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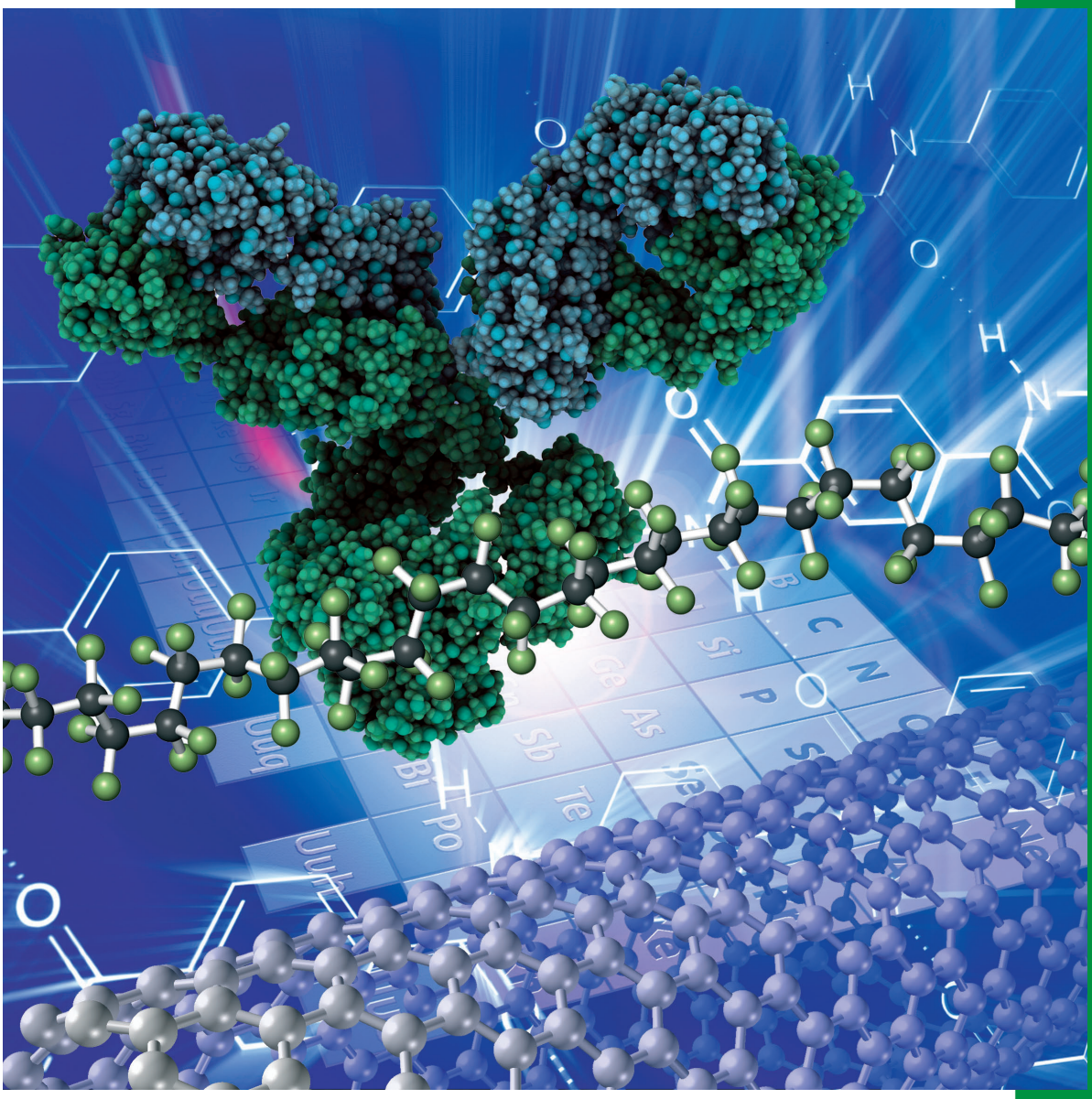

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Organic & Supramolecular Chemistry

Ultrasonic Cavitation Facilitates Rapid Synthesis of Trisubstituted Pyrazole Scaffolds through Michael Addition/Domino Cyclization

