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New hydroxy-pyrazoline intermediates, subtle regio-selectivity and relative reaction rate variations observed during acid catalyzed and neutral pyrazole cyclization†

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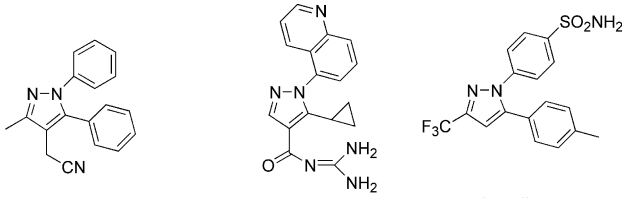
Arylhydrazines **4** and 1,3-dicarbonyl compounds **5** react to form pyrazoles by loss of water *via* hydrazone isomer pairs **6** and **7** which give rise to two possible regio-isomers. Occasionally, 3-hydroxy-3,4-dihydropyrazoles or hydroxy-pyrazolines **8** and **9** are observed as stable isolatable intermediates that can be fully characterized prior to loss of the second molecule of water that gives rise to pyrazoles **10** and **11**. Fully characterized examples of intermediates of type **8** and **9** are relatively rare. We studied the reaction series where R = CH_3, CHF_2 and CF_3 and Ar = Ph and 5-methanesulfonylpyridin-2-yl, (Scheme 2), and observed differences in properties between kinetic behavior and regio-isomerism depending on the degree of electron-withdrawing capability of the R and Ar substituents. The reaction conditions that caused cyclization to pyrazoles varied from direct condensation of the hydrazine and 1,3-dicarbonyl compounds, to reactions requiring catalytic quantities of sulfuric acid to sulfuric acid in excess. Unexpected regio-selectivity was observed in the case of R = CF_3 that depended upon the reaction conditions.

Introduction

Pyrazoles were discovered in the 19th Century and in contrast to the isomeric 1,3 diazole, imidazole they are quite rare in nature and natural products. Recently they have become interesting from a medicinal chemistry view point as HIV-1 reverse transcriptase inhibitors **1**,[1] sodium hydrogen ion exchanger NHE-1 inhibitors **2**[2] and cyclooxygenase-2, COX-2 inhibitors **3**[3] (Scheme 1). In connection with this type of project work we researched the formation of pyrazoles and studied formation and properties of the less well known intermediate hydroxy pyrazolines **8** and **9**.[4] Subtle differences that give quite different results were noted, which allow flexibility in control of the major product obtained.



Scheme 1 Pyrazoles found in reverse transcriptase HIV-1, NHE-1 and COX-2 inhibitors.

In general pyrazoles are conveniently prepared by the condensation of hydrazines and 1,3-dicarbonyl compounds. The overall reaction involves loss of two molecules of water as shown in Scheme 2. Four possible intermediate hydrazone isomers **6** and/or **7** are formed by the initial condensation by loss of one molecule of water. The regio-selectivity of the final products is set at this stage and quite often the intermediate hydrazones can be isolated and characterized.[5] The existence of isolatable cyclic hydroxy dihydropyrazoles isomers **8** and/or **9** is much less common and only documented in more recent literature reports.[6] Several new members of the class were fully characterized and single crystal X-ray data was obtained. When the Ar group is very strongly electron withdrawing such as 2,4-dinitrophenyl the reaction is halted at the hydrazone stage. When R is switched to CF_3 from CH_3 in Scheme 2 the cyclic hydroxy dihydropyrazole can sometimes be isolated. From the perspective of a process chemist, control of the condensation of mono substituted hydrazines and 1,3-dicarbonyl compounds to produce one of the two pyrazole products is desirable to avoid difficult purifications (Scheme 2).

Results and discussion

We conducted a series of experiments in refluxing 2-propanol reacting **4** and **5** with a small, approximately 4% molar excess of the hydrazine **4** using the two hydrazines and three 1,3-dicarbonyl compounds (Table 1). Single crystal X-ray structures were obtained for new hydroxy-pyrazolines **8b, 8c** and **9a** and the pyrazoles **10a, 10b**, and **10d**. The regio-isomerism of the diphenyl series of hydroxy dihydro pyrazoles and pyrazoles **8f, 9f, 10f** and **11f** was determined by preparation of an authentic sample of 1,5-diphenyl-3-methylpyrazole.[7]

The hydroxy-pyrazolines **8b, 8c** and **9a** were obtained using the neutral reaction conditions as described in Table 1 and then purified by chromatography and/or recrystallization. The pyrazoles **10a–f** were obtained using acidic conditions (Table 2) and similarly purified. The reactions were studied by HPLC monitoring[8] using authenticated reference samples as markers for peak identification. Some minor peaks were characterized by LC/MS techniques. All major products were individually synthesized, purified and single crystal X-ray data and/or satisfactory spectroscopic and/or elemental analysis data obtained. Some minor products were isolated by chromatographic techniques from mother liquors of the main reaction product.

The cyclization reaction between hydrazines **4a** and **4b** with 1,3-dicarbonyl compounds **5a–c** to form pyrazoles were observed to take several days under neutral conditions at 85 °C in 2-propanol and the main product was a hydroxy-pyrazoline when two electron-withdrawing groups were present. Thus when Ar = 5-methanesulfonylpyridin-2-yl and R = CF_3 or CHF_2 the main

† Electronic supplementary information (ESI) available: ^{13}C NMR spectrum of **10b** and IR spectrum of compounds **8b** and **9a**. See http://www.rsc.org/suppdata/ob/b5/b500413f/

