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Note

Cyclodehydration reaction in water medium leads to library/multigram synthesis of 1,5-diarylpyrazoles†

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The cyclodehydration reaction leading to 1,5-diarylpyrazoles in water medium has been observed for the first time. The method has been used in generating library of compounds for drug discovery program under microwave condition and tried for a multigram synthesis of celecoxib, a premier COX-2 inhibitor, under normal laboratory condition.

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Pyrazoles are well documented to possess antihypertensive[1], antibacterial[2], antiinflammatory[3] and antitumour[4] properties. Particularly, 1,5-diarylpyrazoles have received immense attention in drug research after the introduction of a block buster COX-2 inhibitor, celecoxib **1** in the market[3a]. Many laboratories are actively pursuing the chemical modification of this class of compounds to have better drug candidates **2** for inflammation and cancer related indications[5] (**Figure 1**).

Of the many methods reported for the synthesis of pyrazoles[6], the one involving coupling of suitable phenylhydrazine hydrochloride with β-diketones (1,3-diketones) is widely practiced from laboratory to production scale[3a,7]. Though this method is simple, it requires refluxing the two components in absolute alcohol for 5-15 hr depending upon their reactivities. In addition, it requires an exhaustive work-up procedure which ultimately delays the drug discovery and development program. Therefore, it became important to explore simpler technique and work-up/isolation procedure to speed up the synthesis of large number of pyrazole analogs for biological screening. In this endeavour, we opted microwave assisted parallel synthesis to address the above issues[8]. Though the method was used for the first time in generating the pyrazole library, its excellent efficiency prompted us to go beyond organic solvent and use water as the reaction medium. Hence, we report herein the condition which afforded library of 1,5-diarylpyrazoles and a multigram synthesis of celecoxib **1** in water in absolutely pollution free environment.

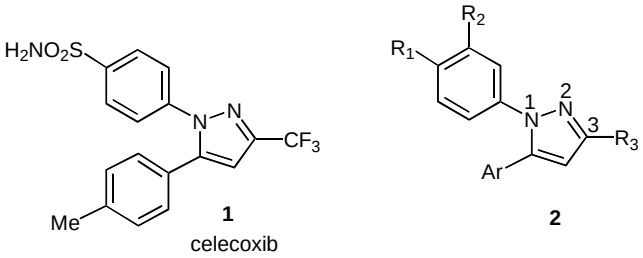

Figure 1

Results and Discussion

The microwave promoted condition was studied and optimized to get a reference sample of 1,5-diarylpyrazole and subsequently implemented to the parallel synthesis of different compounds including celecoxib (**Scheme I**). The starting material, 1,3-diketones **5** were prepared from suitable acetophenones **3** and esters of carboxylic acids **4** by an improved method reported earlier[5b]. The three pilot trial conditions included the microwave irradiation of mixture of phenylhydrazine hydrochloride **6c** (1.1 equiv.) and 1,3-diketone **5c** (1.0 equiv.) for 2-5 min as (i) neat (both solids), (ii) thick paste in dimethylformamide and (iii) dimethylformamide paste soaked in 100-200 mesh silica gel. While the first two reaction mixtures generated impurities along with the desired product **7c** in 2 min, the last one was found to be high yielding with no impurity detected even after extended period of 5-7 min. Keeping this ease of formation of pyrazoles under microwave condition in mind, we interestingly turned towards studying a pilot synthesis of **7c** from its two components in water medium under microwave irradiation. Surprisingly, this cyclodehydration reaction also worked similarly in water medium with high yield under similar condition. A thorough literature search on this subject revealed this methodology to be novel[9].

