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New Synthesis of Fluorinated Pyrazoles

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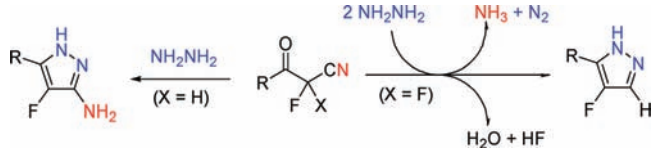
ABSTRACT



A new synthesis of fluorinated pyrazoles, a class of compounds with potential in medicinal chemistry, is described. The treatment of benzoylfluoroacetonitrile with hydrazine yielded the expected new 3-amino-4-fluoropyrazole, while the analogous reaction of α-cyano-α,α-difluoroketones with hydrazine in refluxing isopropanol surprisingly gave rise to 3-unsubstituted 4-fluoropyrazoles via an unprecedented mechanism. The isolation of intermediate hydrazine adducts led to a mechanistic rationale for this transformation.

In recent years, interest in chlorinated and brominated pyrazoles has increased significantly due to their proven usefulness as intermediates in the preparation of new pharmaceuticals and agrochemicals.[1] In contrast to these halopyrazoles, research activities concerning fluorinated pyrazoles are concentrated on perfluoroalkylated pyrazoles, as illustrated by the development of the blockbuster drug Celecoxib, which is an anti-inflammatory trifluoromethylpyrazole.[2] It is well-known that fluorine substituents in organic molecules cause significant physicochemical and biological changes, often resulting in improved bioactivities.[3] In contrast to chlorinated and brominated pyrazoles, which are easily synthesized via direct electrophilic halogenation of the pyrazole ring, the synthesis of ring fluorinated pyrazoles has been more problematic and less well studied.[4] The selective direct fluorination of pyrazoles remains a difficult task because of the high reactivity of these compounds toward electrophiles and the high oxidative properties of electrophilic fluorinating agents. Consequently, the reported yields of the direct ring fluorination of pyrazoles using F_2,[5] CF_3OF,[6] Selectfluor,[7] or NFSI[8] toward 4-fluoropyrazoles are rather low and highly substrate dependent. Other synthetic strategies toward 4-fluoropyrazoles consist of a Balz−Schiemann process,[9] nucleophilic aromatic substitution,[10] condensation reactions of fluorinated β-dicarbonyl com-

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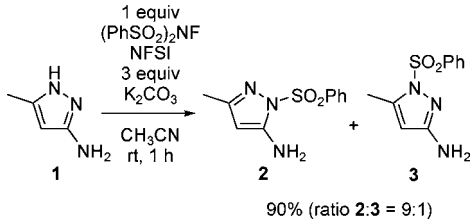
pounds,[11] or α,β-unsaturated compounds[12] with hydrazines and cycloaddition reactions of fluoroalkenes with diazocompounds.[13] In contrast, synthetic strategies toward fluorinated amino- or hydroxypyrazoles have not been studied intensively, although various nonfluorinated amino- and hydroxypyrazoles are often associated with pronounced bioactivities. Indeed, the established activities of Zaleplon, Sildenafil, and Allopurinol have led to a revival of interest in aminopyrazoles.[14] Despite their promising bioactivities, only a few fluorinated 3-amino- and 3-hydroxypyrazoles have been synthesized.[15]

In a first synthetic strategy toward 3-amino-4-fluoropyrazoles, the direct electrophilic fluorination of the commercially available 3-amino-5-methyl-1*H*-pyrazole **1** was investigated. In contrast to the efficient direct chlorination, bromination, and iodination of 3-aminopyrazole **1**,[16] the direct fluorination using Selectfluor or xenon(II) fluoride did not afford the corresponding 4-fluoropyrazole, even when the free 3-amino group was protected as an aldimine derived from benzaldehyde. The obtained complex reaction mixtures confirm the low yields reported in the literature for the direct fluorination of pyrazoles. Surprisingly, pyrazole **1** was entirely converted to a mixture of 5-amino-3-methyl-1-phenylsulfonyl-1*H*-pyrazole **2**[17] and 3-amino-5-methyl-1-phenylsulfonyl-1*H*-pyrazole **3** in a 9:1 ratio upon reaction with *N*-fluorobenzenesulfonimide (NFSI) (Scheme 1). This

