ORGANIC LETTERS

2003
Vol. 5, No. 5
745−748

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

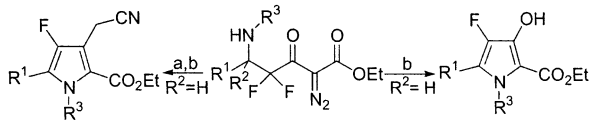
Yanli Wang and Shizheng Zhu*

Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 354 Fenglin Road, Shanghai, 200032, P. R. China

zhusz@pub.sioc.ac.cn

Received December 29, 2002

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, fluoropyrroles have been shown to be valuable targets for elaboration to porphyrins[4] 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

(1) (a) Ramachandran, P. V. In *Asymmetric Fluoroorganic Chemistry: Synthesis, Applications, and Future Directions*; ACS Symposium Series 746; American Chemical Society: Washington, DC, 2000. (b) Ojima, I.; McCarthy, J. R.; Welch, J. T. In *Biomedical Frontiers of Fluorine Chemistry*; ACS Symposium Series 639; American Chemical Society: Washington, DC, 1996. (c) Kukhar', V. P.; Soloshonok, V. A. In *Fluorine-containing Amino Acids: Synthesis and Properties.* Wiley: New York, 1995. (d) Welch, J. T. In *Selective Fluorination in Organic and Bioorganic Chemistry*; ACS Symposium Series 456; American Chemical Society: Washington, DC, 1991. (e) Welth, J. T.; Eswarakrishnan, S. In *Fluorine in Bioorganic Chemistry;* Wiley & Sons: New York, 1991.

(2) (a) Lehuede, J.; Fauconneau, B.; Barrier, L.; Ourakow, M.; Piriou, A.; Vierfond, J.-M. *Eur. J. Med. Chem.* **1999**, *34*, 991. (b) Katritzky, A. R.; Rees, C. W. In *Comprehensive Heterocyclic Chemistry*; Bird, C. W., Cheeseman, G. W. H., Eds.; Pregamon Press: Oxford; Vol. 4, p 370 and references therein.

(3) Koyama, M.; Kodama, Y.; Tsurukoa, T.; Ezaki, N.; Niwa, T.; Inouye, S. *J. Antibiot.* **1981**, *34*, 1569.

(4) (a) Ono, A.; Kawamura, H.; Maruyama, K. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 3386. (b) Ando, A.; Shinada, T.; Kinishita, S.; Arimura, N.; Koyama, M.; Nagai, T.; Miki, T.; Kumadaki, I.; Sato, H. *Chem. Pharm. Bull. Jpn.* **1990**, *38*, 2175.

(5) Wang, J.; Scott, A. I. *Tetrahedron Lett.* **1994**, *35*, 3697.

(6) Wang, J.; Scott, A. I. *J. Chem. Soc., Chem. Commun.* **1995**, 2399.

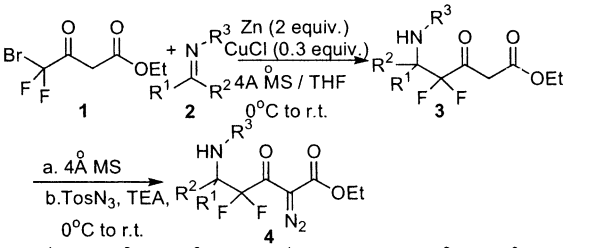
10.1021/ol0275670 CCC: $25.00
Published on Web 02/08/2003

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*-fluorobenzenesulfonimide 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 $Rh_2(OAc)_4$-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

Scheme 1

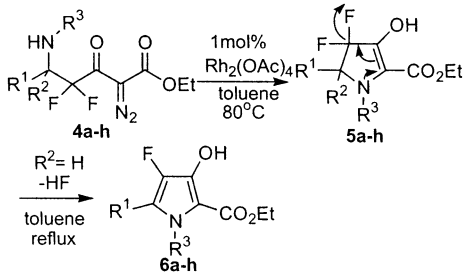


a R^1 = Ph; R^2 = H; R^3 = Ph **b** R^1 = 4-$MeOC_6H_4$; R^2 = H; R^3 = Ph
c R^1 = 4-ClC_6H_4; R^2 = H; R^3 = Ph **d** R^1 = Ph; R^2 = H; R^3 = 4-ClC_6H_4
e R^1 = 4-ClC_6H_4; R^2 = H; R^3 = 4-MeOC6H4
f R^1 = 2-naphthyl; R^2 = H; R^3 = Ph
g R^1 = 2-furyl; R^2 = H; R^3 = Ph **h** R^1 = Ph; R^2 = H; R^3 = Bn
i R^1 = Ph; R^2 = Me; R^3 = Ph **j** R^1 = Ph; R^2 = Me; R^3 = Bn

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 ^{19}F NMR indicated the disappearance of the diazo compounds along with formation of two new substrates. The ^1H NMR and ^{19}F NMR spectra showed that the crude mixtures contained intramolecular N−H insertion products **5a**−**h** and HF elimination products **6a**−**h** (Scheme 2). Slow

Scheme 2



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 R^1 and R^3 substituents in **4a**−**h** did not have a great effect on the yields; even diazo compound **4f** with R^3 as a bulky 2-naphthyl could generate the corresponding pyrrole **6f** in 80% yield (Table 1, entry 6). However, in the case of the $Rh_2(OAc)_4$-catalyzed reaction of **4h** with R^3 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

