

Convenient Synthesis of Polyfunctionalized β -Fluoropyrroles from Rhodium(II)-Catalyzed Intramolecular N–H Insertion Reactions

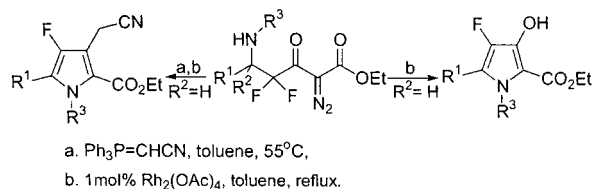
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ABSTRACT



Polyfunctionalized β -fluoropyrrole can be readily prepared from rhodium(II) acetate-catalyzed intramolecular N–H insertion reaction of δ -amino- γ,γ -difluoro- α -diazo- β -ketoesters. A cyanomethylene group can be introduced at C-3 of the pyrrole ring through the Wittig reaction of the diazo compounds followed by rhodium(II)-catalyzed intramolecular N–H insertion reactions.

Replacement of hydrogen by fluorine in biologically active molecules often yields analogues with improved reactivity and selectivity due to the unique physical and chemical properties of fluorine and C–F bond.¹ Polysubstituted pyrroles are highly biologically active molecules and constitute important classes of natural products and synthetic pharmaceuticals,² and certain naturally occurring halopyrroles exhibit a strong antibacterial activity.³ Therefore, it is interesting to introduce fluorine into the pyrrole ring. In fact,

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fluoropyrroles have been shown to be valuable targets for elaboration to porphyrins⁴ and for the preparation of compounds of agricultural and medicinal interest. There have been several methods for synthesizing fluoropyrroles. (a) One method is the introduction of fluorine into a preformed pyrrole either by direct fluorination or by substitution of a functional group. Xenon difluoride was used for direct fluorination at the α -position of a 1-methylpyrrole unit in a drug and was also used for fluorination at the α -position of simple N-H pyrroles bearing electron-withdrawing groups in the α' -position.⁵ The fluorodecarboxylation reaction of α -pyrrole carboxylic acids with F-TEDA- BF_4 gave the corresponding α -fluoropyrroles in mild yields.⁶ β -Fluoropyrrole could also be obtained via a modified Schiemann

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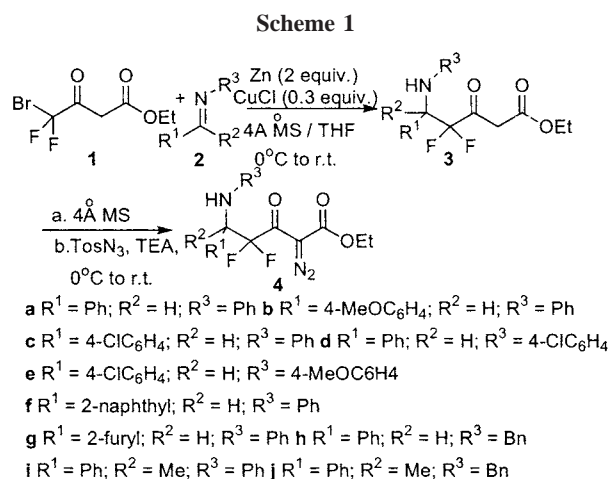
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reaction.⁷ Recently, Barnes and co-workers performed an electrophilic fluorination at the β -position of 1-(triisopropylsilyl)pyrrole and a highly functionalized pyrrole with *N*-fluorobenzenesulfonylimide via their β -lithio derivatives.⁸ (b) Another method is the preparation of an acyclic precursor and its subsequent cyclization. Burton synthesized 2,5-disubstituted β -fluoropyrroles in high yields from the cyclization reaction of α,α -difluoro-iodo ketones under basic conditions.⁹ (c) A third method is a one-step synthesis of fluorinated pyrroles by 1,3-dipolar cycloaddition of fluorine-containing compounds. Thermolysis of aziridine-2-carboxylates in the presence of chlorotrifluoroethylene resulted in 3,4-difluoropyrroles.¹⁰ 1,3-Dipolar reaction of ylide formed from domino reactions of imines with difluorocarbene with electron-deficient alkynes led to 2-fluoropyrrole derivatives.¹¹ However, these methods still suffer from the disadvantage of multistep preparation or limited application. A general synthetic route to fluoropyrroles, particularly to those containing additional functionality appropriate for subsequent formation of biologically interesting molecules, is still not available due to both the high reactivity of pyrroles toward electrophiles and the oxidizing power of electrophilic fluorinating reagents.

