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Improved Regioselectivity in Pyrazole Formation through the Use of Fluorinated Alcohols as Solvents: Synthesis and Biological Activity of Fluorinated Tebufenpyrad Analogs

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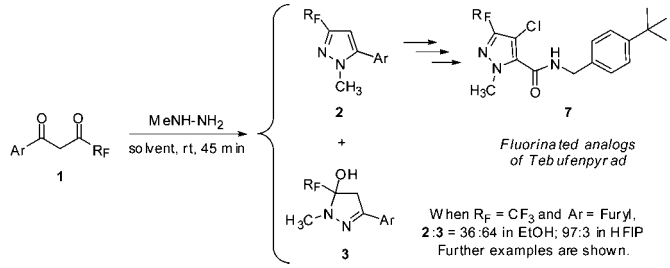
Received January 30, 2008



The preparation of *N*-methylpyrazoles is usually accomplished through reaction of a suitable 1,3-diketone with methylhydrazine in ethanol as the solvent. This strategy, however, leads to the formation of regioisomeric mixtures of *N*-methylpyrazoles, which sometimes are difficult to separate. We have determined that the use of fluorinated alcohols such as 2,2,2-trifluoroethanol (TFE) and 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) as solvents dramatically increases the regioselectivity in the pyrazole formation, and we have used this modification in a straightforward synthesis of fluorinated analogs of Tebufenpyrad with acaricide activity.

Introduction

Pyrazole derivatives have become increasingly important in the past few years because they have proven to be extremely useful intermediates for the preparation of new biological materials. The pyrazole ring is present in numerous pharmacologically and agrochemically important compounds, including those used as inhibitors of HIV-1 reverse transcriptase,[1] sodium hydrogen ion exchanger NHE-1,[2] and dipeptidyl peptidase IV (DPP-IV).[3] Several compounds of this type act as antagonists of the $\alpha_v\beta_3$ receptor, which is present on the surface of many tumor cells,[4] whereas others constitute important agrochemicals used, for instance, as insecticides.[5] Of particular importance as a pharmacophore, the *N*-methylpyrazole unit forms part of several drugs such as the antidepressant Zometapine,[6] the inhibitor of type 5 cGMP phosphodiesterase Sildenafil,[7] and the antibacterial agent FR21818.[8] Good examples of the usefulness

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10.1021/jo800251g CCC: $40.75 © 2008 American Chemical Society
Published on Web 04/10/2008

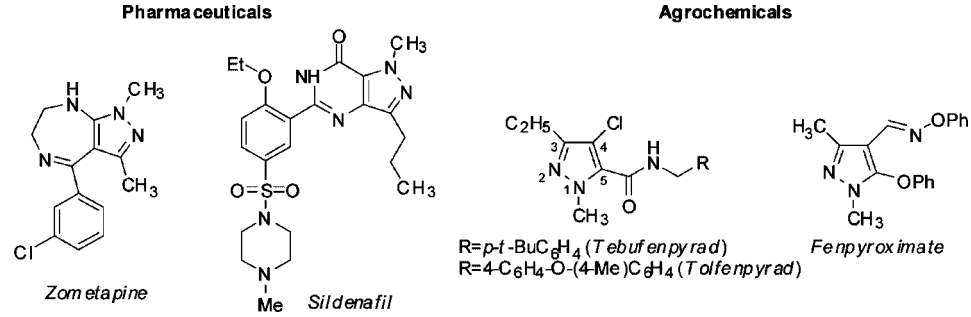
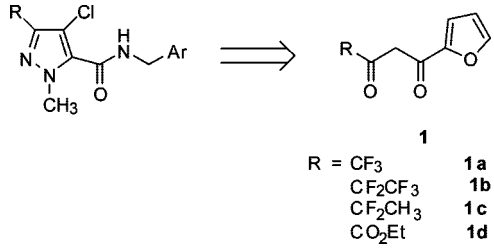


FIGURE 1. Some representative examples of commercial pyrazoles.

of this same unit in the preparation of insecticides and acaricides include the pesticides Tebufenpyrad,[9] Tolfenpyrad,[10] Cyanopyrafen,[11] and Fenpyroximate[12](Figure 1).

The introduction of fluorine atoms or fluorine-containing groups into heterocyclic rings has made possible the discovery of new bioactive products.[13] In particular, pyrazoles containing fluoroalkyl groups are of considerable interest due to their agrochemical and pharmaceutical properties.[14] Because Tebufenpyrad is a commercially available *N*-methylpyrazole derivative that displays important acaricidal activity, we decided to pursue the preparation of fluorinated *N*-methylpyrazoles derived from Tebufenpyrad with several different fluorinated substitution patterns (R_F) to replace the ethyl group on the C-3 of the heterocyclic ring (Scheme 1).

