One-pot multicomponent diastereoselective synthesis of novel dihydro-1H-furo[2,3-c]pyrazoles

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ABSTRACT
An efficient method was developed for the diastereoselective synthesis of novel fused dihydro-1H-furo[2,3-c]pyrazole by a one-pot, four-component reaction of β-keto ester, hydrazine, aromatic aldehyde, and pyridinium ylide in the presence of triethylamine under microwave irradiation in solvent-free conditions in good yields. The merits of this cascade Knoevenagel condensation/Michael addition/cyclization sequence include its high atom economy, good yields, and efficiency of producing three new bonds (two C–C and one C–O) and two stereocenters in a single operation.

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Introduction
Multicomponent reactions (MCRs) are important in organic chemistry for generating high levels of diversity and time savings in one-pot operations, giving rise to complex structures by simultaneous formation of two or more bonds. MCRs contribute to the requirements of an environmentally friendly process by reducing the number of synthetic steps, waste production, and energy consumption in the pharmaceutical industry.

Because of their inherently simple experimental procedures and their one-pot character, they are perfectly suited for automated synthesis. Thus, MCRs have attracted considerable interest owing to their exceptional synthetic efficiency. Pyrazoles are an important structural units in the field of agricultural and medicinal chemistry because of their broad spectrum of biological activities. Many of the therapeutically useful compounds such as phenylbutazone, oxypenbutazone, and celecoxib belonging to pyrazoles exhibit anti-inflammatory, antipyritic, and analgesic properties. Researchers have reported that furopyrazole molecules are antileukemia agents. Furopyrazole-based molecules have...
shown numerous biological activities such as antimicrobial and antitumor properties.[7] However, access to dihydrofuro[1,2-b]pyrazole of type 5 is limited.[8] Microwave-irradiated reactions under solvent-free or low-solvent conditions are attractive, offering reduced pollution and high yields, together with simplicity in processing and handling. The salient features of the microwave approach are shorter reaction times, simple reaction conditions, and enhancements in yields.[9] As a part of our continuous efforts toward the development of new green chemistry synthetic approaches for important heterocyclic compounds,[10] in the present work we report an efficient and ecofriendly four-component reaction protocol in microwave-mediated facile chemo- and stereoselective synthesis of highly substituted furanopyrazole derivatives from β-ketoester, benzaldehyde, hydrazine hydride, and pyridinium ylide. The reactions were completed within 3–10 min and the pure products were isolated in good yields.

Results and discussion

As part of our continued interest in the synthesis of diverse heterocyclic compounds of biological significance, we contemplated to synthesize novel dihydropyrazole[1,2-b]furan derivatives 5 by the one-pot, four-component reaction of β-keto ester 1, hydrazine 2, aromatic aldehydes 3, and pyridinium ylide 4, utilizing microwave irradiation under solvent-free conditions (Scheme 1). We decided to perform the preparation of these compounds under microwave irradiation from a green point of view, and when associated with neat conditions it represents an environmentally benign alternative in organic synthesis. In the reaction protocol, when equimolar amounts of β-keto ester 1, hydrazine 2, aromatic aldehydes 3, and ethyl ester pyridinium bromides 4 were reacted in the presence of 0.1 equivalents of Et₃N in a sealed vial under microwave irradiation at 90 °C for 3 min, they afforded, after workup, dihydrofuro[1,2-b]pyrazole derivative 5a as a racemic trans stereoisomer in very good yield. The reaction did not provide even a trace of another isomer.