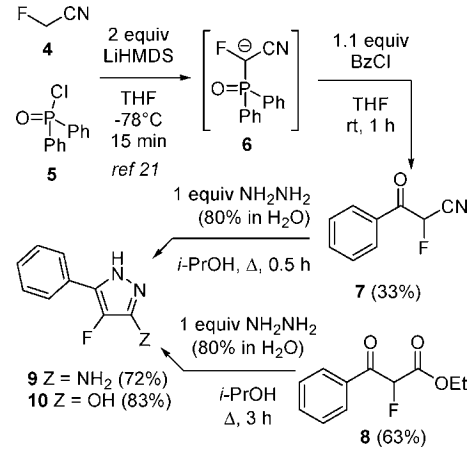
Scheme 1. Reaction of Pyrazole **1** with NFSI



reaction can be compared to the sulfonylation of 3-aminopyrazoles using sulfonyl chlorides.[18] Because of the observed difficulties in the direct fluorination of aminopyrazoles, new strategies were evaluated to synthesize these interesting targets.

The most common method to prepare 3-aminopyrazoles involves the condensation of β-ketonitriles with hydrazines.[19] The corresponding monofluorinated β-ketonitriles have not been used before in analogous condensation reactions, which is probably due to their difficult synthesis.[20] Also in our hands, various strategies to synthesize **7** via electrophilic or nucleophilic monofluorination failed. Fortunately, a good synthetic pathway toward benzoylfluoroacetonitrile **7** in gram quantities was developed by the reaction of the anion of (diphenylphosphinoyl)fluoroacetonitrile **6**, prepared in situ from fluoroacetonitrile **4** and diphenylphosphinyl chloride **5**,[21] with benzoyl chloride followed by aqueous workup (Scheme 2). The synthesis of the desired 3-amino-4-

Scheme 2. Synthesis of 3-Amino- and 3-Hydroxy-4-fluoropyrazoles **9** and **10**



fluoropyrazole **9** was subsequently carried out by heating the obtained benzoylfluoroacetonitrile **7** at reflux temperature with hydrazine hydrate in isopropanol during 30 min. Despite

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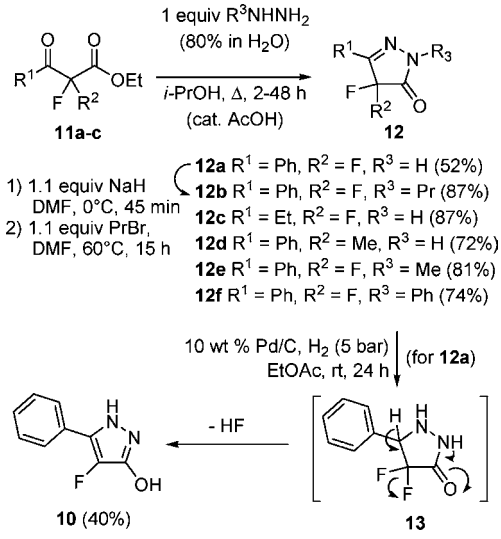
the high-yielding and rapid condensation reaction toward 3-amino-4-fluoropyrazole **9**, this method is rather limited due to the difficult synthesis of the monofluorinated starting material **7**. However, this procedure proved to be much more successful for the synthesis of the corresponding hydroxypyrazoles. In contrast to the nonselective fluorination of β-ketonitriles, the monofluorination of β-ketoesters is well described.[22] Ethyl 2-fluoro-3-oxo-3-phenylpropanoate **8** was treated with hydrazine in isopropanol, affording 4-fluoro-3-hydroxy-5-phenylpyrazole **10** in 83% yield.

Because of the known and observed difficulties in the monofluorination of β-ketonitriles, the synthesis of fluorinated pyrazoles from more easily accessible difluorinated β-ketonitriles via reaction with hydrazine followed by a reduction step was evaluated. As a model study, this strategy was evaluated in the synthesis of fluorinated hydroxypyrazoles. Ethyl benzoyldifluoroacetate **11a** (R^1 = Ph, R^2 = F)[22] was heated with 1 equiv of hydrazine (80% in H_2O) in isopropanol (Scheme 3). A smooth condensation and thermal

