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Modified reaction conditions to achieve high regioselectivity in the two component synthesis of 1,5-diarylpyrazoles☆

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Abstract—The factors affecting regioselectivity during the formation of 1,5-diarylpyrazoles from aryl hydrazines and 1,3-diketones are identified and the regioisomers were characterized by 1D NOESY, LC–NMR and X-ray analyses. A simple alteration in the usual reaction conditions is reported, which allows the exclusive formation of 1,5-diarylpyrazoles.

The pyrazole ring is present in many pharmacologically important compounds.[1] Although many methods are known for the construction of this ring system,[2] the search for novel synthetic methodology addressing the necessity for a particular regioisomer is always desirable.[3,4] Recently, 1,5-diarylpyrazoles gained further importance after the introduction of celecoxib **1** (Fig. 1), a COX-2 inhibitor for the treatment of chronic inflammatory diseases like rheumatoid and osteoarthritis.[4] The widely accepted synthetic method for this class of compounds comprises of the coupling of an appropriate phenylhydrazine hydrochloride with a suitable 1-phenyl-1,3-diketone in hot ethanol.[5] Although it is an excellent method in terms of yield, it suffers from poor regioselectivity in many cases depending on the nature of the 1,3-diketone.[6]

In a discovery project,[7] we were interested in the practical synthesis of 1,5-diarylpyrazoles **2** (Fig. 1) with alkyl and heteroaryl groups at C-3. While the reported regiospecific syntheses of this class of compounds involves low yielding steps,[4,8] it was anticipated that the high yielding coupling method described above would yield a mixture of regioisomers.

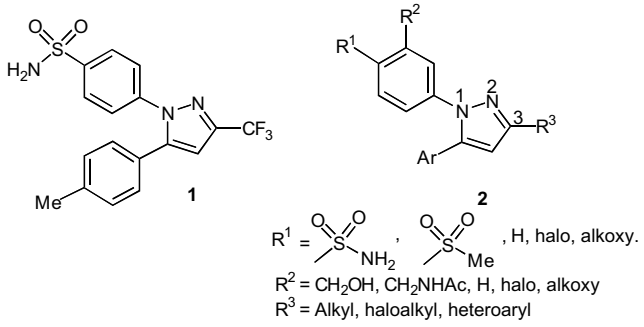

Figure 1.

Previously, the two component synthesis has been conducted in acidic medium and the suitability of the 1,3-diketone has generally been emphasized for the synthesis of 1,5-diarylpyrazoles,[3–6] but, to our knowledge, no systematic study has correlated the control of regiochemistry with reaction conditions and the electronic/steric factors of the 1,3-diketone and phenylhydrazine. We present here the outcome of our study of the effect of substituents on both of the components on the formation of regioisomers. We found that by employing simple methods we could achieve excellent regioisomeric excesses.

Heating arylhydrazine hydrochlorides with 1-aryl-1,3-diketones **3** (CF_3) in ethanol afforded 1,5-diarylpyrazoles as the major products with small quantities of

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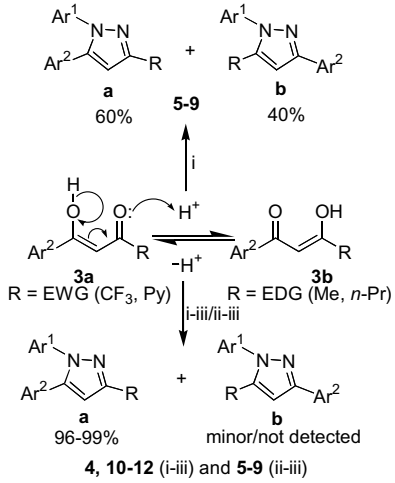
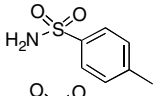
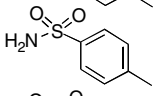
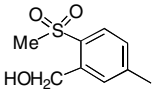
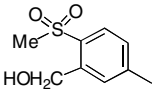
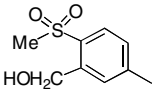
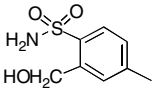
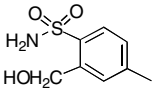
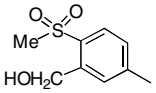
undesired 1,3-diarylpyrazoles, which were discarded by triturating the products, after column purification, with a mixture of ethyl acetate and toluene (Scheme 1 and Table 1). However, this selectivity was limited to those examples where electron-withdrawing groups such as CF_3, CHF_2, CH_2F etc. were attached to C-3 of the 1,3-diketone.[7b,9] In the cases of simple alkyl substituents such as CH_3, C_2H_5 and n-C_3H_7, a ~ 60:40 a nonseparable mixture of the regioisomers was obtained, which could be quantified by integration of the ^1H NMR spectrum of the mixture and by HPLC analysis (Table 1).[9b] The identities of this nonseparable two component mixture was established by a 1D NOESY experiment, and confirmed by the ^1H NMR spectra of the pure components obtained from LC–NMR analysis.