The structure of the compound was fully characterized by ¹H and ¹³C NMR, MS and IR spectra and elemental analysis. In the ¹H NMR spectra, the two protons at 2,3-position of dihydrofuran ring display two doublets at 5.29 and 5.15 ppm with the vicinal coupling constants $J = 4.6$ Hz and 4.6 Hz, respectively. It has been documented that in cis-2,3-dihydrofuran the vicinal coupling constant of the two methine protons $J = 7–10$ Hz, while in trans-2,3-dihydrofuran vicinal coupling constant $J = 4–7$ Hz. So we concluded that thermodynamically stable trans isomer of 2,3-dihydrofuran derivatives was formed.[11] Further, it was confirmed from the analysis of the nuclear Overhauser effect spectroscopy

![Scheme 1. Synthesis of dihydro-1H-furo[2,3-c]pyrazole 5a–q.](image-url)
(NOESY) data of the compound. The mass spectrum shows a sharp distinguishable peak of compound \(5a\) at 295.1053 \([\text{M}+\text{Na}]^+\). Initially, the reaction was investigated in the absence of catalyst (Table 1, entry 1) under microwave irradiation, but no product was formed. Then, we studied the reaction by using different catalysts (Table 2, entries 2–7) but no such satisfactory results were obtained. When the reaction was carried out in the presence of a catalytic amount of triethylamine, the reaction occurred within 3 min. Use of 0.1 eq of \(\text{Et}_3\text{N}\) (Table 1, entry 8), at 540 W for 3 min in microwave irradiation at 90 °C was found to be sufficient for obtaining optimum yield of the desired product, and an increase in the amount of catalyst (Table 2, entry 8) did not improve the yield of the product. The reaction was also carried out in the presence of different solvents under microwave irradiation but no optimum increase in the yield of desired product was observed (Table 2, entries 10–17).

| Entry | Base\(^a\) | Solvent | Time (min) | Yield (%)\(^b\) |
|-------|------------|---------|------------|-----------------|
| 1     | No         | No      | 5          | 0               |
| 2     | Piperidine | No      | 5          | 57              |
| 3     | Piperidine | EtOH    | 3          | 63              |
| 4     | Piperidine | Water   | 3          | 60              |
| 5     | Morpholine | No      | 3          | 55              |
| 6     | Piperazine | No      | 3          | 58              |
| 7     | \(\text{K}_2\text{CO}_3\) | No | 3 | 50 |
| 8     | \(\text{NEt}_3\) | No | 3 | 85 |
| 9     | \(\text{NHEt}_2\) | No | 3 | 65 |
| 10    | \(\text{NEt}_3\) | EtOH | 5 | 61 |
| 11    | \(\text{NEt}_3\) | Water | 5 | 40 |
| 12    | \(\text{NEt}_3\) | DD Water | 10 | 43 |
| 13    | \(\text{NEt}_3\) | DMF | 15 | 51 |
| 14    | \(\text{NEt}_3\) | MeCN | 15 | 45 |
| 15    | \(\text{NEt}_3\) | THF | 15 | 55 |
| 16    | \(\text{NEt}_3\) | \(\text{CH}_2\text{Cl}_2\) | 15 | 58 |
| 17    | \(\text{NEt}_3\) | Toluene | 15 | 32 |
| 18    | \(\text{NEt}_3\) | \(\text{CHCl}_3\) | 15 | 54 |

\(^a\)Catalyst (0.1 eq).

\(^b\)Yields for isolated pure products.