Scheme 3. Synthesis of 4-Fluoropyrazolones **12** and Reduction Towards 3-Hydroxy-4-fluoropyrazole **10**



cyclization afforded the new 4,4-difluoro-1*H*-pyrazol-5-one **12a**. Pyrazol-5-ones are of interest in medicinal chemistry,[23] and in contrast to 4,4-dichloropyrazol-5-ones[24] and 4,4-dibromopyrazol-5-ones,[25] fluorinated analogues have not been reported so far. Therefore, also fluorinated β-ketoesters **11b** and **11c** were transformed into 4,4-difluoro-1*H*-pyrazol-5-one **12c** and 4-fluoro-4-methyl-1*H*-pyrazol-5-one **12d**, respectively. To synthesize the N-substituted fluorinated pyrazol-5-ones, pyrazol-5-one **12a** was treated with NaH and propyl bromide giving rise to 1-propylpyrazol-5-one **12b** in 87% yield. In addition, ethyl benzoyldifluoroacetate **11a** was heated in the presence of substituted hydrazines ($MeNHNH_2$ and $PhNHNH_2$) and a catalytic amount of acetic acid yielding N-substituted pyrazol-5-ones **12e** and **12f**.

To accomplish a synthesis of fluorinated pyrazoles, pyrazol-5-one **12a** was treated with Pd/C under a hydrogen atmosphere. The hydrogenation resulted in the formation of 4,4-difluoro-5-phenylpyrazolidin-3-one **13**, which readily underwent dehydrofluorination to form the desired 4-fluoro-3-hydroxypyrazole **10**. Unfortunately, N-alkylated pyrazolones **12e** and **12f** could not be reduced toward the corresponding fluorinated 5-hydroxypyrazoles using the same reaction conditions. Because the methodology to synthesize fluorinated pyrazole **10** from easily accessible α,α-difluoro-β-ketoester **11a** indeed proved to be a valuable strategy, efforts were made to convert difluorinated β-ketonitriles into 3-amino-4-fluoropyrazoles. It was expected that 2,2-difluoro-3-oxopropanenitrile **14a** (R = Ph) would react with hydrazine to give the targeted 3-amino-4-fluoropyrazole **9** after treatment with hydrogen over Pd/C. Surprisingly, after heating nitrile **14a** with 1 equiv of hydrazine in isopropanol, 4-fluoropyrazole **18a**[13d] was recovered in 45% yield. It is remarkable that during the reaction of **14a** with hydrazine one nitrogen atom is lost, probably in the form of ammonia (NH_3).

To investigate the unknown reaction mechanism in more detail, difluorinated β-ketonitrile **14a** (R = Ph) was reacted with 1 equiv of hydroxylamine (50% in H_2O) under reflux conditions in isopropanol. After 2 h, 2,2-difluoro-*N*′-hydroxy-3-oxo-3-phenylpropanimidamide **16** was isolated in 80% yield. This reaction shows that the nitrile function of difluorinated β-ketonitrile **14a** is the most electrophilic group for nucleophilic attack of nitrogen nucleophiles such as hydroxylamine. The stable *N*′-hydroxyimidamide **16** did not undergo ring closure to isoxazoline compounds. However, when compound **16** was further reacted with 1 equiv of hydrazine in isopropanol at reflux temperature during 15 h, an equimolar mixture of starting material and 4-fluoro-5-phenylpyrazole **18a** was obtained. When compound **14a** was treated with hydrazine in isopropanol at room temperature, hydrazonamide **15** was not observed, but its ring closed product, 3-amino-4,4-difluoro-5-hydroxy-4,5-dihydro-1*H*-pyrazole **17** (Scheme 4), was isolated as white crystals in quantitative yield. The addition of 1 equiv of hydrazine gave a full conversion toward 4-fluoropyrazole **18a** in 83% yield. These experiments all point to the need for 2 equiv of hydrazine in the formation of 4-fluoropyrazole **18a**.

