (s, 1H), 7.61 (d, 2H, J = 8.4 Hz), 7.96 (s, 2H), 8.24 (t, 4H, J = 9.0 Hz); 13C NMR (100 MHz, CDCl3): 23.3, 23.4, 24.3, 31.5, 33.2, 49.9, 52.0, 54.1, 64.3, 67.1, 122.2, 123.2, 127.7, 128.8, 148.4, 149.4; IR (KBr, cm−1): 3303, 3062, 2931, 1747, 1706, 1622, 1471, 1275, 1107, 704; Anal. Calcd. for C27H27N5O10: C, 55.76; H, 4.68; N, 12.04. Found: C, 56.02; H, 4.97; N, 11.86.

Diethyl 5-(cyclohexylamino)-1,2-bis(4-nitrobenzoyl)-2,3-dihydro-1H-pyrazole-3,4-dicarboxylate (4f). Chartreuse solid, mp 177–178°C; 1H NMR (400 MHz, CDCl3): δ ppm 1.28 (t, 3H, J = 8.2 Hz), 1.35 (t, 3H, J = 9.6 Hz), 4.08-4.29 (m, 5H), 5.31 (s, 1H), 7.16–7.51 (m, 6H); 13C NMR (100 MHz, CDCl3): 13.0, 13.3, 23.3, 23.4, 24.1, 32.9, 33.2, 49.9, 51.9, 54.9, 60.7, 79.4, 125.0, 127.9, 128.0, 129.5, 147.4, 149.1, 152.0, 164.6, 168.1; IR (KBr, cm−1): 3285, 2932, 1742, 1617, 1395, 1217, 1102, 761; Anal. Calcd. for C23H28N4O6: C, 60.52; H, 6.18; N, 12.27. Found: C, 60.83; H, 6.38; N, 12.66.

Results and discussion

Initially, a model reaction was conducted by taking N′-benzoylbenzohydrazide 1a (1.0 mmol), dimethyl acetylenedicarboxylate (DMAD) 2a (1.0 mmol) and cyclohexyl isocyanide 3a (1.0 mmol) at room temperature under solvent-free conditions (Scheme 2). The reaction scarcely proceeded to give the desired product, even after prolonged reaction time (24 h). In order to achieve a satisfactory yield, the reaction was conducted with same mole ratio of reactants at 60°C, instead of at room temperature under solvent-free conditions. However, the TLC test showed no more progress in the model reaction after 6 h (15%). To explore the reaction media to get appreciable product yields, we decided to repeat this reaction in the presence of organic ionic salt, TBAB. When 1.0 mmol of fine-powdered TBAB was added to model reaction media, including above-mentioned molar ratios, it was observed by TLC that the reaction was completed after 30 min and the desired product was afforded in 82% yield.

Based on our studies, the common solvent for the synthesis of this type of pyrazole derivatives is acetone at room temperature (28–31). This made us repeat the model reaction with the same mole ratios of reactants in acetone solvent, without TBAB at room temperature. Although the reaction produced the corresponding...
product in good yield (75%), the rate of reaction was very low so that the above yield of product was obtained within 72 h at room temperature.

Next, we studied the model reaction with different amounts of TBAB. This investigation showed that the best yield of product was obtained with 1.0 mmol of TBAB. Therefore, with the best reaction conditions for the model reaction in hand (cyclohexyl isocyanide 1.0 mmol, dimethyl acetylenedicarboxylate 1.0 mmol, $N'$-benzoylbenzohydrazide 1.0 mmol and TBAB 1.0 mmol), we examined the reaction with different types of starting materials. The results are summarized in Table 1.

According to Table 1, in the cases $R = H$, $R_1 = CH_3$, $CH_2CH_3$ and $R_2 = cyclohexyl$ were (Table 1, entries 1,2), corresponding products afforded in good yields in both acetone solvent and the presence of TBAB. However, when $R = H$, $R_1 = CH_3$, $CH_2CH_3$ and $R_2 = C(CH_3)_3$ (Table 1,

Scheme 3. Preparation of compound 6a, 6b in the presence of TBAB under solvent-free conditions.

Scheme 4. Suggestion mechanism for the synthesis of pyrazole systems in the presence of TBAB.
entries 3,4), no product was observed and the starting material 1 was isolated as the only product of reaction at room temperature and 60°C. It can be attributed to increased steric hindrance in tert-butyl isocyanide molecule. Also, using 4-nitro-\(N\)-((4-nitrobenzoyl)benzohydrazide (\(R = \text{NO}_2\)) as the starting material instead of \(N\)-benzoylbenzohydrazide, related products produced good yields (Table 1, entries 5,6).

In order to compare this method with organic solvent methods, we tried to synthesize compounds (6a, 6b) that were prepared before in acetone solvent (30). Thus, for comparison, we used 4-phenylisocyanazole instead of 1,2-dibenzoylhydrazines to synthesize the desired pyrazole under both acetone solvent and solvent-free conditions (Scheme 3). This comparison showed that the reaction performs far faster in the presence of TBAB under solvent-free conditions than in acetone solvent.

The role of TBAB in this reaction can be explained by the plausible mechanism proposed in Scheme 4. The electrostatic attraction between the oxygen atom in the carbonyl group of acetylenic ester (2) and ammonium ion in TBAB increased the electrophilic character of the \(\beta\)-carbon atom of the carbonyl group. This caused the acetylenic ester to undergo a Michael-type addition with isocyanide (3) to generate intermediate (6). The protonation of this intermediate by compound (1) led to the formation of a positively charged ion (7) that acts as a Michael acceptor. Therefore, the adduct (7) immediately undergoes Michael-type addition with anion of the NH-acid (8) to generate the open-chain intermediate (9). Finally, the ketenimine intermediate (9) can be converted to target molecule by intramolecular N-cyclization reaction.

**Conclusions**

In summary, we developed a new, expedient and environment-friendly method for the synthesis of highly functionalized pyrazoles in the presence of organic salt TBAB at room temperature under solvent-free conditions. In this method, the products were produced in shorter times and good yields. It is considerable that commercially available organic salt TBAB was recovered and applied again. Therefore, this simple and clean method would be practical and useful to synthesize potentially valuable pyrazole products.

**Acknowledgements**

Authors are grateful to the laboratories of Tehran and Tabriz University as well as University of Mohaghegh Ardabili for the product analysis.

**Disclosure statement**

No potential conflict of interest was reported by the authors.

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