SCHEME 1. Retrosynthetic Analysis for the Preparation of Tebufenpyrad Analogs



Results and Discussion

In our work, the corresponding fluorinated 1,3-diketone starting materials **1a-c** were either commercially available or synthesized from the appropriate fluorinated ester and ketone. Thus, commercially available compound **1a** was used as received, whereas compound **1b** was prepared in 70% yield through the condensation of 2-acetylfuran and ethyl 2,2,3,3,3-pentafluoroacetate with NaOEt as the base and ethanol as the solvent. For the preparation of **1c**, ethyl pyruvate was treated with Deoxofluor in CH_2Cl_2 to afford ethyl 2,2-difluoropropanoate, which in turn was condensed with 2-acetylfuran with NaOEt as the base and ethanol as the solvent to give the desired starting material in 70% overall yield. In addition, we also decided to synthesize the corresponding pyrazoles with an ethoxycarbonyl group (CO_2Et) as an example of a nonfluorinated electron-withdrawing group. Thus, the condensation of 2-acetylfuran with diethyl oxalate in the presence of *tert*-BuOK in a mixture of THF and DME as solvents afforded compound **1d** in 64% yield.[15,16]

One widely used method for the synthesis of fluorinated *N*-methylpyrazoles consists of the condensation of methylhydrazine with an appropriate 1,3-diketone.[17] In these reactions, ethanol is generally used as the solvent. In principle, the reaction between a monosubstituted hydrazine and a nonsymmetrical 1,3-diketone can lead to the formation of a mixture of two pyrazole regioisomers (Table 1).

Although several papers have been published on the synthesis of *N*-arylpyrazoles from monosubstituted arylhydrazines and 1,3-diketones bearing an electron-withdrawing group, mainly CF_3,[18] studies on the preparation of *N*-methylpyrazoles with methylhydrazine as a reagent are scarce. In the few examples published to date, the observed regioselectivities are generally low.[19] In our experiments, when a mixture of 1-(2-furyl)-4,4,4-trifluoro-1,3-butanedione (**1a**) and methylhydrazine in absolute ethanol was allowed to react at room temperature, the reaction was complete in less than an hour and two products were formed,

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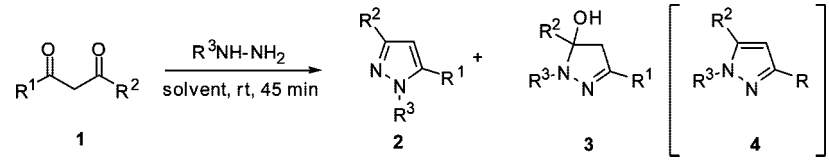
(19) For example, ethyl 2,4-dioxopentanoate or ethyl 2,4-dioxo-4-phenylbutanoate reacted with methylhydrazine in boiling EtOH to yield a 2:1 mixture of the two regioisomeric pyrazoles. See: Schmidt, A.; Habeck, T.; Kindermann, M. K.; Nieger, M. *J. Org. Chem.* **2003**, *68*, 5977–5982. In contrast, reaction between 4-(2-thienyl)-1,1,1-trifluoromethyl-1,3-butanedione and methylhydrazine in EtOH-AcOH (10:1) at reflux afforded 1-methyl-3-trifluoromethyl-5-(2-thienyl)pyrazole in 60% yield (no presence of the other regioisomer was indicated). See: (a) Yonetoku, Y.; Kubota, H.; Okamoto, Y.; Toyoshima, A.; Funatsu, M.; Ishikawa, J.; Takeuchi, M.; Ohta, M.; Tsukamoto, S. *Bioorg. Med. Chem.* **2006**, *14*, 4750–4760. See also: (b) Yonetoku, Y.; Kubota, H.; Okamoto, Y.; Ishikawa, J.; Ishikawa, J.; Takeuchi, M.; Ohta, M.; Tsukamoto, S. *Bioorg. Med. Chem.* **2006**, *14*, 5370–5383.

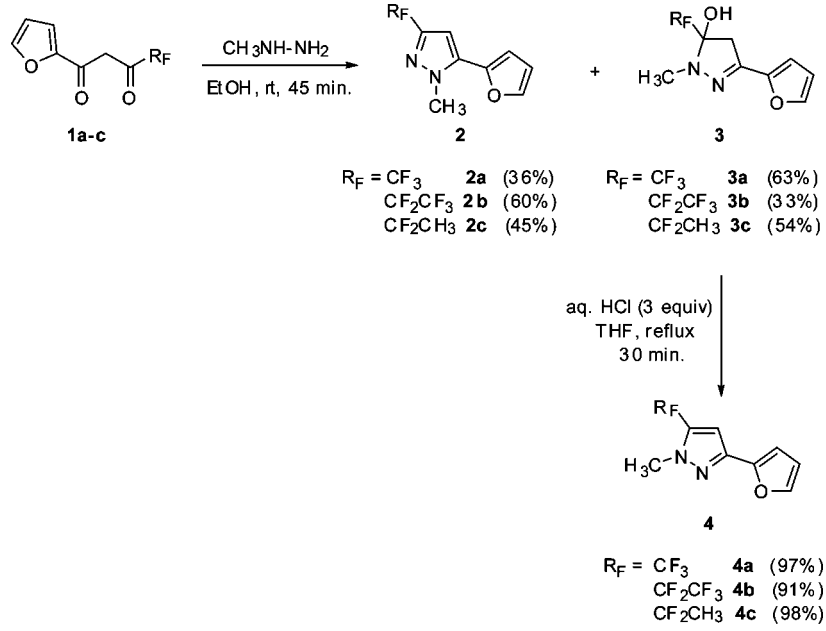
TABLE 1. Results for the Reaction of *N*-Methyl and *N*-Phenylhydrazine with 1,3-Dicarbonyl Derivatives in EtOH, TFE, and HFIP