A possible mechanism can be rationalized by an initial attack of hydrazine at the carbonyl function of **17**, resulting in compound **19**, which can cyclize again by intramolecular attack of the hydrazinyl substituent at the hydrazonamide with loss of ammonia to form 5-hydrazonopyrazolidin-3-ol **21**. After elimination of water and hydrogen fluoride followed

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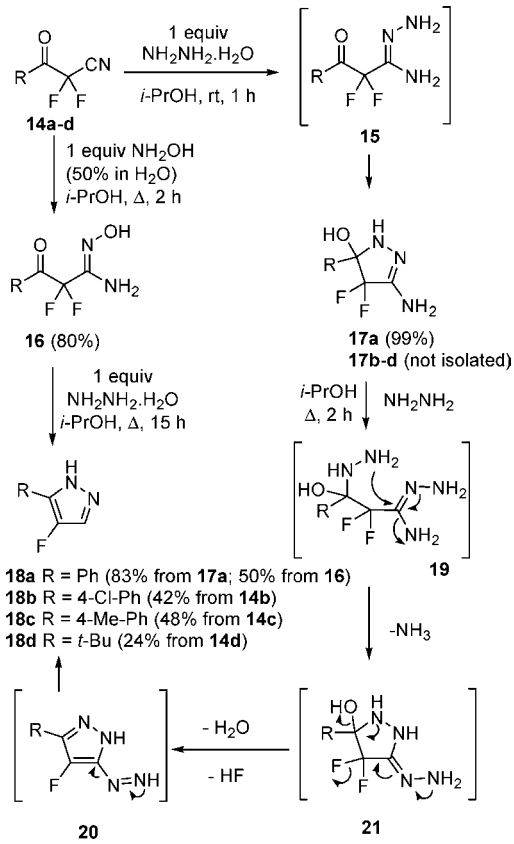
Scheme 4. Synthesis of 4-Fluoropyrazoles **17**



by isomerization, the aromatic 5-diazenyl-4-fluoro-1*H*-pyrazole **20** is obtained. Subsequently, 5-diazenyl-1*H*-pyrazole **20** can eliminate nitrogen gas to form 4-fluoro-5-phenylpyrazole **18a**. This unexpected reaction pathway thus provides a new entry toward 4-fluoropyrazoles. Although 2 equiv of hydrazine is consumed during the reaction of β-ketonitriles **14** toward pyrazoles **18**, it proved impossible to increase the yields of pyrazoles **18** by using more than 1 equiv of hydrazine because of the formation of significant amounts of side products.

The scope of the reaction was further expanded by varying the substituent (R) at the 3-position of 2,2-difluoro-3-oxopropanenitriles **14**. The reaction of compounds **14b** and **14c** with 1 equiv of hydrazine gave the corresponding 5-(4-chlorophenyl)- and 5-(4-methylphenyl)-4-fluoropyrazoles **18b** and **18c** in 42−48% yield. Unfortunately, the synthesis of 5-alkylated pyrazole derivatives was more problematic. Difluorinated pivaloyl acetonitrile **14d** proved to be unstable and could not be purified. However, when the crude compound was reacted with hydrazine, 24% of 4-fluoro-5-*tert*-butylpyrazole **18d** was isolated. It should be noted that the analogous reaction of 2-fluoro-2-methyl-3-phenyl-3-oxopropanenitrile with hydrazine also resulted in the formation of 4-methyl-5-phenylpyrazole in 50% yield, while reactions of 2,2-dichloro-3-oxo-3-phenylpropanenitrile with hydrazine did not give the corresponding chlorinated pyrazole (Supporting Information, section III).

In conclusion, it can be stated that new entries were developed toward new fluorinated pyrazoles, a class of compounds with considerable potential as building blocks in medicinal chemistry. As the direct fluorination of pyrazoles is problematic, the reactivity of mono- and difluorinated β-ketonitriles and β-ketoesters with hydrazines toward fluorinated pyrazoles was studied. The monofluorinated β-ketonitrile and β-ketoester reacted with hydrazine affording the corresponding 3-amino-4-fluoropyrazole for the first time and the monofluorinated β-ketoester condensed toward 4-fluoro-3-hydroxypyrazole. The more easily accessible difluorinated β-ketoesters reacted with hydrazines toward new 4,4-difluoropyrazol-5-ones, from which an N−*H* derivative was hydrogenated toward 4-fluoro-3-hydroxypyrazole. Finally, the reaction of difluorinated β-ketonitriles with hydrazine unexpectedly gave rise to new 4-fluoropyrazoles bearing no amino group at C-3, via condensation with hydrazine followed by a hydrazine-mediated reduction.

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Supporting Information Available: General experimental methods and ^{1}H NMR and ^{13}C NMR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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