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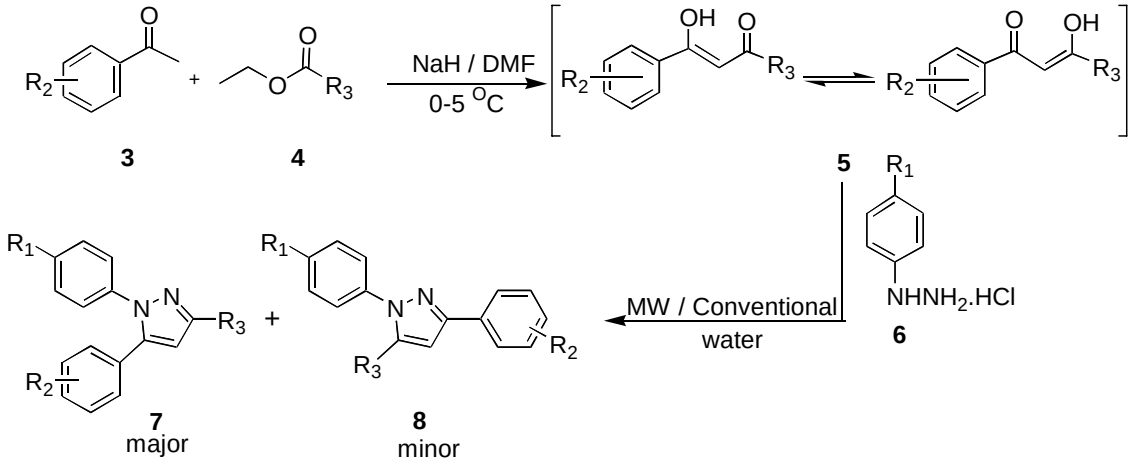

7a. R_1 = 4-SO_2NH_2, R_2 = H, R_3 = CHF_2.
7b. R_1 = 4-SO_2NH_2, R_2 = 2,4-Cl_2, R_3 = CF_3
7c. R_1 = 4-SO_2NH_2, R_2 = 4-OMe, R_3 = CF_3
7d. R_1 = 4-SO_2NH_2, R_2 = 4-Cl, R_3 = CF_3
7e. R_1 = 4-SO_2NH_2, R_2 = 4-NHAc, R_3 = CH_3
7f. R_1 = 4-Cl, R_2 = 4-Cl, R_3 = CF_3
7g. R_1 = 4-Cl, R_2 = 4-OPh, R_3 = CF_3
7h. R_1 = 4-Cl, R_2 = 4-OPh, R_3 = CH_3
7i. R_1 = 4-OMe,R_2 = 4-NHAc, R_3 = CH_3
7j. R_1 = 4-OMe, R_2 = 4-OPh, R_3 = CF_3
7k. R_1 = 4-SO_2NH_2, R_2 = 4-CH_3, R_3 = CF_3 (celecoxib)

Scheme I

Looking forward to try still simpler condition, we heated the heterogeneous mixture of the two components (in above proportion) of **7c** in water under normal laboratory condition. To our delight, we still observed the same results. It led us to conclude that the driving force in this cyclodehydration reaction could be the generation of highly stable aromatic pyrazole ring. And, if such was the case, why not the largest selling COX-2 inhibitor celecoxib **1** could industrially be synthesized in water in an absolutely pollution free environment. To check its feasibility in the laboratory, a 10 g batch of celecoxib was prepared which matched with the standard sample in all respect. The only major difference between the reaction under microwave and laboratory condition was the time taken in their completion. The earlier reaction took only 2-5 min whereas the latter required 12-16 hr. Therefore, it was decided to generate library of 1,5-diarylpyrazoles in water medium for discovery program under microwave condition and optimize the process for the production of celecoxib in water medium under laboratory condition. The experimental success of the quick generation of library samples and that of the 10 g batch of celecoxib in hetero-phase (undissolved in water) lies with the use of slightly excess proportion of phenylhydrazine hydrochloride **6** which completely consumes the 1,3-diketone **5** and gets washed away with water on decantation. A thorough trituration with a mixture of ethyl alcohol and water removes the traces of unreacted 1,3-diketone and other minor impurities and provides pure sample of 1,5-diarylpyrazoles. To confirm the working ability of the described process, ten different 1,5-diarylpyrazoles **7a-k** were synthesized in parallel under the optimized microwave condition in water medium in 50-100 mg scale for *in vitro* screening. A further scale up of celecoxib in water medium under laboratory condition is in progress. The structures of these products were confirmed by IR, ^{1}H NMR and mass spectroscopy, and by comparing with the literature data[3a]. The compounds were highly pure (97-99% by HPLC) and contained minimum quantities of the undesired 1,3-diarylpyrazoles **8** (0.07-1.59%). A few reported compounds such as **7a-d, f** and **k** were also synthesized for comparison purpose[3a].