						2: 3 or 4 (%)[a]		
entry	1	R^1	R^2	R^3	products	EtOH	TFE	HFIP
1	**1a**	2-Furyl	CF_3	CH_3	**2a**, **3a**	36:64 (99)	85:15 (99)	97:3 (98)
2	**1b**	2-Furyl	CF_2CF_3	CH_3	**2b**, **3b**	64:36 (93)	98:2 (99)	>99:<1 (99)
3	**1c**	2-Furyl	CF_2CH_3	CH_3	**2c**, **3c**	45:55 (99)	98:2 (99)	98:2 (98)
4	**1d**	2-Furyl	CO_2Et	CH_3	**2d**, **4d**	44:56 (86)	89:11 (99)	93:7 (98)
5	**1e**	Ph	CF_3	CH_3	**2e**, **3e**	36:64 (99)	79:21 (98)	92:8 (98)
6	**1f**	PMP	CF_3	CH_3	**2f**, **4f**	30:70 (99)	80:20 (99)	88:12 (99)
7	**1a**	2-Furyl	CF_3	Ph	**2g**, **4g**	48:52 (75)	87:13 (93)	97:3 (92)
8	**1e**	Ph	CF_3	Ph	**2h**, **3h**	24:76 (60)	81:19 (98)	99:1 (96)
9	**1f**	PMP	CF_3	Ph	**2i**, **3i**	55:45 (60)	90:10 (80)	99:1 (85)
10	**1b**	2-Furyl	CF_2CF_3	Ph	**2j**, **3j**	18:72 (52)	91:9 (92)	99:1 (93)
11	**1c**	2-Furyl	CF_2CH_3	Ph	**2k**, **3k**	33:67 (62)	99:1 (65)	99:1 (65)
12	**1d**	2-Furyl	CO_2Et	Ph	**2l**,[b] **4l**[b]	49:51 (69)	89:11 (65)	94:4 (67)
13	**1g**	CH_3	CF_3	CH_3	**2m**, **3m**	65:35 (98)	88:12 (99)	96:4 (98)
14	**1g**	CH_3	CF_3	Ph	**2n**, **3n**	5:95 (60)	30:70 (50)	99:1 (73)
15	**1h**	*p*-ClC_6H_4	CF_3	CH_3	**2o**, **3o**	12:88 (90)	80:20 (85)	88:12 (94)
16	**1h**	*p*-ClC_6H_4	CF_3	Ph	**2p**, **3p**	33:67 (90)	86:14 (89)	99:1 (94)
17	**1i**	2,4-$Cl_2C_6H_3$	CF_3	CH_3	**2q**, **3q**	70:30 (93)	75:25 (97)	80:20 (90)
18	**1i**	2,4-$Cl_2C_6H_3$	CF_3	Ph	**2r**, **3r**	87:13 (63)	99:1 (40)	99:1 (61)

[a] The results show the proportion of compounds **2** and **3** formed or, in the case of entries 4 and 12, compounds **2** and **4**. The reaction yield is shown in parentheses. [b] Compounds **2l** and **4l** had been previously described in the literature, but NOESY experiments on the alcohols that resulted from DIBALH reduction of the CO_2Et group showed that the original structural assignment was incorrect. See: Flores, A. F.; Brondani, S.; Pizzuti, L.; Martins, M. A.; Zanatta, N.; Bonacorso, H. G.; Flores, D. C. *Synthesis*, **2005**, 2744−2750.

SCHEME 2. Formation of Fluorinated Pyrazoles 2 and 5-Hydroxypyrazolines 3



namely the 3-trifluoromethylpyrazole (**2a**) and the 5-hydroxy-5-trifluoromethylpyrazoline (**3a**), in almost quantitative overall yield and in a ratio of 1:1.8. Compound **3a** is the hydrated precursor of **4a**, the regioisomeric pyrazole of **2a** (Scheme 2).[20]

(20) 5-Hydroxy-5-trifluoromethylpyrazoline derivatives have been previously isolated and identified as intermediates in reactions between non-alkylated hydrazines and trifluoromethyl 1,3-diketones. See: (a) Elguero, J.; Yranzo, G. I. *J. Chem. Res., Synopses* **1990**, 120–121, and references 18a−g. These intermediates have also been observed in reactions with methylhydrazine when $R_F = CF_3$. See: (b) Khudina, O. G.; Shchegol'kov, E. V.; Burgart, Y. V.; Kodess, M. I.; Kazheva, O. N.; Chekhlov, A. N.; Shilov, G. V.; Dyachenko, O. A.; Saloutin, V. I.; Chupakhin, O. N. *J. Fluorine Chem.* **2005**, *126*, 1230–1238.

(21) A possible alternative to the general method for the synthesis of *N*-methylpyrazoles entails the preparation of the *N*-unsubstituted pyrazole, followed by methylation with methyl iodide or dimethyl sulphate under basic conditions. See: Hamper, B. C.; Leschinsky, K. L.; Mischke, D. A.; Prosch, S. D. In *Asymmetric Fluoroorganic Chemistry. Synthesis, Applications and Future Directions*; ACS Symposium Series 746; Ramachandran, P. V., Ed.; American Chemical Society: Washington, D.C., 2000; pp 274−275.

Compounds **2a** and **3a** were readily separated by means of column chromatography and spectroscopically identified. Under the same reaction conditions, 1-(2-furyl)-4,4,5,5,5-pentafluoro-1,3-pentanedione **1b** afforded pyrazole **2b** and the 5-hydroxypyrazoline **3b**, whereas 1-(2-furyl)-4,4-difluoro-1,3-pentanedione **1c** afforded the pyrazole **2c** and the 5-hydroxypyrazoline **3c**. In both cases, compounds **2** and **3** were obtained with very low regioselectivity, with a ratio of ca. 1:1 (Scheme 2). We were able to assign the structures for the reaction products **2** and **3** through ^{13}C and NOESY NMR experiments (see Supporting Information).