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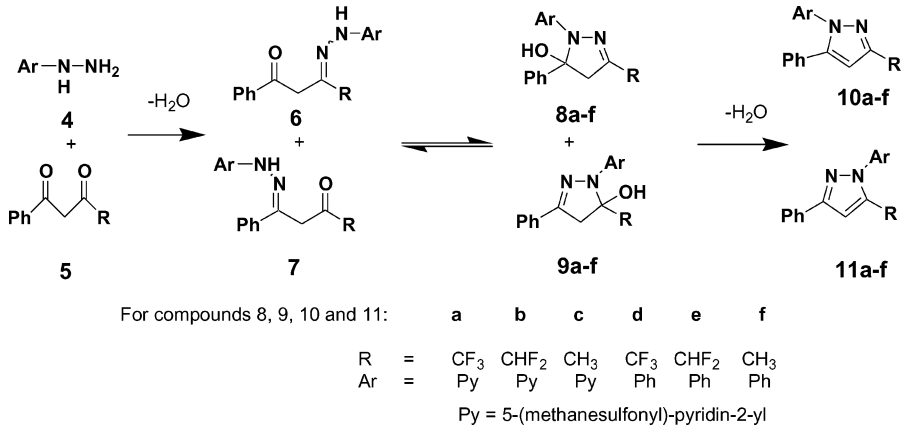
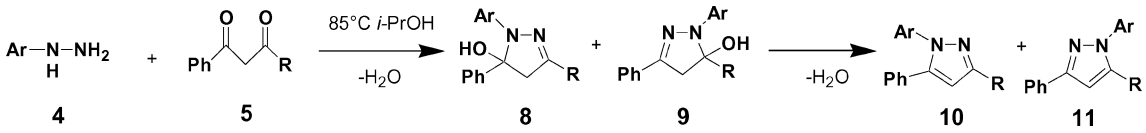


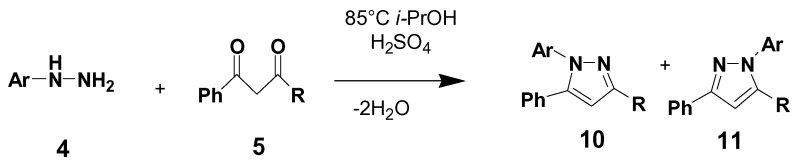
Scheme 2 Formation of pyrazole and intermediates from condensation of arylhydrazines with 1,3-diketones.

Table 1 Pyrazoles and hydroxy-pyrazolines formed under neutral conditions



Entry	4(a–b)	Ar	5(a–c)	R	Main product (%)	Isolated yield	Reaction conditions	Minor products(s) (%)
1	**4a**	MeO_2S-Py	**5a**	CF_3	**9a** (100%)	48%	5 d 85 °C *i*-PrOH	none significant
2	**4a**	MeO_2S-Py	**5b**	CHF_2	**8b** (87%)	99%	1 d 85 °C *i*-PrOH	**10b** (12%)
3	**4a**	MeO_2S-Py	**5b**	CH_3	**8c** (70%)	66%	2 h 85 °C *i*-PrOH	**10c** (10/%)
4	**4a**	MeO_2S-Py	**5c**	CH_3	**10c** (95%)	86%	8 d 85 °C *i*-PrOH	**8c** (5%)
5	**4b**	Ph	**5a**	CF_3	**10d** (82%)	97%	6 d 85 °C *i*-PrOH	**8d** (8%), **11d** (10%)
6	**4b**	Ph	**5b**	CHF_2	**10e** (72%)	100%	5 d 85 °C *i*-PrOH	**11e** (25%)
7	**4b**	Ph	**5c**	CH_3	**10f** (89%)	100%	5 d 85 °C *i*-PrOH	**11f** (11%)

Table 2 Pyrazoles formed under acidic conditions (hydroxy-pyrazolines transient)

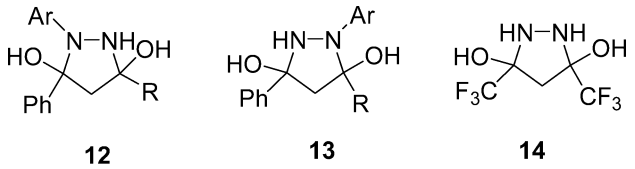


Entry	4(a–f)	Ar	5(a–f)	R	Main product (%)	Isolated yield	Reaction conditions	Minor products(s) (%)
1	**4a**	MeO_2S-Py	**5a**	CF_3	**10a** (100%)	65%	H_2SO_4 1.5 mole 1 h 85 °C *i*-PrOH	none significant
2	**4a**	MeO_2S-Py	**5b**	CHF_2	**10b** (99%)	93%	cat. H_2SO_4 0.1 mole 1 h 85 °C *i*-PrOH	**11b** (<1%)
3	**4a**	MeO_2S-Py	**5c**	CH_3	**10c** (96%)	83%	cat. H_2SO_4 0.1 mole 1 h 85 °C *i*-PrOH	**11c** (4/%)
4	**4b**	Ph	**5a**	CF_3	**10d** (87%)	98%	H_2SO_4 1.5 mole 1 h 85 °C *i*-PrOH	**11d** (13%)
5	**4b**	Ph	**5a**	CF_2	**10e** (97%)	98%	cat. H_2SO_4 0.1 mole 1 h 85 °C *i*-PrOH	**11e** (3%)
6	**4b**	Ph	**5c**	CH_3	**10f** (93%)	98%	cat. H_2SO_4 0.1 mole 1 h 85 °C *i*-PrOH	**11f** (7%)

products under these conditions were **9a** and **8b**, respectively. The difference between the regio-selectivity for CF_3 and CHF_2 is quite remarkable when Ar = 5-methanesulfonylpyridin-2-yl, as in each case the main product predominates to the extent of 100% and 87% for **9a** and **8b** respectively. In cases when only one, or no strong electron-withdrawing groups are present then the reaction proceeds to the pyrazole product, which has always been observed as the regio-isomer from the series **10c–f**. However, with one strong electron-withdrawing group the reaction conversion to the pyrazole is only 90% complete and the hydroxy-pyrazolines **8c** and **8d** are observed. For cases where Ar = Ph, the selectivity favoring the pyrazole regio-isomers **10d–f** is reduced measurably in most cases when compared to the situation when Ar = 5-methanesulfonylpyridin-2-yl, but **10d–f** are still the predominant regio-isomers.