With increasing frequency, the intramolecular N–H insertion reaction of diazo compounds catalyzed by a transition-metal provides a powerful strategy for nitrogen heterocyclic synthesis, especially five-membered nitrogen cycles.¹² Here we report a convenient and versatile method for the synthesis of polyfunctionalized β -fluoropyrroles by $\text{Rh}_2(\text{OAc})_4$ -catalyzed intramolecular N–H insertion reaction of difluorinated diazo compounds.

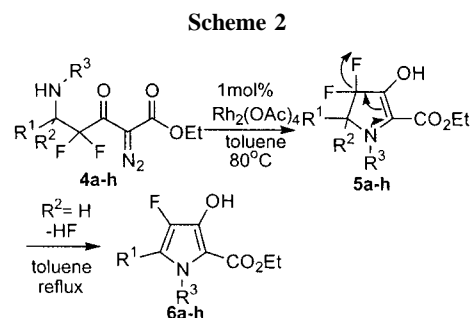
Recently, we reported that the Zn–CuCl-promoted Reformatsky–imine addition reaction of 4-bromo-4,4-difluoroacetoacetate with aldimines provided efficient and practical access to δ -amino- γ,γ -difluoro- β -ketoesters **3a–j** (Scheme 1).¹³ Due to the strong electron-withdrawing ability of



difluoromethylene, the adjacent carbonyl to difluoromethylene in **3a–h** had a marked proclivity for becoming hydrated. A complete dehydration of the substrates could

be obtained by simply treating it with 4 Å molecular sieves in benzene for 1–2 h. Subsequent diazo transfer reaction of **3a–j** with *p*-methylbenzenesulfonyl azide and triethylamine yielded the corresponding δ -amino- γ,γ -difluoro- α -diazo- β -ketoesters **4a–j** in 71 to 90% yields, respectively. All of the diazo compounds **4a–j** were stable to purification by silica gel chromatography.

After treating diazo compounds **4a–h** with 0.5 mol % rhodium(II) acetate in toluene at 80 °C for 30 min, TLC and ¹⁹F NMR indicated the disappearance of the diazo compounds along with formation of two new substrates. The ¹H NMR and ¹⁹F NMR spectra showed that the crude mixtures contained intramolecular N–H insertion products **5a–h** and HF elimination products **6a–h** (Scheme 2). Slow



conversion of **5a–h** into **6a–h** was observed upon standing at room temperature. Moreover, conducting the reaction in refluxing toluene converted **5a–h** to **6a–h** completely within 6–12 h. Thus, in the presence of 0.5 mol % rhodium (II) acetate, **4a–h** were first heated in toluene at 80 °C for 0.5 h, and then the reaction mixtures were refluxed in toluene for another 6–12 h, giving β -fluoropyrroles **6a–h** as the sole products. The reaction time and yields of products **6a–h** are summarized in Table 1. Variation of R¹ and R³ substituents in **4a–h** did not have a great effect on the yields; even diazo compound **4f** with R³ as a bulky 2-naphthyl could generate the corresponding pyrrole **6f** in 80% yield (Table 1, entry 6). However, in the case of the $\text{Rh}_2(\text{OAc})_4$ -catalyzed reaction of **4h** with R³ as a benzyl group, we could not detect the C–H insertion intermediate **5h**, but only the final pyrrole product **6h** (Table 1, entry 7). We assumed that the HF elimination reaction proceeded more quickly in this case than the other diazo compounds with the nitrogen atom substituted by an aryl group since the electron density in the nitrogen