In all cases, it was possible to transform the 5-hydroxy-5-trifluoromethylpyrazolines **3a-c** into their respective 5-trifluoromethylpyrazoles **4a-c** in almost quantitative yields through treatment with 3 M HCl in THF solution under reflux conditions (Scheme 2).

In contrast, the condensation of the nonfluorinated ethyl 4-(2-furyl)-2,4-dioxobutanoate **1d** with methylhydrazine led directly to the formation of a ca. 1:1.3 mixture of the two isomeric pyrazoles **2d** and **4d**. In this case, the corresponding 5-hydroxy-5-trifluoromethylpyrazoline was not detected (Table 1).

The results obtained up to this point showed that under these reaction conditions there was either no regioselectivity or, if there was, the major product was the undesired 5-fluoroalkyl pyrazole regioisomer.[21] *In an effort to find simple regioselective routes to compounds* **2**, we thus decided to investigate the effect of using fluorinated alcohols instead of ethanol in the pyrazole formation.

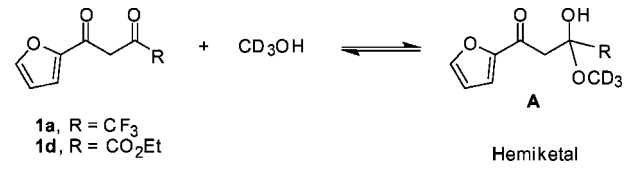
Fluorinated alcohols have been shown to display unique properties as solvents, cosolvents, and additives in synthetic chemistry. The presence of fluoroalkyl groups lends specific properties to fluorinated alcohols, differentiating them from their nonfluorinated counterparts and other protic solvents in that they are neither nucleophilic nor are they hydrogen bond acceptors.[22] For this reason, we decided to investigate the effect of substituting trifluoroethanol (TFE) or hexafluoroisopropanol (HFIP) for ethanol in the key pyrazole-forming step of our synthesis.

In our first assay with TFE as the solvent at room temperature, **1a** reacted with methylhydrazine to afford a mixture of 3-trifluoromethylpyrazole **2a** and 5-hydroxy-5-trifluoromethylpyrazoline **3a** in less than 1 h. In contrast with the previous results for this reaction when performed in EtOH, the regioselectivity was much higher, with a ratio for the two compounds of 85:15 in favor of the desired 3-trifluoromethyl derivative. The selectivity was further improved to 97:3 when the condensation reaction was carried out with HFIP as the solvent (entry 1, Table 1).

Subsequent assays with the 1,3-diketones **1b-f** and methylhydrazine (entries 2−6, Table 1) confirmed the influence of the fluorinated alcohols in the regioselectivity of this reaction, especially with HFIP as the solvent.[23] In this case, the 5-(2-furyl)pyrazole derivatives **2** were obtained almost exclusively (Table 1, entries 1−4, 7, and 10−12).

As mentioned above, most of the previously published pyrazole syntheses that start with 1,3-diketones with both aryl and CF_3 groups have been carried out with monosubstituted hydrazines derived from aromatic structures. In all cases, the 3-CF_3 pyrazole derivatives were obtained as the major isomers when either phenylhydrazine or 4-methoxyphenylhydrazine was used under neutral (EtOH, *i*-PrOH), basic (NaOAc, TEA), or acidic (HCl, H_2SO_4, *p*-TsOH) reaction conditions at reflux.[18a,d,f–h] Only when a strong electron-withdrawing substituent was attached to the hydrazine group were 5-hydroxy-5-trifluoromethylpyrazolines **3** isolated as the major or exclusive products.[24] With this in mind, we further extended our study to examine the influence of the fluorinated solvents TFE and HFIP on the regioselectivity of the synthesis of 5-arylpyrazoles bearing an electron-withdrawing group at C-3. We thus examined the reactions between 1,3-diketones **1** and phenylhydrazine in absolute EtOH, TFE, and HFIP at room temperature. The results are summarized in Table 1 (entries 7−12). In absolute EtOH, the observed regioselectivities for the reactions with phenylhydrazine were very similar to those obtained with methylhydrazine, with isomer ratios in the reaction mixtures from about 1:1 to 3:1, the latter in favor of the 5-hydroxypyrazoline. As was the case in the analogous reaction with methylhydrazine, the 5-ethoxycarbonyl-5-hydroxypyrazoline **3l** was not detected as a product in the reaction of **1d** with phenylhydrazine (entry 12, Table 1). In sharp contrast, when the reactions were carried out in TFE or HFIP, the regioselectivities improved up to 99:1 in favor of the 5-arylpyrazole isomers (entries 7−12, Table 1). This increase in regioselectivity was also observed when R^1 = methyl (Table 1, entries 13−14). However, when R^1 is an aryl group with electron-withdrawing groups, as in diketones **1 h** and **1i**, the reactivity of the two carbonyl groups is expected to be more similar than when the substituents are neutral or electron-donating. Although lower regioselectivity might be anticipated in these cases, in fact this only occurs with methylhydrazine in HFIP (Table 1, entries 15 and 17 versus entry 5). In the other cases, the observed regioselectivity does not change significantly (Table 1, entries 16 and 18). The increased regioselectivity thus seems to be general, although it is more noticeable with phenylhydrazine in HFIP.