The cyclization reaction is much more rapid when carried out in the presence of sulfuric acid. At 85 °C in 2-propanol complete conversion occurs to pyrazoles in 1–2 hours, with the regio-isomer **10a–f** predominating. Even here though there is a significant difference between 1,3-dicarbonyl compound **5a** and **5b** containing the CF_3 and CHF_2 groups, respectively. The following subtle differences were noted depending on the presence of CF_3 or CHF_2 substituent. When a CHF_2 group is present the cyclization is promoted by a catalytic quantity of 10% mole sulfuric acid, but in order for the reaction to proceed in a similar time frame in the CF_3 case 150% mole of sulfuric acid is required. When acid is used to promote cyclization, 1-aryl-5-phenylpyrazoles **10a–f** are always formed even in the case where **4a** and **5a** are condensed. In this latter case under neutral conditions **9a** is formed, which on treatment with 150% mole excess of sulfuric acid in 2-propanol slowly converts to the pyrazole **11a** over a period of a day.

Other workers[9] recently have studied the products formed as a result of cyclization of hydrazines and 1,3-dicarbonyl compounds under several conditions; mildly alkaline conditions in the presence of sodium acetate in ethanol, acetic acid and large molar excesses of sulfuric acid and ethanol and large molar excesses of hydrochloric acid. They believe that experimental observations concerning the regio-isomerism observed are a result of the equilibrium between two isomeric 3,5-dihydroxypyrazolidines that would correspond to **12** and **13** in our study series (Scheme 3).

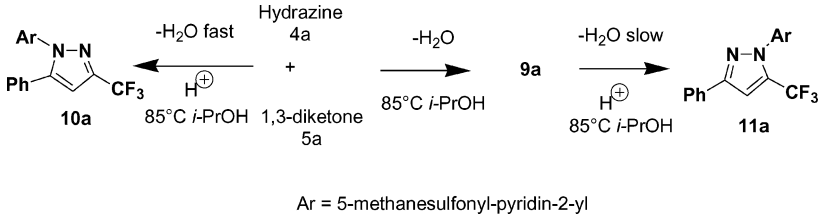


Scheme 3 Potential dihydroxy-pyrazolidine intermediates (not observed to date) and known example **14**.

We observed that there were significant differences between the condensation of hydrazines substituted with electron-withdrawing Ar groups such as 5-methanesulfonylpyridin-2-yl and phenyl and when R was varied with increasing electron-withdrawing power from methyl, difluoromethyl to trifluoromethyl in the 1,3-dicarbonyl compound **5**. The outcome of the reaction also depended on the reaction conditions. The cyclization reaction though apparently simple probably proceeds by a number of different mechanisms depending on the reaction media and conditions. A single mechanism or single intermediate types cannot explain reaction rate differences noted between neutral and acidic conditions, such as **12** and **13**, which have been proposed as key intermediates. During the course of our studies we found no evidence of intermediates analogous to **12** and **13**, but did monitor the progress of the reaction by HPLC. Dihydroxy-pyrazolidines though relatively rare are isolable when two CF_3 substituents are present as in **14**.[10] Under the conditions we examined it appeared that the process proceeded by a stepwise path since we observed a high degree of regio-selectivity. We saw an example of complete reversal of the regio-selectivity in one case. Hydrazine **4a** was condensed with 1,3-diketone **5a** in 2-propanol in the presence of 150% mole of sulfuric acid at 85 °C to yield exclusively **10a**, but when reacted under the same conditions without acid we observed formation of the 3-hydroxy-pyrazoline **9a** also exclusively (Scheme 4).

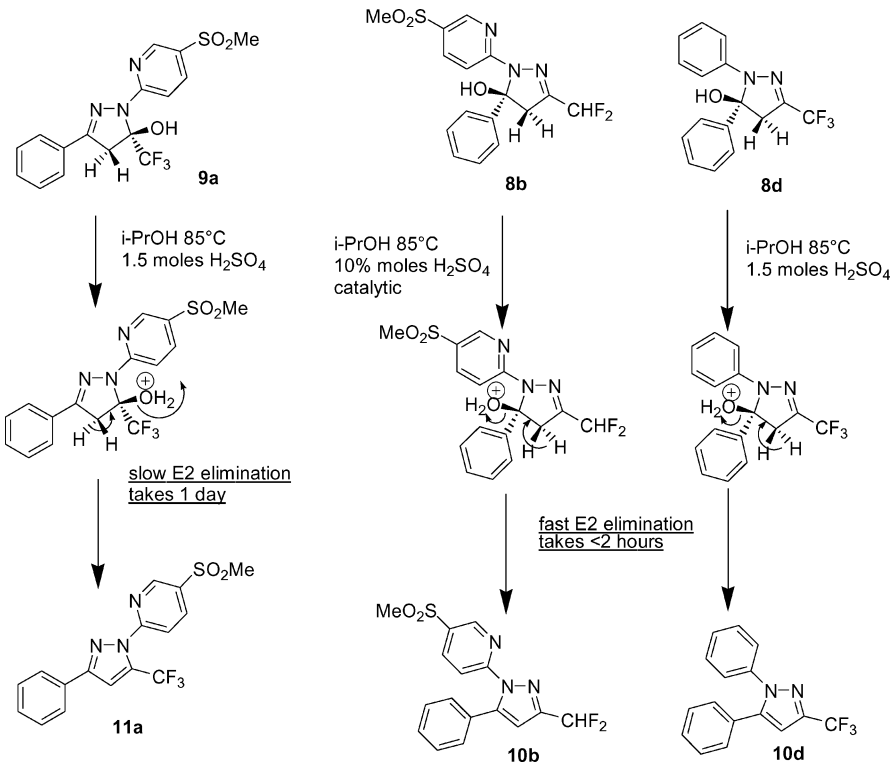
Compound **9a** does react in the presence of 150% mole sulfuric acid to yield pyrazole **11a**. However, in this case the dehydration reaction is much slower and requires 1 day using the same conditions of solvent and temperature, compared to the regio-isomers **8a–f**, which dehydrate within 1–2 hours sometimes with catalytic quantities of 10% sulfuric acid (Scheme 5, Table 2). The general observations can be explained by characterized 3-hydroxy-pyrazoline intermediates, which are also observed *in situ* by HPLC in this series and suggests a sequential loss of two molecules of water (Scheme 2). We have isolated and characterized with single crystal X-ray structure determination, examples of 2-aryl-5-fluoroalkyl-3-hydroxy-3-phenyldihydropyrazoles **8b** and **8c** (Fig. 1a and 1b) and an example of a 2-aryl-3-fluoroalkyl-3-hydroxy-5-phenyldihydropyrazole **9a** (Fig. 2). Hydroxy-pyrazoline **8d** was isolated and characterized by spectroscopic methods and recrystallization from hexane provided pyrazole **10d**. The 1,5-diaryl pyrazole regio-isomerism was indicated by the facile dehydration and confirmed for **8d** by single crystal X-ray structure determination of the pyrazole product **10d**. Thus far we have not been able to detect physical evidence of dihydroxy-pyrazolidines corresponding to **12** and **13** (Scheme 3), and if present must rapidly lose one molecule of water to provide the stable intermediates hydroxy-pyrazolines of the class **8** and **9**.