Various arylhydrazine hydrochlorides were reacted with 1-aryl-hexane-1,3-diones under acidic conditions to study the regioselectivity. While arylhydrazines having electron-donating and weakly electron-withdrawing



Scheme 1. Reagents and conditions: (i) $Ar^1NHNH_2{\cdot}HCl$, absolute ethanol, 50–60 °C, 4–5 h; (ii) $Ar^1NHNH_2{\cdot}HCl$, TEA, absolute ethanol, 50–60 °C, 4–5 h; (iii) Ar^1NHNH_2, absolute ethanol, 50–60 °C, 4–5 h.

Table 1. Regioselectivity achieved in the synthesis of 1,5-diarylpyrazoles

Compound	Ar^1	Ar^2	R	Reaction conditions[a]	**a** (%)[b]	**b** (%)[b]
4	4-MeO–C_6H_4–	4-MeO–C_6H_4–	CF_3	i[c]	99	0
5	4-MeO–C_6H_4–	4-MeO–C_6H_4–	CH_3	i	71	29
5	4-MeO–C_6H_4–	4-MeO–C_6H_4–	CH_3	ii	100	0
5	4-MeO–C_6H_4–	4-MeO–C_6H_4–	CH_3	iii	100	0
6	4-MeO–C_6H_4–	4-MeO–C_6H_4–	n-C_3H_7	i	62	38
6	4-MeO–C_6H_4–	4-MeO–C_6H_4–	n-C_3H_7	ii	96	3
6	4-MeO–C_6H_4–	4-MeO–C_6H_4–	n-C_3H_7	iii	99	1
7	4-O_2N–C_6H_4–	4-MeO–C_6H_4–	n-C_3H_7	i	21	79
7	4-O_2N–C_6H_4–	4-MeO–C_6H_4–	n-C_3H_7	ii	99	0
8		4-MeO–C_6H_4–	n-C_3H_7	i	67	32
8		4-MeO–C_6H_4–	n-C_3H_7	ii	98	0
9		4-MeO–C_6H_4–	n-C_3H_7	i	52	48
9		4-MeO–C_6H_4–	n-C_3H_7	ii	99	1
9		4-MeO–C_6H_4–	n-C_3H_7	iii	98	1
10		4-MeO–C_6H_4–		i[c]	99	1
11		4-MeO–C_6H_4–		i[c]	99	0
12		4-MeO–C_6H_4–		i[c]	100	0

[a] See Scheme 1.
[b] By ^1H NMR and HPLC.
[c] Reaction conditions (ii)–(iii) also provided similar results.