SCHEME 3. Addition of CD_3OH to Compounds 1a and 1d



To explain the enhanced regioselectivity induced by the use of fluorinated alcohols in the pyrazole ring formation, we performed an NMR experiment. Addition reactions of nucleophiles such as water,[25] alcohols,[26] ethanethiol, and pyrrolidine[18a] to the $COCF_3$ carbonyl group have been previously reported. In our case, when an excess of CD_3OH was added to an NMR sample tube containing the 1,3-diketone **1a**, the ^1H spectrum showed the presence of a mixture of the adduct at the $COCF_3$ carbonyl (hemiketal **A**, Scheme 3) and the diketone starting material in a ratio of 8:1 in favor of the former. Under the same conditions, CD_3OH also reacted with the $COCO_2Et$ ketone

(22) Review: (a) Bégué, J.-P.; Bonnet-Delpon, D.; Crousse, B. *Synlett* **2004**, 18–29. For a recent paper, see: (b) Dubrovina, N. V.; Shuklov, I. A.; Birkholz, M.-N.; Michalik, D.; Paciello, R.; Börner, A. *Adv. Synth. Catal.* **2007**, *349*, 2183–2187.

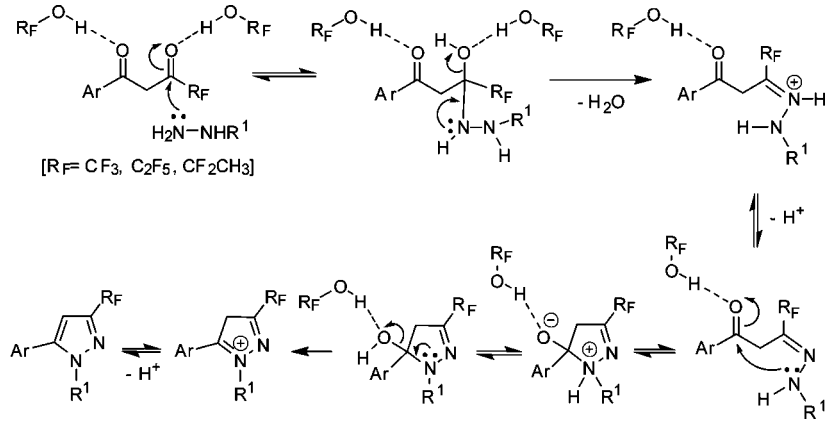
(23) Diketone **1e** (R^1 = Ph, R^2 = CF_3) is commercially available whereas **1f** (R^1 = *p*-$MeOC_6H_4$, R^2 = CF_3) can be easily prepared. See Supporting Information.

(24) (a) Singh, S. P.; Kumar, V.; Aggarwal, R.; Elguero, J. *J. Heterocyclic Chem.* **2006**, *43*, 1003–1014. (b) Habeeb, A. G.; Rao, P. N. P.; Knaus, E. E. *J. Med. Chem.* **2001**, *44*, 3039–3042. See also refs18b−e, g. .

(25) Camps, F.; Coll, J.; Messeguer, A.; Roca, A. *Tetrahedron* **1977**, *33*, 1637–1640, and references cited therein.

(26) Moriyasu, M.; Kato, A.; Hashimoto, V. *J. Chem. Soc., Perkin Trans.* **1986**, *2*, 515–520.

SCHEME 4. Possible Mechanism for the Formation of Fluorinated Pyrazoles 2 When Fluorinated Alcohols Are Used As Solvents

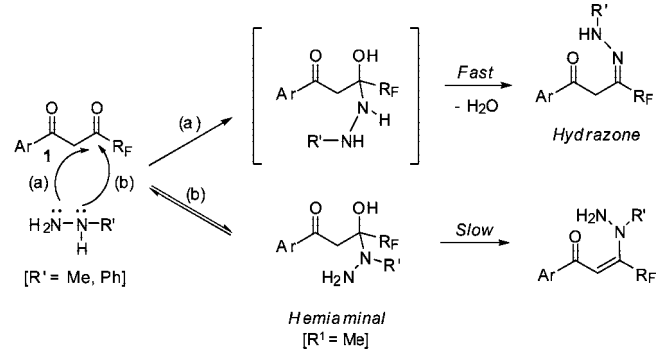


carbonyl of **1d** to afford a mixture containing one-third of the corresponding adduct in equilibrium with the starting material (Scheme 3). These results confirm the stronger electrophilic character of carbonyl groups attached to electron-withdrawing groups such as CF_3 or CO_2Et as compared with those attached to an aryl group. In sharp contrast, when deuterated TFE or HFIP were added to **1a**, the corresponding adduct was not detected, which is not surprising because both fluorinated alcohols are non-nucleophilic. The low regioselectivities observed when methyl- and phenylhydrazine react with these 1,3-diketones in EtOH may thus be due to the competition between the two nucleophiles, hydrazine and alcohol, toward the more reactive carbonyl group. Because both TFE and HFIP are non-nucleophilic, they do not compete with hydrazine in the attack to the more reactive carbonyl group, thus increasing the regioselectivity of the attack.