Elguero and coworkers[8] in contrast report three examples of 2,5-diaryl-3-trifluoromethyl-3-hydroxy-pyrazolines based on NMR structural evidence, these compounds were made by condensing the 1-arylhydrazine with the 1,3-dicarbonyl compounds in slightly alkaline conditions in the presence of sodium acetate. This corresponds to the 1,3-diaryl substitution pattern we observed in **9a**, but we largely observed a strong preference for the diaryl substitution pattern observed in **8b–f** under neutral or acidic conditions of condensation. In summary, condensations of arylhydrazines **4a–b** with 1,3-dicarbonyl compounds **5a–c** under acid catalyzed or acid media favor overwhelming predominance of pyrazole regio-isomers **10a–f** derived from hydroxy-pyrazolines **8a–f**. Reaction time is extremely rapid taking <2 hours at 85 °C. In contrast conversion to the pyrazoles under neutral conditions is very slow taking several days to go to completion especially when electron-withdrawing substituents are present. Hydroxy-pyrazolines could be crystallized and isolated



Ar = 5-methanesulfonyl-pyridin-2-yl

Scheme 4 Relative reaction rate and pathway using acidic and neutral conditions for pyrazole cyclization leading to different regio-isomeric products.



Scheme 5 Relative rates of dehydration of specific 3-hydroxy-pyrazolines.

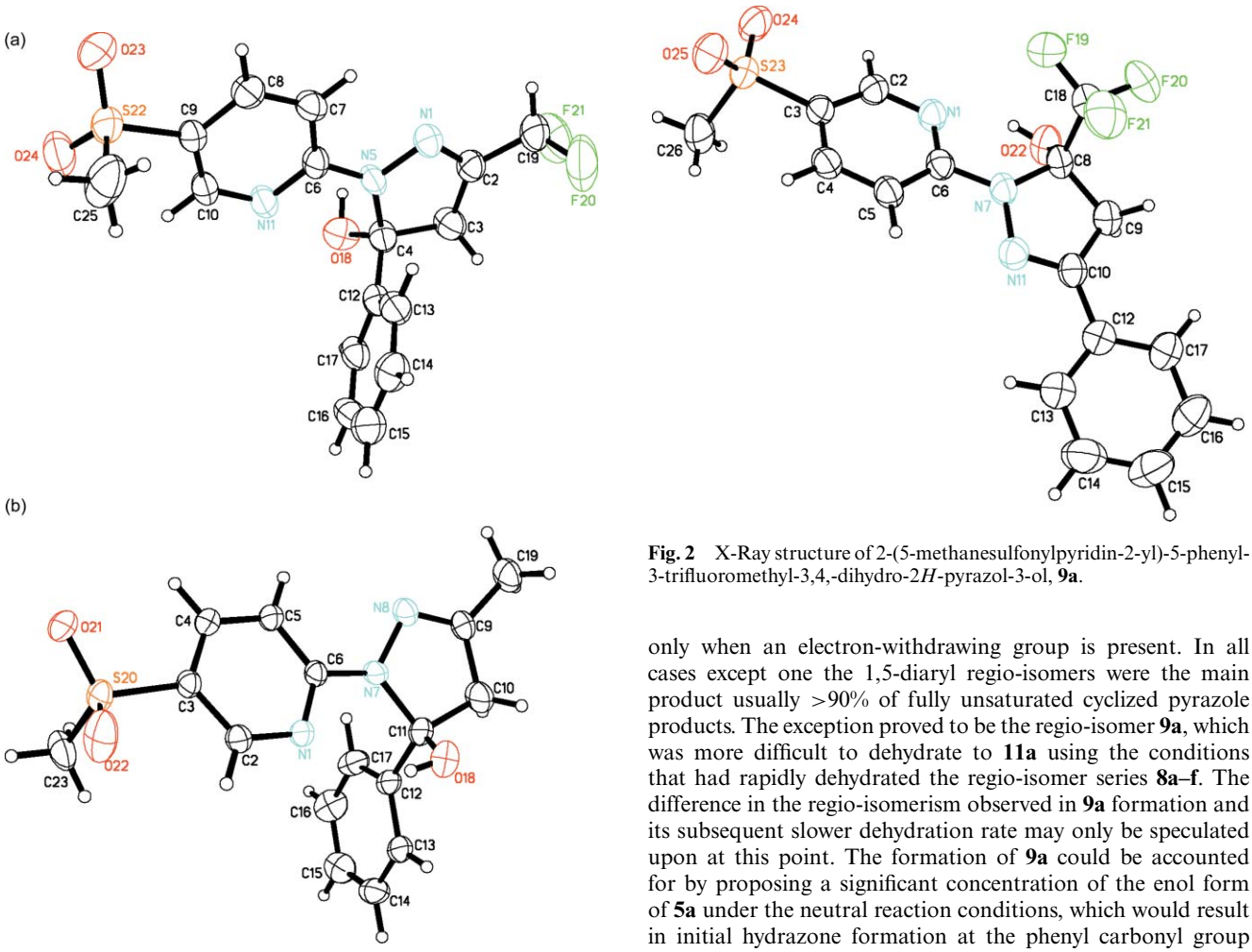


Fig. 1 **a** X-Ray structure of 5-difluoromethyl-2-(5-methanesulfonyl-pyridin-2-yl)-3-phenyl-3,4-dihydro-2*H*-pyrazol-3-ol, **8b**. **b** X-Ray structure of 2-[5-(methylsulfonyl)pyridin-2-yl]-5-methyl-3-phenyl-3,4-dihydro-2*H*-pyrazol-3-ol, **8c**.

