Highly Regioselective Synthesis of 1-Aryl-3,4,5-Substituted Pyrazoles

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Abstract: A highly regioselective synthesis of 1-aryl-3,4,5-substituted pyrazoles based on the condensation of 1,3-diketones with arylhydrazines is described. The reaction proceeds at room temperature in *N*,*N*-dimethylacetamide and furnishes pyrazoles in 59–98% yields.

Key words: 1,3-diketones, arylhydrazines, cyclocondensation, regioselectivity, amide solvents

Pyrazole heterocycles are found as core structural components of numerous agrochemicals and pharmaceutical agents such as antiinflammatories,[1] anticoagulants,[2] cannabinoid receptor ligands,[3] and antimicrobials.[4] The cyclocondensation of 1,3-dicarbonyl compounds with hydrazine derivatives represents one of the simplest and most general approaches to the synthesis of pyrazoles. However, with unsymmetrical 1,3-dicarbonyl substrates this method often suffers from the formation of regioisomeric pyrazoles with generally poor selectivity.[5] Moreover, the two pyrazole regioisomers can often be difficult to separate by chromatography and repeated crystallization may be necessary to reject the undesired regioisomer. This usually results in substantial decrease in isolated yields of the desired heterocycles. Therefore, various alternative strategies have appeared in the literature as potential solutions to the problem of regioselective synthesis of pyrazoles.[6] We wish to report herein an improved protocol for the highly regioselective synthesis of 1-aryl-3,4,5-substituted pyrazoles of pharmaceutical importance. The reaction proceeds under operationally simple, mild, safe, volumetrically efficient and readily scaleable conditions.

We have found that in the cyclocondensation of arylhydrazine hydrochlorides with 1,3-diketones, aprotic solvents with strong dipole moments and dielectric constants consistently gave much improved results relative to polar, protic solvents such as ethanol and acetic acid which are typically used for this type of reaction.[7] Our initial evaluation of solvents for the condensation of aryl-1,3-diketones with phenylhydrazine hydrochloride indicated that amide solvents such as *N*,*N*-dimethylacetamide (DMAc), *N*,*N*-dimethylformamide (DMF), *N*-methylpyrrolidinone (NMP) and urea solvents such as 1,3-dimethyl-3,4,5,6-tetrahydro-2-(1*H*)-pyrimidinone (DMPU) and *N*,*N*-tetramethylurea (TMU) provided highest and consistent regioselectivity (>99.8:0.2) of condensation. After optimization of reaction parameters with amide solvents, we found that addition of 50 mol% of 10 N aqueous hydrochloric acid gave increased yields by presumably favoring the second dehydration reaction of the N-arylhydrazone intermediate towards the pyrazole heterocycle. For operational convenience and consistency, pyrazole syntheses presented in Tables 1– 4 were run on gram-scale at room temperature for 24 hours and at 0.25 M in DMAc.

As illustrated in Table 1, the condensation of 4-substituted arylhydrazines with 4,4,4-trifluoro-1-arylbutane-1,3-diones **1a**–**d** proceeded to afford pyrazoles **2a**–**l** in 59–83% yields with selectivity ranging from 96.7:3.3 to >99.8:0.2.[8] By comparison, reactions run in ethanol at room temperature generally gave poor selectivity. The cyclocondensations of 1,3-diketones with 4-sulfonamidophenylhydrazine hydrochloride gave good yields of pyrazoles **2a**–**d** and were found to be extremely selective (>99.8:0.2) in many cases.

The 4,4-difluoromethyl-1-arylbutane-1,3-dione **1e**–**h** series gave pyrazoles **3a**–**i** in 60–98% yields and selectivity ranging from 86:14 to >99.8:0.2 (Table 2). Although we observed a slight decrease in regioselectivity in the CF_2H-substituted series relative to the CF_3-substituted pyrazoles **2a**–**l**, the reaction remained synthetically useful and gave results superior to those obtained using ethanol as solvent.

The 4-methyl-1-arylbutane-1,3-dione series **1i**–**j** was found to exhibit regioselectivity of cyclocondensation ranging from 93:7 to >99.8:0.2 and provided 3-methyl-substituted pyrazoles **4a**–**f** in 77–98% yields (Table 3). We presume that a subtle balance of electronic and steric effects may be operative and may influence the regioselectivity since the 3-methyl-substituted series gave levels of regioselectivity intermediates between the CF_3- and CF_2H-substituted pyrazole series.