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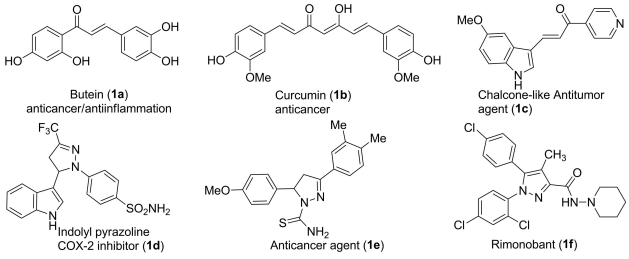
A series of aryl/indolyl substituted 4, 5-dihydro-1H-pyrazole derivatives were synthesized via a domino method based on Michael addition mediated cyclization of appropriate chalcones. The chalcones were prepared by Witting reaction in which substituted aromatic aldehydes were treated with stable ylides under eco-friendly ultrasonic cavitation. The pyrazole scaffolds were obtained in excellent yields within a short span of time.



Scheme 1. Some examples of biologically active chalcones and pyrazole derivatives.

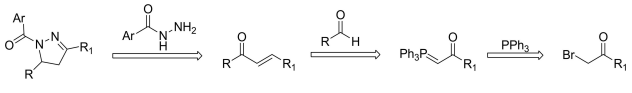
Introduction

The indole and pyrazole moieties are among the privileged structures found in medicinally active substances, and they are well known for their wide range of biological and pharmacological activities. Besides, the pyrazole skeleton encompasses numerous pharmacological activities such as anticancer, antiviral, antioxidant, antimicrobial, antipyretic, anti-diabetic, anti-inflammatory, anticonvulsant and analgesic activities.[1–5] The range of compounds represented in Scheme 1 includes chalcone based antitumor agents[6] and indolylpyrazole- based COX-2 inhibitors.[7] Several synthetic routes have been accorded to the development of pyrazole hybrid scaffolds, which are important intermediates in medicinal chemistry. The present investigation was undertaken to develop an efficient eco-friendly method for synthesizing pyrazole derivatives containing indole moiety. Indolylpyrazole derivatives have been synthesized from chalcones using hydrazine, substituted hydrazines, and hydrazides. Liu *et al.* and Lim *et al.* have reported the synthesis of pyrazole scaffolds using chalcone and hydrazine hydrate.[8] Tiwari *et al.*[9] have reported the synthesis of pyrazoles through cyclo-condensation of chalcone derivatives with benzotriazolyl acetyl hydrazine in glacial acetic acid. Selvam *et al.* have synthesized a series of 1-(4-substituted phenyl)-3-phenyl-1H-pyrazole-4-carbaldehydes through microwave method using acetophenone, arylhydrazine and Vilsmeier-Haack reagent.[10] Recently, pyrazole derivatives possessing anti-bacterial, anti-fungal,[11] anti-diabetic,[12] anti-inflammatory[13] and anti-mycobacterial properties[14] have been synthesized using chalcones and pyridine-4-carbohydrazide (isoniazid). Isoniazid is still considered to be a prominent drug for chemotherapy and tuberculosis.

Therefore, we put forth our attention towards the assemblage of indolylpyrazole- and pyrazolylpyridinyl- methanone architectures. In the present work, we report the preparation of novel chalcones through Witting reaction and the synthesis of pyrazole scaffolds *via* a domino cyclization reaction.

Results and Discussion

To accomplish the synthesis of pyrazole scaffolds, we followed the chalcone-hydrazide as outlined in the retrosynthetic strategy (Scheme 2). The yield of pilot experiments in one-pot



Scheme 2. Retrosynthetic strategy for pyrazole scaffolds.

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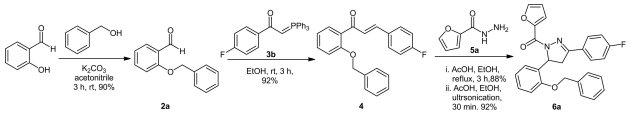
strategy was not impressive. Hence, starting from chiefly available compounds, stable ylides were prepared[15] in quantitative yields, and the ylides were subsequently reacted with aryl aldehydes under Wittig reaction conditions to obtain the desired chalcones.[16] Michael-addition of aryl hydrazides with chalcones and the consequent cyclization reaction yielded the corresponding pyrazole scaffolds.[17]

Initially, we reacted the substituted chalcone **4** (1.0 mmol) with furylhydrazide **5a** (1.2 mmol) under reflux in ethanol for 3 h in the presence of catalytic amounts of acetic acid. After completion of the reaction and work up, the corresponding pyrazole scaffold **6a** was isolated in 88% yield as illustrated in scheme 3.