Fig. 2 X-Ray structure of 2-(5-methanesulfonylpyridin-2-yl)-5-phenyl-3-trifluoromethyl-3,4,-dihydro-2*H*-pyrazol-3-ol, **9a**.

only when an electron-withdrawing group is present. In all cases except one the 1,5-diaryl regio-isomers were the main product usually >90% of fully unsaturated cyclized pyrazole products. The exception proved to be the regio-isomer **9a**, which was more difficult to dehydrate to **11a** using the conditions that had rapidly dehydrated the regio-isomer series **8a–f**. The difference in the regio-isomerism observed in **9a** formation and its subsequent slower dehydration rate may only be speculated upon at this point. The formation of **9a** could be accounted for by proposing a significant concentration of the enol form of **5a** under the neutral reaction conditions, which would result in initial hydrazone formation at the phenyl carbonyl group and subsequent dehydration to **9a**, (Scheme 5). The slower dehydration of **9a** relative to **8a–f** may be connected with the hydroxy group being adjacent to the CF_3 group, which stabilizes the hydroxy-pyrazoline structure.

Experimental

Proton and ^{13}C spectra were collected at 298 K using a Varian 5 mm dual gradient probe on a Varian Unity Inova NMR spectrometer operating at 400 MHz. ^{13}C NMR spectra were recorded at 100 MHz. Chemical shifts (δ) are quoted in ppm, and coupling constants (J) are given in Hz. IR spectra were recorded using ThermoNicolet Magna 560 series. Combustion analyses were performed by Schwarzkopf Microanalytical Laboratory (Woodside, NY) or Quantitative Technologies, Inc. (Whitehouse, NJ). Mass spectral data was collected on a Micromass QTOF mass spectrometer (electrospray ionization). DSC data were collected using a Thermal Analysis Q1000 or a Mettler Toledo 821.

The structures of hydroxy pyrazolines and pyrazoles, **8b, 8c, 9a, 10a, 10b**, and **10d** were confirmed by single crystal X-ray data.[11] Compounds that are either new or synthesized in a new way are noted below.

5-Difluoromethyl-2-(5-methanesulfonyl-pyridin-2-yl)-3-phenyl-3,4-dihydro-2*H*-pyrazol-3-ol (8b)

Ketone **5b**, 5.9 g (30 mmol, 1.0 equiv.), hydrazine **4a**, 5.8 g (31.2 mmol, 1.04 equiv.), and 2-propanol (100 ml), were stirred for 3.0 hours at 83 °C. The reaction mixture was cooled to room temperature and water (230 ml) added to form a slurry. Stirred at ambient temperature for 24 h. Isolated solid, washed with 2-propanol (50 ml) and water (50 ml), re-dissolved in 2-propanol (100 ml) and stirred at reflux for 30 min., filtered while hot, followed by 2-propanol (500 ml). The resultant solution was cooled to <45 °C to initiate crystallization. The product was isolated and washed with 2-propanol (50 ml), and dried, yielding **8b** (4.6 g, 43%). HPLC purity was 99.9%. DSC: 142.1–143.4 °C, 110.1 J g^{-1} (3.2 mg). Calc. for $C_{16}H_{15}F_2N_3O_3S$: C, 52.31; H, 4.12; F, 10.34; N, 11.44; O, 13.07; S, 8.73. Found: C, 52.38; H, 3.94; F, 10.29; N, 11.24; S, 8.69%; IR (KBr) ν cm^{-1} 3458, 3086, 3058, 1937, 1878, 1792, 1592, 1160, 1127, 1105, 1076, 1022; ^1H NMR (400 MHz, $CDCl_3$) δ 8.40 (d, 1 H, J = 2.3 Hz), 8.02 (dd, 1 H, J = 2.3, 6.8 Hz), 7.37 (m, 5 H), 6.49 (t, 1 H, J = 54.1 Hz), 5.78 (bs, 1 H), 3.42 (dd, 2 H, J = 1.54, 2.48, 117.17 Hz), 3.00 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 157.5, 147.7, 143.4, 137.4, 129.1, 128.7, 128.3, 124.5, 111.1, 95.9, 47.7, 45.3; HRMS m/z (M^+) $C_{16}H_{15}F_2N_3O_3SH^+$ requires 368.0880, obsd 368.0872.

2-[5-(Methylsulfonyl)pyridin-2-yl]-5-methyl-3-phenyl-3,4-dihydro-2*H*-pyrazol-3-ol (8c)

Ketone **5c**, 15.0 g (92.5 mmol, 0.96 equiv.), hydrazine **4a**, 18 g (96.2 mmol, 1.0 equiv.), and 2-propanol (555 ml) were stirred for 30 min at room temperature, then 2.0 h. at 75 °C. The reaction mixture was then cooled down to <45 °C and water (1000 ml) added, to form a slurry, stirred at ambient temperature for 24 h, isolated solid, washed with water (50 ml) and 2-propanol (50 ml) and dried at room temperature to constant weight. Obtained **8c** (20.2 g, 66%). HPLC purity was 90.4%. DSC: 133.3–135.9 °C 102.9, J g^{-1} (3.9 mg); ^1H NMR (400 MHz, $CDCl_3$) δ 8.34 (d, 1 H, J = 2.5 Hz), 7.92 (dd, 1 H, J = 2.5, 6.6 Hz), 7.42–7.26 (m, 7 H), 5.96 (s, 1 H, OH), 3.22 (dd, 2 H, J = 18.7, 125.7), 2.99 (s, 3 H) 2.12 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 154.06, 147.95, 144.50, 136.69, 128.9, 128.1, 126.3, 124.6, 109.6, 94.9, 55.0, 45.4, 16.4; HRMS m/z (M^+) $C_{16}H_{17}N_3O_3SH^+$ requires 332.1069, obsd 332.1071.