Finally, we explored the use of 2-alkyl-substituted 1,3-diketones in condensation reactions (Table 4). Gratifyingly, we found that condensation of 4,4,4-trifluoro-1-phenyl-2-ethylbutane-1,3-dione (**1k**) with arylhydrazines gave 1-aryl-3,4,5-trisubstituted pyrazoles **5a**–**c** in 79–89% yields and regioselectivity >99.8:0.2 in all cases. In

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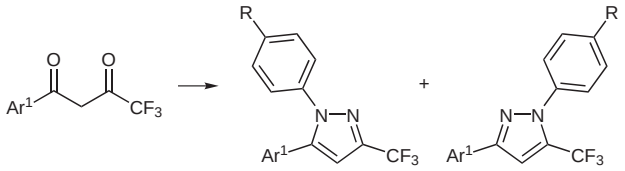
Table 1 Synthesis of 3-Trifluoromethyl-Substituted Pyrazoles[a]

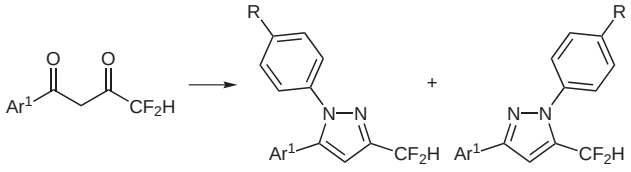


1a–d **2a–l** **2a'–l'**

Entry	**1**, Ar^1	R	Product	Yield (%)[b]	**2**/**2′**[c]
1	**a**: Ph	SO_2NH_2	**2a**	77	>99.8:0.2 (55:45)
2	**b**: 4-BrC_6H_4	SO_2NH_2	**2b**	78	>99.8:0.2
3	**c**: 4-$MeOC_6H_4$	SO_2NH_2	**2c**	71	>99.8:0.2
4	**d**: 4-$NO_2C_6H_4$	SO_2NH_2	**2d**	79	>99.5:0.5
5	**a**: Ph	Br	**2e**	83	99:1
6	**b**: 4-BrC_6H_4	Br	**2f**	74	97:3 (50:50)
7	**c**: 4-$MeOC_6H_4$	Br	**2g**	71	>99.8:0.2
8	**d**: 4-$NO_2C_6H_4$	Br	**2h**	60	98:2
9	**a**: Ph	H	**2i**	74	98:2
10	**b**: 4-BrC_6H_4	H	**2j**	74	98:2 (67:33)
11	**c**: 4-$MeOC_6H_4$	H	**2k**	59	99:1
12	**d**: 4-$NO_2C_6H_4$	H	**2l**	60	>99.8:0.2 (55:45)

[a] Conditions: arylhydrazine hydrochloride (1 equiv), DMAc, 10 N HCl (50 mol%), r.t., 24 h.
[b] Isolated yield after crystallization or column chromatography.
[c] Isomer ratios determined by HPLC analysis of the crude products, ratios in parentheses refer to reaction in EtOH at 50 °C.

Table 2 Synthesis of 3-Difluoromethyl-Substituted Pyrazoles[a]

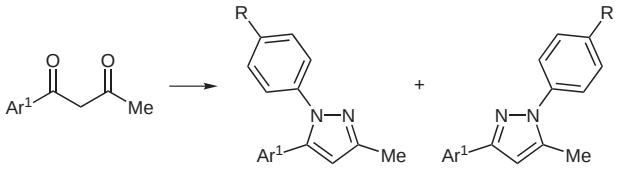


1e–h **3a–i** **3a'–i'**

Entry	**1**, Ar^1	R	Product	Yield (%)[b]	**3**/**3′**[c]
1	**e**: Ph	SO_2NH_2	**3a**	66	95.8:4.2 (91:9)
2	**f**: 4-BrC_6H_4	SO_2NH_2	**3b**	78	>99.8:0.2
3	**g**: 4-$MeOC_6H_4$	SO_2NH_2	**3c**	85	>99.8:0.2 (98:2)
4	**h**: 4-$NO_2C_6H_4$	SO_2NH_2	**3d**	60	99:1 (86:14)
5	**e**: Ph	Br	**3e**	68	88:12
6	**f**: 4-BrC_6H_4	Br	**3f**	96	92:8
7	**g**: 4-$MeOC_6H_4$	Br	**3g**	67	94:6 (86:14)
8	**f**: 4-BrC_6H_4	H	**3h**	98	86:14
9	**g**: 4-$NO_2C_6H_4$	H	**3i**	83	90:10 (91:9)

[a] Conditions: arylhydrazine hydrochloride (1 equiv), DMAc, 10 N HCl (50 mol%), r.t., 24 h.
[b] Isolated yield after crystallization or column chromatography.
[c] Isomer ratios determined by HPLC analysis of the crude products, ratios in parentheses refer to reaction in EtOH at 50 °C.