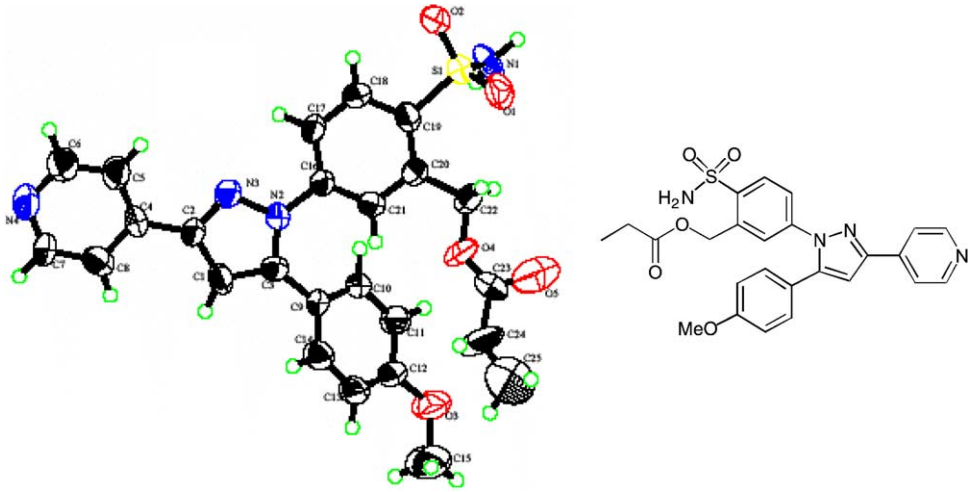


Figure 2. X-ray crystal structure of the *O*-propanoate of 3-(4-pyridyl)-1,5-diarylpyrazole **10**.

groups afforded ~50–65% of the 1,5-diarylpyrazoles **8** and **9**, those with strongly electron-withdrawing groups such as a nitro group afforded ~80% of the 1,3-diarylpyrazole **7**. But, with these diketones we never achieved formation of a single regioisomer. However, the diketones with pyridyl rings exclusively afforded 3-pyridyl analogues **10**–**12**. Apart from the spectroscopic evidence, the structures of these 3-pyridyl derivatives were confirmed by a single crystal X-ray diffraction study of the *O*-propanoate of 3-(4-pyridyl)pyrazole **10** (Fig. 2).[10]

We explored alternative reaction conditions, hoping to enhance the selectivity for 3-alkylated 1,5-diarylpyrazoles. A few pyrazoles had been prepared using an organic base,[11] but there was no systematic study reported regarding their regiochemistry. In the synthesis of **6**, changing to basic conditions using TEA, exclusively afforded 96% of the 1,5-diarylpyrazole with the *n*-C_3H_7 group at C-3. We performed another reaction by heating the mixture of the arylhydrazine and 1,3-diketone in absolute ethanol without TEA. This experiment produced even better regioselectivity (99%). To demonstrate the generality of this methodology, a variety of arylhydrazines and 1,3-diketones were used for the exclusive synthesis of several 1,5-diarylpyrazoles (Scheme 1 and Table 1). The regioselectivity of compounds **4** and **10**–**12** was retained even under these new conditions.

In our new method,[12] an ethanolic solution of the arylhydrazine hydrochloride was basified (pH ~ 11.0) using 3–5 equiv of TEA under an argon atmosphere and an ethanolic solution of the 1,3-diketone (0.95 equiv) was added. The reaction mixture was heated at 50–60 °C for 4–5 h to afford 1,5-diarylpyrazoles with excellent regioselectivity and in very high yields (70–80%). Alternatively, an ethanolic solution of the arylhydrazine was mixed with the diketone (0.95 equiv) under an argon atmosphere and heated at the same temperature for the same period of time to afford 1,5-diarylpyrazoles (e.g., compound **6**) with improved regioselectivity and yield. In the ^{1}H NMR spectra, the C-4 proton appeared at ~6.2 ppm for the desired 1,5-diarylpyrazoles whereas the undesired 1,3-diarylpyrazoles could be recognized by the appearance of the C-4 proton at ~6.5 ppm. The regioisomers were neither distinguishable on TLC nor separable by column chromatography and thus had to be detected by ^{1}H NMR and HPLC analysis.

The first step in the regioselective synthesis of the 1,5-diarylpyrazole is reported to be the formation of a hydrazone through the C-3 carbonyl group of the 1-aryl-1,3-diketone.[6] Presumably, the 1-aryl-1,3-diketones having electron-withdrawing groups exclusively exist in the enolic form **3a** (R = CF_3, Py) under all the conditions tested and afforded 1,5-diarylpyrazoles **4** and **10**–**12** whereas those having electron-donating groups existed as enolate **3a** (R = CH_3, *n*-C_3H_7) only in TEA and neutral media to afford the desired 1,5-diarylpyrazoles **5**–**9** (Scheme 1).