2-(5-Methanesulfonylpyridin-2-yl)-5-phenyl-3-trifluoromethyl-3,4-dihydro-2*H*-pyrazol-3-ol (9a)

Ketone **5a** 2.0 g (9.3 mmol, 0.96 equiv.), hydrazine **4a**,1.8 g (9.6 mmol, 1.0 equiv.), and 2-propanol (55 ml) were stirred for 30 min at room temperature then heated for 6 d at 83 °C. Cooled and 2-propanol (50 ml) added, stirred at ambient temperature for 24 h. Isolated solid and washed with 2-propanol (30 ml), dried at room temperature to constant weight. Obtained **9a** (1.7 g, 48%). HPLC purity was 100%. DSC: 175.8–175.0 °C, 101.9 J g^{-1} (4.6 mg); IR (KBr) cm^{-1} ν 3187, 3071, 3021, 3006, 2980, 2927, 2565, 2369, 2286, 1966, 1884, 1798, 1594, 1488, 1413, 1315, 1293, 1183, 1158, 1106, 1028; ^1H NMR (400 MHz, $CDCl_3$) δ 8.7 (d, 1 H, J = 2.5 Hz), 8.02 (dd, 1 H, J = 2.5, 9.1 Hz), 7.74 (m, 2 H), 7.69 (s, 1 H), 7.61 (d, 1 H, 9.1 Hz), 7.46 (m, 3 H), 3.72 (dd, 2H, J = 18.5, 41.5 Hz), 3.1 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 158.8, 153.0, 147.0, 137.5, 131.1, 130.4, 129.2, 128.6, 126.7, 111.2, 45.4, 44.2; HRMS m/z (M^+) $C_{16}H_{14}F_3N_3O_3SH^+$ requires 386.0786, obsd 386.0791.

2-(3-Difluoromethyl-5-phenyl-pyrazol-1-yl)-5-methanesulfonyl-pyridine (10b)[12]

Ketone **5b**, 26.4 g (133.2 mmol, 0.96 equiv.), hydrazine **4a** 25.9 g (138.5 mmol, 1.0 equiv.), and 2-propanol (800 ml) were stirred for 30 minutes at 30 °C, conc. H_2SO_4 747 µl (13.32 mmol, 0.1 equiv.) was added and the mixture heated at 83 °C for 60 min. The reaction mixture was cooled <45 °C and water (1000 ml) added to form a slurry, stirred at ambient temperature for 2 h. Crude **10b** was isolated, washed with the mother liquor then water until filtrate pH was neutral, and dried at room temperature to constant weight. Obtained (43.2 g, 92.9%). HPLC purity was 99.1% contained 0.85%, **11b**. Crude **10b** was dissolved in 2-propanol (912 ml) and stirred at reflux for 30 min, filtered hot solution, washed with hot 2-propanol (200 ml). Combined filtrate and wash were concentrated to 740 ml, cooled <45 °C and initiated crystallization. Isolated and washed residue with the mother liquor and 2-propanol (200 ml), dried at room temperature to constant weight. Obtained **10b** (38.7 g, 83.2%). HPLC purity was 99.4% along with 0.59% **11b**. Overall yield 77.3%. Differential Scanning Spectroscopy: 125.2–127.0 °C 95.23 J g^{-1} (4.8 mg); Calc. for $C_{16}H_{13}F_2N_3O_2S$: C, 55.01; H, 3.75; F, 10.88; N, 12.03; O, 9.16; S, 9.18. Found: C, 55.22; H, 3.65; F, 10.79; N, 11.99; S, 9.13%; ^1H NMR ($CDCl_3$) δ 8.77 (d, 1 H, J = 1.5 Hz), 8.27 (dd, 1 H, J = 2.5, 6.2 Hz), 7.29 (m, 5 H), 6.78 (t, 1 H, J = 54.6 Hz), 6.74 (s, 1 H), 3.09 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 147.9, 147.7, 147.3, 144.9, 139.7, 129.9, 129.3, 128.8, 128.4, 125.6, 119.9, 111.6, 109.3, 105.0; HRMS m/z (M^+) $C_{16}H_{13}F_2N_3O_2SH^+$ requires 350.0775, obsd 350.0780.

5-Methanesulfonyl-2-(3-methyl-5-phenyl-pyrazol-1-yl)-pyridine (10c)

Ketone **5c** 2.0 g (12.4 mmol, 0.96 equiv.), hydrazine **4a**, 2.4 g (12.8 mmol, 1.0 equiv.), and 2-propanol (74 ml) were stirred for 30 min. at 30 °C, then for 8 days at 83 °C. The reaction mixture was cooled to room temperature and a slurry formed. Isolated and washed with 2-propanol (50 ml), dried at room temperature until constant weight. Obtained, **10c** (3.3 g, 86%). HPLC purity, 95.0%. Regio-isomer ratio 99/1. Differential Scanning Spectroscopy: 145.62–147.23 °C 65.72 J g^{-1} (1.7 mg); IR (KBr) cm^{-1} ν 3065, 3011, 1960, 1892, 1767, 1693, 1582, 1155, 1103,; ^1H NMR (400 MHz, $CDCl_3$) δ 8.74 (d, 1 H, J = 2.5 Hz), 8.18 (dd, 1 H, J = 2.5, 6.2 Hz), 7.76 (d, 1 H, J = 8.7 Hz), 7.32 (m, 5 H), 6.34 (S, 1 H), 3.07 (s, 3 H), 2.34 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 155.81, 152.32, 147.98, 145.71, 137.58, 134.02, 131.44, 128.98, 128.76, 128.52, 126.24, 116.97, 111.71, 45.18, 13.97; HRMS m/z (M^+) $C_{16}H_{15}N_3O_2SH^+$ required 314.0978, obsd 314.0963.