Experimental Section

Microwave irradiation was performed in LG-MC-804 AAR kitchen type oven. Reactions were monitored by TLC on silica gel plates (60 F_{254}; Merck), visualizing with ultraviolet light or iodine

spray. The flash column chromatographic purification was performed over 230-400 mesh silica gel using mixture of ethyl acetate and petroleum ether. The reported yields are unoptimized. Melting points were determined on Buchi melting point B-540 apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer FT-IR 1650 spectrometer; ^{1}H NMR spectra at 200 MHz on a Varian Gemini 200 spectrometer; and mass spectra on a HP-5989A spectrometer. All the analyses were performed by the Analytical Research group of Discovery Research, Dr. Reddy's Laboratories Ltd. The purity of the final compounds were determined by HPLC using "System 1" which consisted column Hichrom RPB (250 mm), mobile phase 0.01 M KH_2PO_4/CH_3CN (50:50) and "System 2" which comprised column Intersil ODS 3V (250 mm), mobile phase H_2O/CH_3CN (50:50), both running at 1.0 mL/min with UV detection at respective $\lambda_{max.}$.

Optimized condition for the synthesis of 1,5-diarylpyrazole library 7. Ten different 1,3-diketones **5** (100 mg each), taken separately in conical flasks were mixed with phenylhydrazine hydrochlorides **6** (1.1 equiv. each), and water (1 mL each) was added. The mixture was manually shaken to get slurry and each flask was covered with small funnel to avoid the loss of solvent due to evaporation. All the flasks were irradiated at 510 W [(60% of the maximum power (850 W)] for 4 min. The temperature of the reaction mixture was recorded as 95-100 ^oC at the end of the irradiation. The flasks were cooled to room temperature and the contents were stirred with ethanol (1 mL each) to get off white solid which was filtered and washed with minimum volume of a mixture of ethyl acetate-pet. ether which afforded white coloured compounds. In few cases where solid was not obtained, the product was isolated by extraction with ethyl acetate and purified by column chromatography using ethyl acetate-pet. ether (10%) as eluent.

***N*^{1}- {4-[3-Methyl-1-(4-sulfamoylphenyl)-1*H*-5-pyrazolyl]phenyl}acetamide 7e**: Yield 57%, mp 208-10°C; IR (KBr): 3349, 1664, 1595, 1516, 1430 cm^{-1}; ^{1}H NMR ($CDCl_3$+ DMSO-d_6): δ 9.47 (bs, 1H, D_2O exchangeable), 7.84 (d, *J* = 8.2 Hz, 2H), 7.63 (d, *J* = 9.6 Hz, 2H), 7.37 (d, *J* = 8.4 Hz, 2H), 7.13 (d, *J* = 8.4 Hz, 2H), 6.66 (bs, 2H, D_2O exchangeable), 6.29 (s, 1H), 2.36 (s, 3H), 2.14 (s, 3H); MS (CI method): 371 $(M+1)^+$; HPLC (method 1): 97.9%. Anal. Calcd for $C_{18}H_{18}N_4O_3S$: C, 58.37; H, 4.90; N, 15.13. Found: C, 58.21; H, 4.66; N, 14.85%.

1-(4-Chlorophenyl)-5-(4-phenoxyphenyl)-3-trifluoromethyl-1*H*-pyrazole 7g: Isolated as viscous liquid; yield 77%. IR (Neat): 3066, 2927, 1590, 1555, 1491 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.42-7.25 (m, 5H), 7.24-7.17 (m, 4H), 7.04 (d, *J* = 7.8 Hz, 2H), 6.94 (d, *J* = 8.8 Hz, 2H), 6.71 (s, 1H); MS (CI method): 414 $(M+1)^+$; HPLC (method 2): 98.6%. Anal. Calcd for $C_{22}H_{14}ClF_3N_2O$: C, 63.70; H, 3.40; N, 6.75. Found: C, 63.45; H, 3.05; N, 8.02%.