Scheme 3. Synthesis of furyl substituted pyrazole scaffold from *o*-benzylated chalcone precursor.

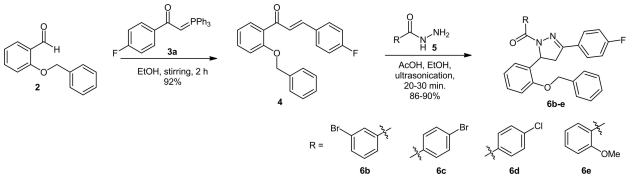
Table 1. Synthesis of various substituted pyrazole scaffolds (**6a-p**) from chalcones (**4**, **7**, **9**).

Entry	Chalcone	Product[d]	Time (min)[b]	Yield (%)[c]
1	4	**6a**	180[a]/30[b]	88[a]/92[b]
2	4	**6b**	25	86
3	4	**6c**	25	88
4	4	**6d**	20	86
5	4	**6e**	30	90
6	7a	**6f**	15	92
7	7b	**6g**	20	90
8	7a	**6h**	20	92
9	7c	**6i**	18	92
10	9	**6j**[e]	35	90
11	9	**6k**[e]	40	92
12	9	**6l**	45	85
13	9	**6m**[e]	45	86
14	9	**6n**[e]	30	85
15	9	**6o**	45	90
16	9	**6p**	45	92

[a] Reaction was conducted using **4** (1 mmol) and **5a** (1.2 mmol) in AcOH/EtOH medium and reflux for 180 min. [b] All the reactions were carried out under ultrasonic irradiation for 20–45 minutes. [c] Isolated yield of the pure products. [d] Compounds were characterized using IR, NMR, and mass spectra analysis. [e] The structures were confirmed by single-crystal XRD analysis.

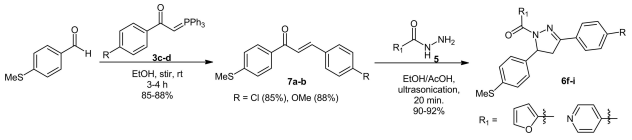
When the same reaction was carried out under ultrasonic irradiation,[18] the temperature of sonication bath raised above ambient temperature, gratifyingly the reaction was complete within a short span of time (30 minutes), and the product **6a** was isolated in comparable yield.

Encouraged by this result, we then treated various hydrazides (**5**) with the chalcone **4** under ultrasonic reaction conditions, which successfully afforded the desired cyclic pyrazole derivatives (**6b-e**) in 86–90% yields (Scheme 4). The isolated yields of pure products (**6a-e**) are shown in Table 1.



Scheme 4. Synthesis of various substituted pyrazole derivatives **6b-e**.

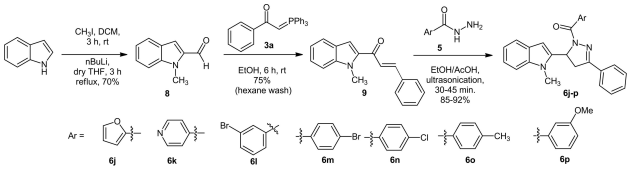
To check the generality of the reaction, we utilized the thiomethylbenzaldehyde and chloro/methoxy substituted 1-phenyl-2-(triphenylphosphoranylidene)ethanone derivatives **3c-d** for Wittig reaction for the synthesis of chalcones **7a-b**. The resulting chalcones **7a-b** upon reaction with respective carbohydrazide **5** provided the anticipated pyrazole scaffolds (**6f-i**) in 90–92% yields as shown in scheme 5. Delighted by



Scheme 5. Synthesis of methylthiophenyl/pyridinyl substituted pyrazoles.