To explain the excellent levels of regioselectivity observed in the synthesis of pyrazoles in fluorinated solvents, especially in HFIP, we agree with Norris et al.[27] that the process must proceed via a step-by-step pathway. The highly electrophilic character of the carbonyl group attached to CF_3, CF_2CH_3, CF_2CF_3, or CO_2Et is probably enhanced by the high hydrogen bond donating ability of the fluorinated solvents, which causes the rate of the attack of the hydrazine NH_2 group to be faster than that of the other carbonyl group, COAr. Subsequent loss of a water molecule from the adduct would afford the hydrazone intermediate, a process that is facilitated by both the strong ionizing power of the fluorinated alcohols as solvents and their ability to solvate water. Finally, the attack of the substituted nitrogen of the hydrazone to the activated COAr carbonyl and the subsequent loss of water would give rise to the major isomer of the pyrazole derivative (Scheme 4).[28]

Interestingly, analogous 5-aryl regioisomers **2** were obtained as major pyrazole formation products with either methyl- or phenylhydrazine in spite of the fact that the NH_2 is the more nucleophilic nitrogen in phenylhydrazine and the less nucleophilic one in methylhydrazine. The major product in pyrazole

SCHEME 5. Addition of Methyl- Or Phenylhydrazine to Compounds 1



formation can be easily predicted by taking into account that the more nucleophilic NH_2 group of phenylhydrazine would be expected to react preferentially with the more reactive carbonyl group. In contrast, in the case of methylhydrazine, the observed results can be explained by considering that the attack of the NH group of methylhydrazine on the more reactive carbonyl group leads to a hemiaminal which does not dehydrate easily to yield a hydrazone and can therefore revert to the starting materials if equilibrium is achieved. The dehydration of the hemiaminal to the enamine is disfavored due to the presence of the R_F group, as the persistent formation of 5-hydroxy-5-trifluoromethylpyrazolines **3** in similar cases shows (see Table 1). In contrast, the NH_2 group of methylhydrazine can attack the more electrophilic carbonyl leading to irreversible hydrazone formation (since hydrazone hydrolysis is probably slow under these reaction conditions), thus preventing a return to the starting compounds (Scheme 5).

Having obtained the required fluorinated pyrazoles, we continued our synthesis by unmasking the carboxyl group through oxidation of the furan ring with sodium periodate in the presence of catalytic amounts of $RuCl_3 \cdot 3H_2O$ at room temperature.[29] The reactions were fast and proceeded with good to excellent yields (Scheme 6). The pyrazole carboxylic acids were then chlorinated in excellent yields upon the addition of an aqueous solution of sodium hypochlorite to the substrate dissolved in acetic acid. For the final amide formation step, we chose to transform the carboxylic acids into their corresponding acyl chlorides, followed by in situ addition of the amine. Thus,

(27) These authors proposed a mechanism with a sequential loss of two water molecules that could explain the observed high regioselectivity. The first loss of water would be fast, corresponding to the formation of the *C*═N bond conjugated with the aryl ring, whereas the second loss of water would be much slower, even requiring acid catalysis for the elimination to proceed. See ref 18g.

(28) An alternative mechanism would involve addition to the carbonyl attached to the R_F group followed by a second addition to the other carbonyl to form a 3,5-dihydroxypyrazoline, which would then evolve to the corresponding pyrazole through sequential double dehydration. See ref 20a.

(29) Danishefsky, S. J.; DeNinno, M. P.; Chen, S.-h. *J. Am. Chem. Soc.* **1988**, *110*, 3929–3940.

SCHEME 6. Synthesis of Fluorinated Analogs of Tebufenpyrad 7 and 10

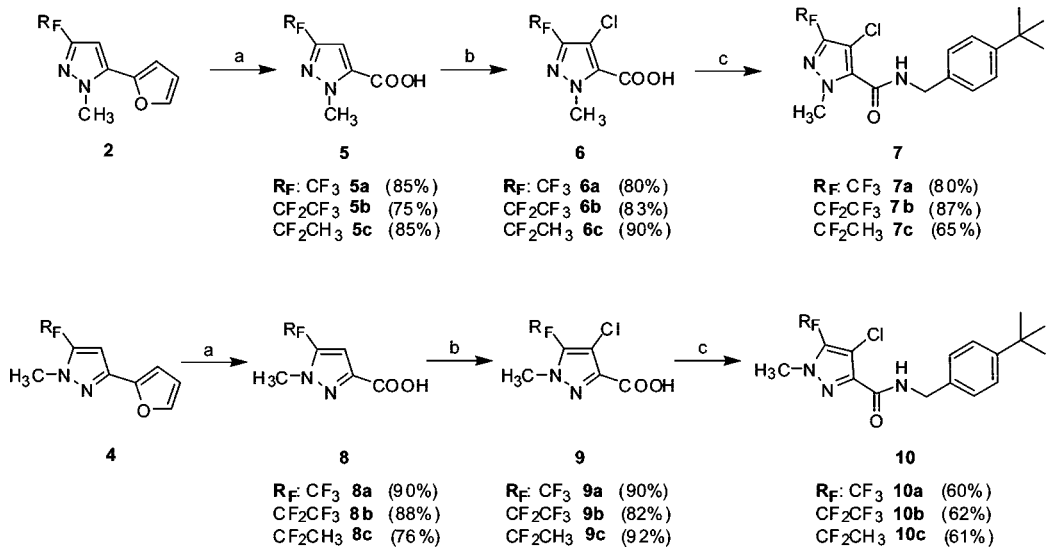


TABLE 2. Biological Activity of the Fluorinated Tebufenpyrad Analogs on *Tetranychus urticae*[a]

		mortality (%)			fertility inhibition (%)		
entry	compound [R_F]	24 h	4 days	6 days	24 h	4 days	6 days
1	**7a** [CF_3]	3	23	50	41	49	52
2	**7b** [CF_2-CF_3]	0	0	0	0	0	0
3	**7c** [CF_2-CH_3]	4	31	90	69	83	84
4	**10a** [CF_3]	0	0	0	0	0	0
5	**10b** [CF_2-CF_3]	0	0	0	0	0	0
6	**10c** [CF_2-CH_3]	0	0	0	0	0	0
7	Tebufenpyrad	100	100	100	100	100	100

[a] Concentration of active principle in the assay: 5 g/L.

oxalyl chloride was added to a solution of the carboxylic acid in dichloromethane, followed by the addition of the amine plus Et_3N and DMAP at room temperature. The desired amides **7** were obtained with yields that ranged from good to excellent. In a similar manner, regioisomeric fluorinated derivatives of Tebufenpyrad **10** were prepared when pyrazoles **4** were used as starting materials (Scheme 6).