1-(4-Chlorophenyl)-3-methyl-5-(4-phenoxyphenyl)-1*H*-pyrazole 7h: Yield 72%, mp 112-14°C; IR (KBr): 3435, 1588, 1491, 1362 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.40-7.19 (m, 9H), 7.04 (d, *J* = 8.2 Hz, 2H), 6.92 (d, *J* = 8.4 Hz, 2H), 6.27 (s, 1H), 2.37 (s, 3H); MS (CI method): 361 $(M+1)^+$; HPLC (method 2): 98.2%. Anal. Calcd for $C_{22}H_{17}ClN_2O$: C, 73.23; H, 4.75; N, 7.76. Found: C, 72.85; H, 4.65; N, 7.49%.

***N*^{1}-{4-[1-(4-Methoxyphenyl)-3-methyl-1*H*-5-pyrazolyl]phenyl}acetamide 7i**: Yield 68%, mp 148-50°C; IR (KBr): 3307, 2932, 1668, 1599, 1517 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 10.30 (bs, 1H, D_2O exchangeable), 7.50 (d, *J* = 6.4 Hz, 2H), 7.20-7.00 (m, 4H), 6.95 (d, *J* = 6.4 Hz, 2H), 6.35 (s, 1H), 3.76 (s, 3H), 2.24 (s, 3H), 2.03 (s, 3H); MS (CI method): 322 $(M+1)^+$; HPLC (method 1): 97.6%. Anal. Calcd for $C_{19}H_{19}N_3O_2$: C, 71.01; H, 5.96; N, 13.08. Found: C, 70.75; H, 6.23; N, 12.77%.

1-(4-Methoxyphenyl)-5-(4-phenoxyphenyl)-3-trifluoromethyl-1*H*-pyrazole 7j: Yield 70%, mp 94-96°C; IR (KBr): 3149, 1589, 1523, 1470 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.41-7.33 (m, 2H), 7.26-7.14 (m, 5H), 7.03 (d, *J* = 7.8 Hz, 2H), 6.93-6.86 (m, 4H), 6.86 (s, 1H), 3.82 (s, 3H); MS (CI method): 411 $(M+1)^+$; HPLC (method 2): 98.0%. Anal. Calcd for $C_{23}H_{17}F_3N_2O_2$: C, 67.31; H, 4.18; N, 6.83. Found: C, 67.11; H, 4.29; N, 7.20%.

Process for the synthesis of 4-[5-(4-methylphenyl)-3-trifluoromethyl-1*H*-1-pyrazolyl]-1-benzenesulfonamide (celecoxib) 7k. A mixture of 4-sulfamoylphenylhydrazine hydrochloride **6k** (9.16 g, 41.73 mmoles) and 4,4,4-trifluoro-1-(4-methylphenyl)-1,3-butanedione **5k** (8.0 g, 34.78 mmoles), suspended in water (200 mL), was refluxed for 14 hr in argon atmosphere. The reaction mixture was cooled to room temperature and the solvent was decanted. The sticky mass lying in the flask was triturated with a 3:1 mixture of alcohol and water (50 mL), filtered and finally washed with a mixture of ethyl acetate-pet. ether to get a white solid of celecoxib (10.75 g, 81%). This product matched with the standard sample in all respect and the HPLC purity (method 1) was found to be 98.2% (ref. 3a).

Conclusions

We described herein an excellent method for the rapid generation of 1,5-diarylpyrazole library **7** using microwave in water medium along with a 10 g batch of celecoxib **1**, the largest selling COX-2 inhibitor, synthesized in water medium under normal laboratory condition. Both the experiments put forward a vast scope in drug discovery as well as in the commercial production of this class of compounds in an absolutely pollution free environment.

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