| Entry | Compound | \(\text{Ar}\) | Yield (%)\(^a\) |
|-------|----------|---------------|-----------------|
| 1     | \(\text{5a}\) | \(\text{C}_6\text{H}_5\) | 89 |
| 2     | \(\text{5b}\) | \(p\)-\(\text{ClC}_6\text{H}_4\) | 82 |
| 3     | \(\text{5c}\) | \(o\)-\(\text{ClC}_6\text{H}_4\) | 72 |
| 4     | \(\text{5d}\) | 2,6-\(\text{Cl}_2\text{C}_6\text{H}_3\) | 71 |
| 5     | \(\text{5e}\) | 2,4,6-\(\text{Cl}_3\text{C}_6\text{H}_2\) | 73 |
| 6     | \(\text{5f}\) | \(p\)-\(\text{BrC}_6\text{H}_4\) | 78 |
| 7     | \(\text{5g}\) | \(p\)-\(\text{MeC}_6\text{H}_4\) | 80 |
| 8     | \(\text{5h}\) | 2,4-(\(\text{CH}_3\))_2\(\text{C}_6\text{H}_3\) | 72 |
| 9     | \(\text{5i}\) | \(p\)-\(\text{N(CH}_3)_2\)\(\text{C}_6\text{H}_4\) | 75 |
| 10    | \(\text{5j}\) | \(p\)-\(\text{OH})\(\text{C}_6\text{H}_4\) | 75 |
| 11    | \(\text{5k}\) | \(p\)-\(\text{OMe})\(\text{C}_6\text{H}_4\) | 76 |
| 12    | \(\text{5l}\) | 3,4-(\(\text{OMe})_2\)\(\text{C}_6\text{H}_3\) | 77 |
| 13    | \(\text{5m}\) | \(p\)-\(\text{NO}_2\)\(\text{C}_6\text{H}_4\) | 72 |
| 14    | \(\text{5n}\) | \(m\)-\(\text{NO}_2\)\(\text{C}_6\text{H}_4\) | 78 |
| 15    | \(\text{5o}\) | Furyl | 81 |
| 16    | \(\text{5p}\) | Thiophenyl | 78 |
| 17    | \(\text{5q}\) | 3-Pyridyl | 84 |

\(^a\)Yields for isolated pure products.
Similarly, compounds 5b–q were synthesized and characterized. Then, the substrate scope of the reaction was explored by using various aromatic aldehydes in the model reaction. All the reactions, consisting of those involving ortho and para-substituted benzaldehydes, proceed smoothly, giving dihydrofuro[1,2-\(b\)]pyrazole in moderate to high yields. Electronic effects were also observed in the reaction process.

The electron-donating group (EDG) at the para position of the aldehyde required less reaction time to give comparatively high yields of the product (Table 2, entries 9–12) while stronger EWG-substituted ones gave evidently poor yields (Table 2, entries 13 and 14). Ortho-substituted benzaldehydes, irrespective of EDG or EWG, afforded the corresponding dihydropyrazole[1,2-b]furans in relatively lower yields, indicating an obvious steric effect (Table 2, entries 3–5 and 8). The aliphatic aldehyde did not show any effect in that reaction. The synthetic route is facile and convergent and allows easy placement of a variety of substituents around the periphery of the heterocyclic ring system (Scheme 1).

A probable mechanism for the formation of product is depicted in Scheme 2. The reaction occurs via an initial Knoevenagel condensation between 1,3-pyrazolone A and aromatic aldehyde 3 to give the intermediate D. On the other hand, the pyridinium ylide 4, which forms from the reaction of N-phenacyl pyridinium bromide 3 with triethyl amine, undergoes Michael addition with an intermediate F to afford the enolate intermediate G. The enolate G eliminates pyridine and cyclizes instantly to give dihydrofuro[1,2-b]pyrazole 5. The eliminated pyridine releases triethylamine from the Et\(_3\)N/HBr salt which further catalyzes the reaction. Exclusive arrival of product 5 with trans-stereochemistry for COOEt and aryl ring can be attributed to stereoelectronic interaction in the approach of phenyl

![Scheme 2. Plausible mechanism for the formation of dihydro-furopyrazole.](image-url)
and pyridinium rings during transformation of enolate intermediate G to 5. Overall, this microwave-promoted four-component domino reaction leads to the generation of one C–O and two C–C bonds. This methodology can be further explored towards the synthesis of diverse dihydrofurropyrazole derivatives by using different ylides with active methylene compounds.