Finally, a standard method was used to test the fluorinated analogs of Tebufenpyrad as acaricides against *Tetranychus urticae*.[30] The activity of the fluorinated compounds was thus compared to that of the commercial product Masai, the active principle of which is Tebufenpyrad.[31] The effects of applying the assayed compounds as adulticides and fertility inhibitors was evaluated for each compound 24 h, 4 days, and 6 days after application. Table 2 lists the obtained results.

The results indicate that the regioisomeric pyrazole analogs **10a-c** are completely devoid of acaricidal activity. Among the Tebufenpyrad fluorinated analogs **7a-c**, whereas compound **7b** is inactive, analogs **7a**, and particularly **7c** display significant acaricidal activity. Although they are slower to take effect than Tebufenpyrad, the final activity after 6 days is only slightly inferior in the case of **7c**.

In summary, we have prepared a series of biologically active fluorinated analogs of the commercial acaricide Tebufenpyrad. The preparation of these compounds involves the use of the fluorinated alcohols TFE and HFIP as solvents in the key pyrazole ring formation step, an essential point for improving the regioselectivity toward the desired isomer. Two of the prepared fluorinated analogs display acaricidal activity within the same order of magnitude as that of Tebufenpyrad. We are currently working on the development of other fluorinated analogs of Tebufenpyrad with the purpose of improving its biological activity as acaricide.

Experimental Section

4,4-Difluoro-1-(2-furyl)-1,3-pentanedione (1c). Deoxofluor (0.046 mol, 50% in toluene) was added slowly to a solution of ethyl pyruvate (27 mmol, 3.13 g) in CH_2Cl_2 (45 mL) at 0 °C under nitrogen atmosphere. The mixture was stirred overnight at room temperature. The reaction mixture was cooled to 0 °C, hydrolyzed with 5% aq sodium bicarbonate solution (25 mL), and extracted with CH_2Cl_2 (2 × 20 mL). The organic layer was dried over Na_2SO_4. The solvent was removed cautiously under reduced pressure in order not to lose the resulting crude ethyl 2,2-difluoropropanoate, which has a low boiling point. This solution was then added at 0 °C to a previously prepared solution of acetylfuran enolate, which was obtained by adding acetylfuran (23 mmol, 3.11 g) to a solution of Na (35 mmol, 790 mg) in EtOH (35 mL). The reaction mixture was stirred at room temperature for 3 h. The solvent was concentrated *in vacuo*, hydrolyzed with H_2O (15 mL), and acidified with 3 M aq H_2SO_4 until neutral pH was reached. The aqueous layer was extracted with EtOAc (3 × 20 mL), washed with brine, dried over anhyd Na_2SO_4, and filtered. The solvent was concentrated to give a yellow oil, which was purified through column chromatography on silica gel (6:1 hexane:EtOAc) to afford pure compound **1c** (70%, 3.25 g). Pale-yellow oil; R_f 0.3 (3:1 hexane:EtOAc). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.75 (t, J_{HF} = 18.6 Hz, 3H; C*H*$_3$), 6.39 (s, 1H; C*H*), 6.52 (dd, J_1 = 3.6 Hz, J_2 = 1.7 Hz, 1H; C*H*), 7.19 (dd, J_1= 3.6 Hz, J_2= 0.6 Hz, 1H; C*H*), 7.56 (dd, J_1 = 1.7 Hz, J_2 = 0.6 Hz, 1H; C*H*) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 20.2 (t, $^1J_{CF}$ = 26.0), 90.8 (t, $^3J_{CF}$ = 3.6), 111.9, 116.3 (t, $^1J_{CF}$ = 244.0), 116.5, 146.2, 148.6, 175.9, 180.9 (t, $^2J_{CF}$ = 31.0) ppm; ^{19}F-NMR ($CDCl_3$, 282.4 MHz): δ −100.3 (q, J_{FH} = 18.6 Hz, 2F; CF_2) ppm. HRMS: calcd for $C_9H_8F_2O_3$ (M^+): 202.0441; found 202.0393.

General Procedure for Preparation of Pyrazoles 2 and 5-Hydroxypyrazolines 3. The substituted hydrazine ($MeNHNH_2$ or $PhNHNH_2$) (0.45 mmol) was slowly added to the corresponding 1,3-diketone **1** (0.3 mmol) in the chosen solvent (0.5 mL), and the mixture was stirred at room temperature for 45 min. The solvent was evaporated and the residue was taken up in EtOAc, washed

(30) García-Marí, F.; Roca, D.; Fonbuena, P.; Ferragut, F.; Costa-Comelles, J. *Bol. San. Veg. Plagas* **1988**, *14*, 163–169.
(31) Masai is commercialized by BASF.

with water and brine, dried over anhyd Na_2SO_4, filtered, and concentrated *in vacuo* to give the corresponding pyrazoles, which were purified by means of column chromatography on silica gel to afford pure compounds **2** and **3/4**.