10c was also prepared by heating **8c** in 2-propanol for 8 days. The transformation was monitored by HPLC.

1,5-Diphenyl-3-(trifluoromethyl)-1*H*-pyrazole (10d)

Ketone **5a**, 2.0 g (9.3 mmol, 0.96 equiv.), hydrazine **4b**, 1.8 g (9.62 mmol, 1.0 equiv.), and 2-propanol (50 ml) were stirred for 30 minutes at 30 °C, conc. H_2SO_4 779 µL (13.9 mmol, 1.5 equiv.) was added and the mixture heated at reflux 83 °C for 90 min. The reaction mixture was cooled <45 °C and water (93 ml) added to form a slurry, stirred at ambient temperature for 2 h,

isolated and washed with mother liquor, then with water until filtrate pH is neutral, dried at room temperature to constant weight. Obtained, **10d** (2.2 g, 65.3%). HPLC purity was 100%. IR (KBr) cm^{-1} ν 3132, 3066, 1595, 1495, 1472, 1446, 1375, 1236, 1154, 1136; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.76 (s, 5 H), 7.25 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 129.6, 129.4, 129.4, 129.2, 129.1, 129.0, 128.9, 128.7, 126.1, 126.0, 125.7, 105.8; HRMS *m/z* (M^+) $C_{16}H_{11}F_3N_2H^+$required 289.0952, obsd 289.0950.

3-(Difluoromethyl)-1,5-diphenyl-1*H*-pyrazole (10e)

Ketone **5b**, 1.5 g (7.6 mmol, 0.96 equiv.), hydrazine **4b**, 800 μL (7.9 mmol, 1.04 equiv.), and 2-propanol (45 ml) were stirred for 30 min at 30 °C, added conc. H_2SO_4 43 μl (0.8 mmol, 0.1 equiv.) heated at 83 °C for 60 min. The reaction mixture was cooled <45 °C and water (50 ml) added, extracted with ethyl acetate (3 × 20 ml). The combined organic phase was dried over Na_2SO_4. Concentrated to obtain **10e** (2.01 g, 98%). HPLC purity was 92%; 97/3 regio-isomer ratio. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.77 (dd, 1 H, J = 20.53, 54.95 Hz), 7.28–7.38 (m, 10 H); ^{13}C NMR ($CDCl_3$) δ 139.7, 129.9, 129.3, 129.3, 129.0, 129.0, 128.9, 128.8, 128.4, 125.6, 113.9 (CHF_2), 111.6 (CHF_2), 109.3 (CHF_2), 105.0; HRMS *m/z* (M^+) $C_{16}H_{12}F_2N_2H^+$ 271.1047, obsd 271.1048.

5-(Methylsulfonyl)-2-[3-phenyl-5-(trifluoromethyl)-pyrazol-1-yl]pyridine (11a)

Pyrazoline **9a** 130 mg (0.34 mmol, 1.0 equiv.), 2-propanol (20 ml) and conc. H_2SO_4 72 μl (0.8 mmol, 1.5 equiv.) were heated at 83 °C for 24 h. A second portion of conc. H_2SO_4 was added (57 μL, 1.0 mmol, 3.0 equiv.) and heating continued for 48 h. The reaction mixture was cooled and stirred at ambient temperature for 1 h. Isolated precipitated solid, washed with water until neutral pH filtrate was obtained, dried at room temperature to constant weight. Obtained pyrazole **11a** (104 mg, 83%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.03 (d, 1 H, J = 2.5 Hz), 8.27 (dd, 1 H, J = 8.7, 60.6 Hz), 7.73 (m, 1 H, 3 H), 7.42–7.52 (m, 5 H), 7.26 (s, 1 H), 3.2 (s, 3 H); ^{13}C (100 MHz, d_6-DMSO) δ 153.7, 153.1, 147.8, 139.6, 136.6, 133.5 (q, J = 40.8 Hz), 130.9, 130.2, 129.6, 127.3, 126.6, 116.3, 111.8, 44.3; HRMS *m/z* (M^+) $C_{16}H_{12}F_3N_3O_2SH^+$ found: 368.0680, calc: 368.0681

2-(5-Difluoromethyl-3-phenylpyrazol-1-yl)-5-methanesulfonyl-pyridine (11b)

The source of **11b** was from a mixture of previous mother liquors obtained from the synthesis of **10b**. **11b** was purified by column chromatography using silica gel as stationary phase (Biotage System, 75 L) and dichloromethane as the mobile phase. This separation yielded **11b** (3.5 g). HPLC purity of 99.0%. ^{1}H NMR (400 MHz, $CDCl_3$) 8.97 (d, 1 H, J = 1.7 Hz), 8.15 (dd, 1 H, J = 2.1, 6.6 Hz), 7.9 (d, J = 6.64 Hz, 1 H) 7.76 (t, 1 H, J = 54.8 Hz), 7.46 (m, 3 H), 7.19 (s, 1 H), 3.15 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 147.88, 138.48, 134.47, 129.62, 129.15, 126.37, 114.57, 109.13, 108.32, 45.31; Anal. Cald. for $C_{16}H_{13}F_2N_3O_2S$: C, 55.01; H, 3.75; F, 10.88; N, 12.03; O, 9.16; S, 9.18. Found: C, 54.97; H, 3.58; F, 10.83; N, 11.90; S, 9.34%. HRMS *m/z* (M^+) $C_{16}H_{13}F_2N_3O_2SH^+$ requires 350.0775, obsd. 350.0779.