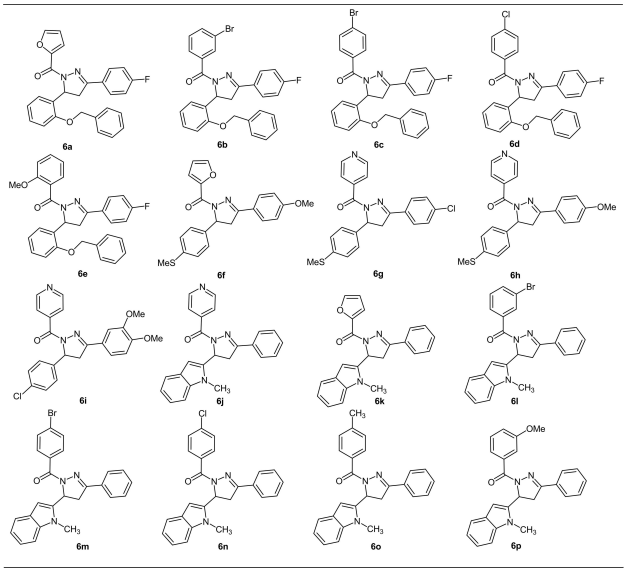
these results, we decided to extend the methodology to indole-based chalcone, thus the *N*-Methyl indole-2-carboxaldehyde was prepared,[19] and the same was treated with phenyl-2-(triphenylphosphoranylidene) ethanone **3a** to yield the corresponding indolylchalcone **9**.[20]

The indolylchalcone (9), upon further reaction with various carbohydrazides (5) under the above mentioned ultrasonication condition, provided the anticipated products (6j-p) in 85–92% yields (Scheme 6 & 7). Interestingly, four out of the seven



Scheme 6. Synthesis of substituted pyrazole derivatives from *N*-methylated indolyl chalcone.

indolylpyrazole scaffolds offered diffraction quality single crystals (Figure 1). Apparently, the structural elucidation of all the products (**6a-p**) involved the assignment of chemical shifts and determination of coupling constants using the ^{1}H and ^{13}C NMR spectral data. A perspective view of the spatial orientation of different substituents with respect to the pyrazole ring was obtained from the single crystal XRD analysis of four indolylpyrazole derivatives (**6j, 6k, 6m** and **6p**), and



Scheme 7. Synthesis of various pyrazole derivatives from chalcone

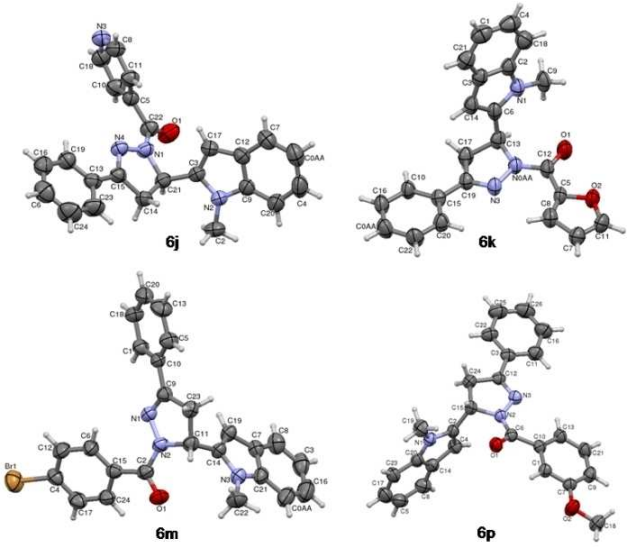


Figure 1. ORTEP diagram of compounds **6j, 6k, 6m** and **6p**.

their CCDC numbers are 1859520, 1859522, 1859521 and 1859518 respectively.

Conclusions

Ultrasonic cavitation facilitated synthesis of sixteen new aryl/indolylpyrazole scaffolds from chalcone precursors, is presented. The reaction involves the formation of new C–C, C–N, C=N bonds in a single step through a domino process, that includes the Michael addition followed by domino cyclization. All the compounds were characterized by IR, NMR, mass spectral analyses. Four of the indolylpyrazole molecular structures were further confirmed without any ambiguity through single crystal X-ray analysis. The ultrasonic cavitation provided a good strategy to synthesize a library of trisubstituted pyrazole frameworks in high yield, short time and high atom efficiency. The newly synthesized pyrazole molecules are, currently, screened for biological activities.

Supporting Information Summary

Procedure for the synthesis of title compounds, ^{1}H and ^{13}C NMR spectroscopic data are provided. ORTEP diagrams corresponding to crystal structures of four indolylpyrazole derivatives (6j, 6k, 6 m and 6p) and their CCDC numbers are also available in the supporting information.

Acknowledgments

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: Carbohydrazide · Chalcone · Domino cyclization · Indolylpyrazole · Isoniazid · Michael addition · Witting reaction

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