**Conclusion**

In conclusion, we have developed an efficient microwave-promoted reaction protocol for diastereoselective synthesis of dihydrofurano[1,2-b] pyrazole via one-pot, four-component reaction of β-keto ester, hydrazine, aromatic aldehyde, and pyridinium ylide in the presence of triethylamine in solvent-free conditions. Short reaction times in microwave-assisted conditions along with very simple workup, better yields, and absence of solvent make the protocol more environmentally benign for the synthesis of furopyrazoles.

**Experimental**

The progression of all the reactions were monitored by thin-layer chromatography (TLC) using hexanes (60–80 °C boiling mixture)/ethyl acetate mixture as eluent. Column chromatography was carried on silica gel (100–200 mesh, SRL chemicals) using an increasing percentage of ethyl acetate in hexanes. All microwave reactions were performed in a monomode Biotage Emery’s Creator 540-W system with sample absorption set to “normal.” ¹H NMR (400 MHz), ¹³C NMR (100 MHz), and DEPT-135 spectra were recorded for CDCl₃ solutions on a Bruker 400 spectrometer with tetramethylsilane (TMS) as internal standard; J values are in hertz. The number of hydrogens attached to each carbon was determined from DEPT spectra and is given next to the corresponding ¹³C NMR spectral data. IR spectra were recorded as KBr pellets on a Nicolet-6700 spectrometer. Melting points were recorded using open-ended capillary tubes on a VEEGO VMP-DS instrument. High-resolution mass spectra were recorded on a Waters Micromass Q-TOF micro mass spectrometer using electron spray ionization mode. Organic solvents were distilled and dried before use.

**General procedure for synthesis of dihydrofurropyrazole (5a–q)**

*rac-(4R,5R)-Ethyl 3-methyl-4-phenyl-4,5-dihydro-1H-furo[2,3-c]pyrazole-5-carboxylate 5a*

Mixture of ethyl acetoacetate 1 (211 mg, 0.153 mmol), hydrazine 2 (81 mg, 0.153), benzaldehyde 3a (172 mg, 0.153 mmol), 1-(2-ethoxy-2-oxoethyl) pyridinium ylide 4 (272 mg, 0.153 mmol), and 0.1 equivalents of trimethylamine (16 mg, 0.015 mmol) were mixed in a process glass vial. The vial was capped properly and thereafter the mixture was heated under microwave irradiating conditions at power level 540 W at 90 °C for 3 min without solvent. The residue was purified by column chromatography on silica gel (hexane–ethyl acetate 3:7). Analytical samples were obtained through from the recrystallization in EtOH. Light yellow solid. Yield 89% (394 mg), mp 123.4 °C; IR (KBr) v max 3205, 3085, 2981, 2690, 2639, 1644, 1491, 1404, 1370, 1338, 1215, 1179, 1119, 1086, 1026, 998, 965, 883, 842, 769, 742, 692 cm⁻¹; ¹H NMR (400 MHz, DMSO-d₆) δ 12.27 (s, 1H), 7.22–7.30 (m, 5H), 5.29 (d, J = 4.6 Hz, 1H), 5.16 (d, J = 4.6 Hz, 1H), 4.16 (q, J = 6.6 Hz, 2H), 1.91 (s, 3H), 0.95 (t, J = 7.4 Hz, 3H).
Hz, 3H) ppm; $^{13}$C NMR (100 MHz, DMSO-d$_6$) δ 191.4 (C=O), 161.4 (C), 142.17 (C), 138.1 (C), 126.7 (CH), 124.6 (CH), 123.3 (CH), 109.4 (C), 88.0 (CH), 62.7 (CH$_2$), 44.2 (CH), 26.7 (CH$_3$), 14.2 (CH$_3$) ppm; HRMS (ESI, m/z) 295.1053 calcd. for C$_{15}$H$_{16}$N$_2$O$_3$ (M+Na), found 295.1051. Analysis calcd. for C$_{15}$H$_{16}$N$_2$O$_3$: C, 66.16; H, 5.92; N, 10.29; Found C, 66.14; H, 5.90; N, 10.27.

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