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References

1 M. J. Genin, C. Biles, B. J. Keiser, S. M. Poppe, S. M. Swaney, W. G. Tarpley, Y. Yagi and D. L. Romero, *J. Med. Chem.*, 2000, **43**, 1034.
2 A. Guzman-Perez, R. T. Webster, M. C. Allen, J. A. Brown, A. R. Buchholz, E. R. Cook, W. W. Day, E. S. Hamanaka, S. P. Kennedy, D. R. Knight, P. J. Kowalczyk, R. B. Marala, C. J. Mularski, W. A. Novomisle, R. B. Ruggeri, W. R. Tracy and R. J. Hill, *Bioorg. Med. Chem. Lett.*, 2001, **11**(6), 803.
3 T. D. Penning, J. J. Talley, S. R. Bertenshaw, J. S. Carter and P. W. Collins, *J. Med. Chem.*, 1997, **40**, 1347.
4 J. Li, K. M. L. DeMello, H. Cheng, S. M. Sakya, B. S. Bronk, R. J. Rafka, B. H. Jaynes, C. B. Ziegler, C. Kilroy, D. W. Mann, E. L. Nimz, M. P. Lynch, M. L. Haven, N. L. Kolosko, M. L. Minich, C. Li, J. K. Dutra, B. Rast, R. M. Crosson, B. J. Morton, G. W. Kirk, K. M. Callaghan, D. A. Koss, A. Shavnya, L. A. Lund, S. B. Seibel, C. F. Petras and A. Silvia, *Bioorg. Med. Chem. Lett.*, 2004, **14**, 95.
5 K. von Auwers and W. Schmidt, *Chem. Ber.*, 1925, **58**, 528.
6 K. N. Zetenin, V. V. Alekseyev, A. R. Tygysheva and S. I. Yakimovitch, *Tetrahedron*, 1995, **51**(41), 11251.
7 (**10f**) is prepared as the exclusive (>99%) pyrazole isomer by condensing phenylhydrazine (**4b**) with benzoylacetone (**5c**) in ethanol–water 2 : 1 in the presence of sodium acetate at reflux, see reference 3, page 1036. This compound has been used to prepare other 1,5-diphenylpyrazoles that have known regio-isomerism.
8 Main and minor products were estimated by normalized chromatograms using authentic reference samples to confirm correct identification by retention time. Column; Kromasil C8. 5 mm spherical particles 150 mm × 4.6 mm, mobile phase; 55% 20 mM potassium phosphate buffer, pH 3.0, 45% acetonitrile, flow rate; 1.0 mL g^{-1}, injection vol., 10 μL wavelength of detection; 250 nm, temperature; 35 °C, instrument; HP 1100 series.
9 S. P. Singh, D. Kumar, H. Batra, R. Nathani, I. Rozas and Jose Elguero, *Can. J. Chem.*, 2000, **78**, 1109.
10 J. Elguero and G. I. Yranzo, *J. Chem. Res. Synop.*, 1990, 120.
11 Single crystal X-ray data. Compound **8b**: $C_{16}H_{15}N_3O_3SF_2$; (*M*), 367.37; unit cell dimensions (Å, °) a = 10.5772(4), b = 17.2951(7), c = 9.3940(4), α = 90, β = 109.7810(10), γ = 90; vol. 1617.08(11) Å^3; space group, *P*2(1)/*c*; (*Z*), 4; (μ), 2.188 mm^{-1}; independent reflections 1285[*R*(int) = 0.1021]; final *R* indices [$I > 2\sigma(I)$], R_1 = 0.0505, wR_2 = 0.1276. Compound **8c**: $C_{16}H_{17}N_3O_3S$; (*M*), 331.39; unit cell dimensions (Å, °) a = 15.9809(10), b = 9.4557(6), c = 10.5313(7), α = 90, β = 90.4710(10), γ = 90; vol. 1591.34(18) Å^3; space group, *P*2(1)/*c*; (*Z*), 4; (μ), 0.222 mm^{-1}; independent reflections 1663 [*R*(int) = 0.0592]; final *R* indices [$I > 2\sigma(I)$], R_1 = 0.0370, wR_2 = 0.0928. Compound **9a**: $C_{16}H_{14}F_3N_3O_3S$; (*M*), 385.36; unit cell dimensions (Å, °) a = 8.3741(5), b = 19.8459(13), c = 10.4665(7), α = 90, β = 108.8450(10), γ = 90; vol. 1646.20(18) Å^3; space group, *P*2(1)/*n*; (*Z*), 4; (μ), 0.252 mm^{-1}; independent reflections 1721[*R*(int) = 0.0542]; final *R* indices [$I > 2\sigma(I)$], R_1 = 0.0295, wR_2 = 0.0767. Compound **10a**: $C_{16}H_{12}F_3N_3O_3S$; (*M*), 367.35; unit cell dimensions (Å, °) a = 31.208(4), b = 5.0510(10), c = 21.756(2), α = 90, β = 110.080(10), γ = 90; vol. 3221.0(8) Å^3; space group, *C*2/*c*; (*Z*), 8; (μ), 2.245 mm^{-1}; independent reflections 1639 [*R*(int) = 0.0130]; final *R* indices [$I > 2\sigma(I)$], R_1 = 0.0445, wR_2 = 0.1021. Compound **10b**: $C_{16}H_{13}F_2N_3O_2S$; (*M*), 349.35; unit cell dimensions (Å, °) a = 10.614(2), b = 7.4840(10), c = 20.523(3), α = 90, β = 96.250(10), γ = 90; vol. 1620.6(4) Å^3; space group, *P*2(1)/*c*; (*Z*), 4; (μ), 2.108 mm^{-1}; independent reflections 1674 [*R*(int) = 0.0181]; final *R* indices [$I > 2\sigma(I)$], R_1 = 0.0419, wR_2 = 0.1017. Compound **10d**: $C_{16}H_{11}F_3N_2$; (*M*), 288.27; unit cell dimensions (Å, °) a = 8.4600(10), b = 16.282(2), c = 10.7060(10), α = 90, β = 107.520(10), γ = 90; vol. 1406.3(3) Å^3; space group, *P*2(1)/*n*; (*Z*), 4; (μ), 0.935 mm^{-1}; independent reflections 1449 [*R*(int) = 0.0306]; final *R* indices [$I > 2\sigma(I)$], R_1 = 0.0461, wR_2 = 0.1104. CCDC reference numbers 263085–263090. See http://www.rsc.org/suppdata/ob/b5/b500413f/ for crystallographic data in CIF or other electronic format.
12 D. E. Bourassa, M. J. Castaldi and D. H. B. Ripin, US Patent 6646128, 11 November 2003.