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Table 1. Rh₂(OAc)₄-Catalyzed Intramolecular N–H Insertion Reactions of **4**

entry	4	time (h)	pyrroles 6	yield (%)
1	4a	12	6a	91
2	4b	20	6b	95
3	4c	10	6c	93
4	4d	12	6d	92
5	4e	9	6e	90
6	4f	10	6f	93
7	4g	10	6g	91
8	4h	10	6h	93
9	4i	6		
10	4j	4		

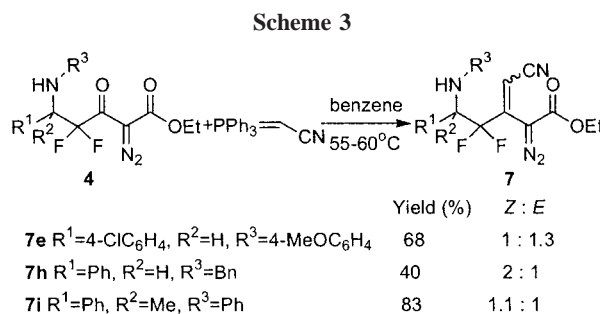
atom of **4h** was less delocalized. The mechanism for pyrrole formation involved insertion of the rhodium carbenoid into the adjacent N–H bond to first produce 4,4-difluoro-5-phenylpyrrolidine-2-carboxylate **5**, which then underwent HF elimination promoted by the lone β -electron pair on the nitrogen atom to yield the final pyrroles. All of the β -fluoropyrroles were stable in air except substrate **6g** with R¹ as a furyl substituent, which gradually became brown upon standing at room temperature. The formation of the β -fluoropyrroles **6a–h** was strongly supported by their NMR spectroscopic data. In particular, the ¹⁹F NMR spectra (282 MHz, CDCl₃) of **6a–h** showed the indicative single peak of a fluorine atom on the pyrrole ring in a narrow range from δ –174 to –179 ppm. The ¹H NMR spectra signal of **6a–h** (300 MHz, CDCl₃) indicated the identical 3-OH at δ 8.23–8.76 ppm. However, the reaction of diazo compounds **4i** and **4j** containing quaternary substitution at C-5 with 1 mol % Rh₂(OAc)₄ in toluene at 80 °C or reflux resulted in a complex mixture of products that could not be characterized. We were unable to identify any of the products, making it impossible to determine whether the products resulted from decomposition of insertion products or the reaction took an entirely different path.

The former rhodium(II)-catalyzed cyclization intramolecular N–H insertion reaction of δ -amino- γ,γ -difluoro- α -diazo- β -ketoesters, however, does not allow the introduction of other substituents except for the hydroxyl group to the C-3 position of the pyrrole ring. To elaborate the utility of this method and introduce more useful functional groups into the pyrrole ring, we further investigated the intramolecular N–H insertion reaction of vinylidiazomethanes. Although the rhodium(II)-catalyzed intermolecular X–H (X = O, N, S, Si, etc.) insertion reactions of vinylidiazomethanes have been previously studied,¹⁴ the intramolecular N–H insertion reaction of vinylcarbenoids has not been reported until now.

The Wittig reaction of diazo ketoesters **4e**, **4h**, and **4i** with Wittig reagent triphenylphosphoranylideneacetonitrile (Ph₃P=CHCN) proceeded readily at 55 °C in toluene, affording

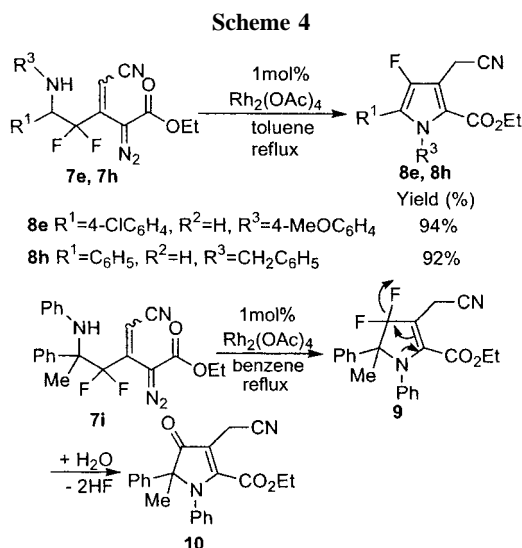
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difluorinated vinylidiazomethanes **7** in medium yields, existing as a mixture of (*Z*)-/(*E*)-isomers of the double bond (Scheme 3). The configuration of the double bond in **7** was