Table 3 Synthesis of 3-Methyl-Substituted Pyrazoles[a]



1i–j **4a–f** **4a'–f'**

Entry	**1**, Ar^1	R	Product	Yield (%)[b]	**4**/**4′**[c]
1	**i**: Ph	SO_2NH_2	**4a**	77	94:4 (86:14)
2	**j**: 4-$MeOC_6H_4$	SO_2NH_2	**4b**	91	98:2
3	**i**: Ph	Br	**4c**	98	94:6 (83:17)
4	**j**: 4-$MeOC_6H_4$	Br	**4d**	91	97:3
5	**i**: Ph	H	**4e**	83	93:7 (80:20)
6	**j**: 4-$MeOC_6H_4$	H	**4f**	87	>99.8:0.2

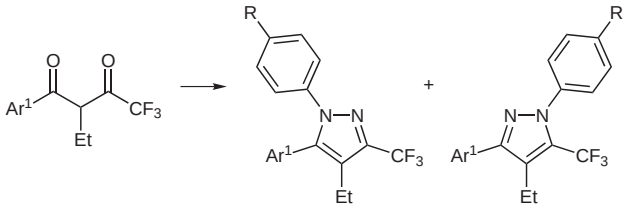
[a] Conditions: arylhydrazine hydrochloride (1 equiv), DMAc, 10 N HCl (50 mol%), r.t., 24 h.
[b] Isolated yield after crystallization or column chromatography.
[c] Isomer ratios determined by HPLC analysis of the crude products, ratios in parentheses refer to reaction in EtOH at 50 °C.

striking comparison and illustrated in Table 4, all reactions run in ethanol at 50 °C gave poor regioselectivity of condensation.

The structure of the major pyrazole isomer was established for each series by gradient-enhanced NOE NMR experiments.[9] In series **2**, **3** and **4** irradiation of the pyrazole ring proton (at C_4) readily gave the assignment for the *ortho* protons of the adjacent aromatic ring on C_5. Subsequent irradiation of these aromatic resonances provided NOE enhancement to the aromatics protons on the hydrazine system thus establishing the regiochemistry as shown. An analogous method was used for series **5**, irradiating the methylene protons at C_4 to establish the adjacent aromatic ring and subsequent irradiation, as stated above, which showed an NOE enhancement to the *ortho* protons of the aromatic from the hydrazine moiety.

In conclusion, we have found an unusual and preparatively useful solvent modification that increases significantly the regioselectivity observed in the condensation of 1,3-diketones with arylhydrazines to form pyrazoles.[10]

Table 4 Synthesis of 3,4,5-Trisubstituted Pyrazoles[a]



1k **5a–c** **5a'–c'**

Entry	R	Product	Yield (%)[b]	**5**/**5′**[c]
1	SO_2NH_2	**5a**	79	>99.8:0.2 (83:17)
2	H	**5b**	89	>99.8:0.2 (75:25)
3	Br	**5c**	83	>99.8:0.2 (67:33)

[a] Conditions: arylhydrazine hydrochloride (1 equiv), DMAc, 10 N HCl (50 mol%), r.t., 24 h.
[b] Isolated yield after crystallization or column chromatography.
[c] Isomer ratios determined by HPLC analysis of the crude products, ratios in parentheses refer to reaction in EtOH at 50 °C.

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(7) For example: DMAc: ε = 37.78, μ = 3.72 D; EtOH: ε = 24.55, μ = 1.69 D; AcOH: ε = 6.15, μ = 1.74 D; In *Lange's Handbook of Chemistry*, 13th ed.; Dean, J. A., Ed.; McGraw-Hill: New York, **1985**, Chap. 10, 103–116.

(8) Pyrazoles obtained by condensation of arylhydrazine hydrochloride salts with 1,3-diketones often gave isolable solvates of DMAc that could be broken to give pyrazoles by simple recrystallization from *i*-PrOH–H_2O.

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(10) **Representative Procedure:** To a solution of 4,4,4-trifluoro-1-(4-bromophenyl)butane-1,3-dione (**1b**; 1.47 g, 5 mmol) in *N*,*N*-dimethylacetamide (20 mL) at r.t. was added phenylhydrazine hydrochloride (723 mg, 5 mmol), followed by 10 N HCl (250 μL, 50 mol%). The mixture was let to stir for 24 h at r.t., cooled to 0 °C and H_2O (20 mL) was slowly added. After diluting with toluene (30 mL), the organic layer was washed with H_2O (3 × 20 mL) and concentrated to a brown oil that crystallized. The crystals were washed with cold heptane (3 × 5 mL) to give phenyl-3-(trifluoromethyl)-5-(4-bromophenyl)-1*H*-pyrazole(**2j**) as colorless crystals; yield: 1.36 g (74%); mp 103.7–105.4 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.44 (d, *J* = 7.4 Hz, 2 H), 7.36 (m, 3 H), 7.28 (m, 2 H), 7.07 (d, *J* = 7.4 Hz, 2 H), 6.74 (s, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 143.4, 143.3 (q, *J* = 39 Hz), 138.9, 131.9, 130.2, 129.2, 128.7, 128.0, 125.4, 123.4, 121.1 (q, *J* = 269 Hz), 105.6. LRMS: *m*/*z* calcd for $C_{16}H_{10}BrF_3N_2$: 367.16; found [M – 1]: 366.8. Pyrazoles could also be readily purified by column chromatography using 5–20% EtOAc–hexanes as eluent.