In summary, we have described the factors affecting the regioisomeric formation of 1,5-diarylpyrazoles during the two component synthesis, their identification through 1D NOESY, LC–NMR and X-ray analyses, and simple reaction conditions providing excellent regioselectivity and high yields in the synthesis of this pharmaceutically important scaffold.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2004.08.100. The procedure for the preparation of 1,3-diketones **3** and the *O*-propanoate derivative of compound **10**, the spectral data/charts including ^{1}H NMR, 1D NOESY and LC–NMR for the identification

of 1,5-diarylpyrazoles **4–12** and a table of elemental analysis are available.

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10. Tables of atomic coordinates, anisotropic thermal parameters and bond lengths etc. may be obtained free of charge from The Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, on quoting the deposition number CCDC 242156, the names of the authors and the journal citation (fax: +44 1223 336 033; e-mail: deposit@ccdc.cam.ac.uk; web site: http://www.ccdc.cam.ac.uk). Single crystals suitable for X-ray diffraction were grown from a mixture of MeOH and EtOAc. A half mole equivalent of EtOAc is present in the crystal lattice. The compound crystallized as colourless needles in monoclinic space group $Pna2_1$ with cell dimensions $a = 7.736$ (2), $b = 18.365$ (4), $c = 20.742$ (5), and $V = 2946.9$ (11) containing four molecules in the unit cell. The intensity data were collected on a Rigaku AFC-7S single crystal diffractometer using Mo K_α ($\lambda = 0.7107$ Å). The structure was solved by direct methods, and was refined using least squares procedures and the TEXSAN software. The present R factors are: R (Rw) = 0.117 (0.133, with 2808 reflections). Both, the *O*-propanoyl and the lattice ethyl acetate are disordered.
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12. Representative procedure: 1,5-di(4-methoxyphenyl)-3-*n*-propyl-1*H*-pyrazole **6a**. 4-Methoxyphenylhydrazine hydrochloride (2.0 g, 11.46 mmol) was suspended in absolute ethanol (30 mL) under Ar and to the agitated reaction mixture was slowly added TEA (2.89 g, 28.65 mmol) at room temperature, which achieved a pH of ~11.0. After stirring for a further 15 min, an ethanolic solution of 1-(4-methoxyphenyl)-1,3-hexanedione **3** (2.39 g, 10.88 mmol) was added, and the mixture was heated at 50–60 °C for 4–5 h. The solvent was removed and the residue was stirred with ice-cold water. After acidification with 6N HCl, the solution was extracted with EtOAc and the combined organic layers were washed with brine and water. The dried organic layer after solvent evaporation left behind a dark residue, which on column chromatographic purification over 230–400 mesh silica gel using ethyl acetate–petroleum ether (15:85) and repeated trituration with petroleum ether afforded the desired product (2.62 g, 78%) as an off-white low melting solid. Alternatively, the mixture of 4-methoxyphenylhydrazine (2.0 g, 14.49 mmol) and 1-(4-methoxyphenyl)-1,3-hexanedione (3.02 g, 13.76 mmol), dissolved in absolute ethanol (30 mL) which attained a pH of ~5, on heating under Ar at 50–60 °C for 4–5 h, followed by a similar work-up and purification, afforded the same product in almost the same yield. IR (neat) 2959, 1612, 1516, 1453, 1248 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ 7.19 (d, $J = 8.8$ Hz, 2H), 7.13 (d, $J = 8.8$ Hz, 2H), 6.83 (d, $J = 9.2$ Hz, 2H), 6.80 (d, $J = 9.2$ Hz, 2H), 6.23 (s, 1H), 3.80 (s, 3H), 3.79 (s, 3H), 2.67 (t, $J = 7.6$ Hz, 2H), 1.85–1.65 (m, 2H), 1.03 (t, $J = 7.6$ Hz, 3H). MS (CI Method) 323 [$(M+1)^+$, 100%], 294. HPLC 96.3% (in the presence of TEA) and 98.5% (without TEA) [Hichrom RPB (250 mm), mobile phase 0.01 M KH_2PO_4/CH_3CN–CH_3OH (50:50), flow rate 1.0 mL/min and UV detection at 210 nm]. Anal. Calcd ($C_{20}H_{22}N_2O_2$)C: 74.51; found, 74.68; H: calcd, 6.88; found, 6.72; N: calcd, 8.69; found, 8.53.