determined by ¹H NMR. The (*Z*)-isomer with difluoromethylene and cyano group on the same side showed the signal of an alkenyl proton at a lower field than that of the (*E*)-isomer.¹⁵ The (*Z*)- and (*E*)-isomer of compound **7i** could be separated by column chromatography.

Treating vinylidiazomethanes **7e** and **7h** (R² = hydrogen atom) with 1 mol % Rh₂(OAc)₄ in refluxing toluene provided 3-cyanomethylene-substituted pyrroles **8e** and **8h** in 94 and 85% yields, respectively (Scheme 4). The assignment of the



structure of **8e** and **8h** was based on their characteristic ¹H NMR and ¹³C NMR spectra. We believe that the reaction proceeded via the insertion of vinylcarbenoids into the N–H bond, double-bond migration into the cycle, and subsequent HF elimination reaction. We also observed that the (*Z*)-isomer of **7** reacted much faster than the (*E*)-isomer. This was usually due to the weaker hindrance of the substituents

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on the double bond of the (*E*)-isomer with the ligands on the catalyst.¹⁶

However, decomposition of **7i** containing quaternary substitution at the 5-carbon in the presence of 1 mol % Rh₂(OAc)₄ gave rise to different results (Scheme 4). After TLC indicated the disappearance of the diazo compounds and removal of the solvent, the ¹H NMR, ¹⁹F NMR, and IR spectra of the crude mixture indicated the formation of pyrrolidine **9**. However, **9** underwent defluorination–hydrolysis reaction leading to **10** when exposed to air or purified by silica gel chromatography. The structure of **10** was determined from its ¹³C NMR, ¹H NMR, and IR spectra and further elucidated by X-ray diffraction (Figure 1). Alkyl

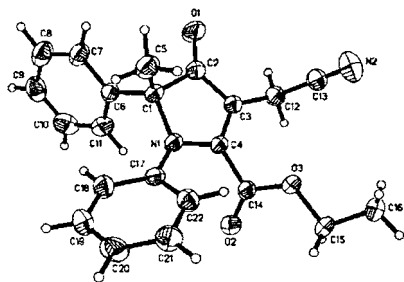


Figure 1.

fluorides are less reactive than other halides and do not react readily in typical nucleophilic displacement reactions because fluorine forms the strongest single bond with carbon and because of the poor stability of fluoride as a leaving group.¹⁷ It is also reported that the β -electron pair on the atom (O, S, N, etc.) or on the double bond could attack from the backside

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to cleave the C–F bond.¹⁸ Therefore, we assumed that **7i** first underwent rhodium (II)-catalyzed intramolecular N–H insertion reaction, giving the difluorinated dihydropyrrole **9**. Then, the lone electron pair on the nitrogen of **9** led to the defluorination–hydrolysis reaction to give final product **10**.

In conclusion, we have demonstrated a concise and efficient synthetic protocol for the synthesis of polyfunctionalized β -fluoropyrrole from the rhodium(II) acetate-catalyzed intramolecular N–H insertion reaction of δ -amino- γ,γ -difluoro- α -diazo- β -ketoesters. The cyanomethylene group was introduced at the C-3 position of the pyrrole ring through the Wittig reaction of the diazo compounds followed by intramolecular N–H insertion reactions. Hydrolysis of difluoromethylene was observed when aromatization by loss of HF was not possible. To our knowledge, the functional substituent on the pyrrole ring could elaborate this kind of compound as the precursors for the synthesis of fluoro-analogues of pharmacophores bearing a pyrrole ring related to the parent compounds.

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

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