3-(1,1-Difluoroethyl)-5-(2-furyl)-1-methylpyrazole (2c). Flash chromatography [*n*-hexane-EtOAc (10:1)] (R_f = 0.40) afforded **2c** as a pale-yellow oil (45% yield in EtOH, 97% in TFE, 96% in HFIP). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.95 (t, J_{HF} = 18.5 Hz, 3H; CH_3), 3.98 (s, 3H; CH_3), 6.45 (dd, J_1 = 3.4 Hz, J_2 = 1.7 Hz, 1H; C*H*), 6.52 (dd, J_1 = 3.4 Hz, J_2 = 0.8 Hz, 1H; C*H*), 6.57 (s, 1H; C*H*), 7.46 (dd, J_1 = 1.7 Hz, J_2 = 0.8 Hz, 1H; C*H*) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 22.0 (t, $^2J_{CF}$ = 27.6), 37.0, 100.3, 107.2, 109.6, 117.0 (t, $^1J_{CF}$ = 232.8), 133.2, 141.1, 142.2, 146.4 (t, $^2J_{CF}$ = 33.3) ppm. ^{19}F-NMR ($CDCl_3$, 282.4 MHz): δ −85.2 (q, J_{FH} = 18.5 Hz, 2F; CF_2) ppm. HRMS: calcd for $C_{10}H_{10}F_2N_2O$ (M^+) 212.0761; found 212.0797.

5-(1,1-Difluoroethyl)-3-(2-furyl)-1-methyl-4,5-dihydro-1H-pyrazol-5-ol (3c). Flash chromatography [*n*-hexane-EtOAc (10:1)] (R_f = 0.25) afforded **3c** as a white solid; mp 92−94 °C (54% yield in EtOH, 2% in TFE, 2% in HFIP). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.67 (t, J = 19.0 Hz, 3H; CF_2CH_3), 2.90 (s, 3H; CH_3), 3.03 (dt, J_1 = 17.7 Hz, $^2J_{HF}$ = 1.3 Hz, 1H; C*H*H), 3.25 (d, J = 17.7 Hz, 1H; CH*H*), 6.39 (dd, J_1 = 3.5 Hz, J_2 = 1.7 Hz, 1H; C*H*), 6.45 (dd, J_1 = 3.5 Hz, J_2 = 0.6 Hz, 1H; C*H*), 7.39 (dd, J_1 = 1.7 Hz, J_2 = 0.6 Hz, 1H; C*H*); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 21.2 (t, $^2J_{CF}$= 26.9), 35.2, 44.5, 95.8 (t, $^2J_{CF}$ = 26.9), 110.1, 112.3, 139.9, 144.1, 148.4; ^{19}F-NMR ($CDCl_3$, 282.4 MHz): δ −112.4 (qd, $^1J_{FH}$ = 19.0 Hz, J_2 = 6.0 Hz, 2F; CF_2); HRMS: calcd for (M^+) $C_{10}H_{12}F_2N_2O_2$ 230.0867; found 230.0862.

General Procedure for Dehydration of Hydroxypyrazolines 3 to Pyrazoles 4. A solution of hydroxypyrazoline **3** (0.014 mol) and HCl 3N (0.042 mol) in THF (60 mL) was heated to reflux for 30 min. The reaction mixture was cooled to room temperature, extracted with EtOAc (3 × 20 mL), and then washed sequentially with H_2O (15 mL) and brine. The organic layer was dried over anhyd Na_2SO_4 and filtered. The solvent was removed under reduced pressure to give pyrazoles **4**, which were purified by means of column chromatography on silica gel.

5-(1,1-Difluoroethyl)-3-(2-furyl)-1-methylpyrazole (4c). Flash chromatography [*n*-hexane-EtOAc (8:1)] (R_f = 0.30) afforded **4c** as a pale-yellow solid; (yield 95%); mp 103−105 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.91 (t, J_{HF} = 18.3 Hz, 3H; CH_3), 3.88 (d, J_{HF} = 0.1 Hz, 3H; CH_3), 6.31 (dd, J_1 = 1.9 Hz, J_2 = 1.5 Hz, 1H; C*H*), 6.45 (d, J = 0.9 Hz, 1H; C*H*), 6.50 (d, J = 3.21 Hz, 1H; C*H*), 7.29 (t, J = 0.8 Hz, 1H; C*H*) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 24.4 (t, $^2J_{CF}$ = 26.9), 38.9 (t, $^3J_{CF}$ = 2.9), 103.7 (t, $^3J_{CF}$ = 4.9), 106.2 (d), 111.7, 117.5 (t, $^1J_{CF}$ = 234.0), 139'3 (t, $^2J_{CF}$ = 28.7), 142.3, 142.7, 148.4 ppm; ^{19}F-NMR ($CDCl_3$, 282.4 MHz): δ −86.3 (c, J_{FH} = 18.3 Hz, 2F; CF_2) ppm. HRMS: calcd for $C_{10}H_{10}F_2N_2O$ (M^+) 212.0761; found 212.0749.

Acknowledgment. We thank the IMPIVA and Industrias Afrasa (IMIDTD/2007/230), the Ministerio de Educación y Ciencia (CTQ2007-61462 and CTQ2006-01317), and the Generalitat Valenciana (GR03/193) for financial support.

Supporting Information Available: Experimental procedures and NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

JO800251G