(7) Onda, H.; Toi, H.; Ogoshi, H. *Tetrahedron Lett.* **1985**, *26*, 4221.
(8) McClinton, M. A.; McClinton, D. A. *Tetrahedron* **1992**, *48*, 6555.
(9) (a) Qiu, Z. M.; Burton, D. J. *Tetrahedron Lett.* **1994**, *35*, 4319. (b) Qiu, Z. M.; Burton, D. J. *Tetrahedron Lett.* **1995**, *36*, 5119.
(10) (a) Leroy, J.; Rubinstein, M.; Wakselman, C. *J. Fluorine Chem.* **1984**, *25*, 255. (b) Leroy, J.; Wakselman, C. *Tetrahedron Lett.* **1994**, *35*, 8605.
(11) Novikov, M. S.; Khlebnikov, A. F.; Sidorina, E. S.; Kostikov, R. R. *J. Chem. Soc., Perkin Trans. 1* **2000**, 231.
(12) (a) Davies, F. A.; Fang, T. N.; Goswami, R. *Org. Lett.* **2002**, *4*, 1599. (b) Honma, T.; Tada, Y.; Adachi, I.; Igarashi, K. *Heterocycles* **1989**, 629. (c) Moyer, M. P.; Feldman, P. L.; Rapoport, H. *J. Org. Chem.* **1985**, *50*, 5223.
(13) Wang, Y. L.; Zhu, S. Z. *Synthesis* **2002**, *13*, 1813.

Table 1. $Rh_2(OAc)_4$-Catalyzed Intramolecular N−H Insertion Reactions of **4**

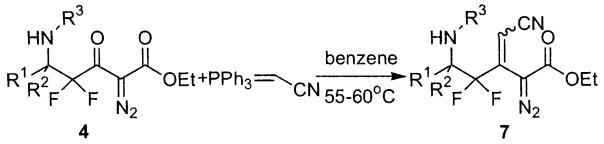
entry	**4**	time (h)	pyrroles **6**	yield (%)
1	**4a**	12	**6a**	91
2	**4b**	20	**6b**	95
3	**4c**	10	**6c**	93
4	**4d**	12	**6d**	92
5	**4e**	9	**6e**	90
6	**4f**	10	**6f**	93
7	**4g**	10	**6g**	91
8	**4h**	10	**6h**	93
9	**4i**	6		
10	**4j**	4		

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 R^1 as a furyl substitutent, 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 ^{19}F NMR spectra (282 MHz, $CDCl_3$) 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, $CDCl_3$) 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 % $Rh_2(OAc)_4$ 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 vinyldiazomethanes. Although the rhodium(II)-catalyzed intermolecular X−H (X = O, N, S, Si, etc.) insertion reactions of vinyldiazoesters 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 (Ph_3P=CHCN) proceeded readily at 55 °C in toluene, affording difluorinated vinyldiazomethanes **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

Scheme 3

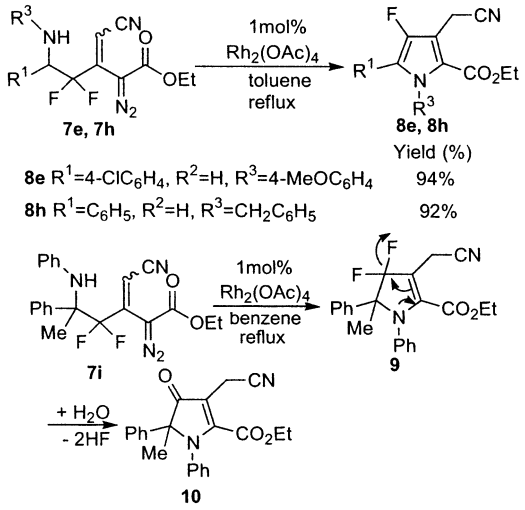


	Yield (%)	*Z* : *E*
7e R^1=4-ClC_6H_4, R^2=H, R^3=4-$MeOC_6H_4$	68	1 : 1.3
7h R^1=Ph, R^2=H, R^3=Bn	40	2 : 1
7i R^1=Ph, R^2=Me, R^3=Ph	83	1.1 : 1

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 vinyldiazomethanes **7e** and **7h** (R^2 = hydrogen atom) with 1 mol % $Rh_2(OAc)_4$ in refluxing toluene provided 3-cyanomethylene-substituted pyrroles **8e** and **8h** in 94 and 85% yields, respectively (Scheme 4). The assignment of the

Scheme 4



structure of **8e** and **8h** was based on their characteristic ^1H NMR and ^{13}C 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

(14) (a) Landais, Y.; Planchenault, D. *Synlett* **1995**, 1191. (b) Davies, H. M. L.; Smith, H. D.; Korkov, O. *Tetrahedron Lett.* **1987**, *28*, 1853. (c) Priyadarshanie, B.; Yannick, L.; Liliana, P.-R.; Denis, P.; Valery, W. *J. Org. Chem.* **1997**, *62*, 1630.

(15) (a) Zhang, X. G.; Qing, F. L.; Yang, Y. G.; Yu, J.; Fu, X. K. *Tetrahedron Lett.* **2000**, *41*, 2953. (b) Allmendinger, T.; Lang, R. W. *Tetrahedron Lett.* **1991**, *32*, 339.

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 % $Rh_2(OAc)_4$ gave rise to different results (Scheme 4). After TLC indicated the disappearance of the diazo compounds and removal of the solvent, the ^{1}H NMR, ^{19}F 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 ^{13}C NMR, ^{1}H NMR, and IR spectra and further elucidated by X-ray diffraction (Figure 1). Alkyl

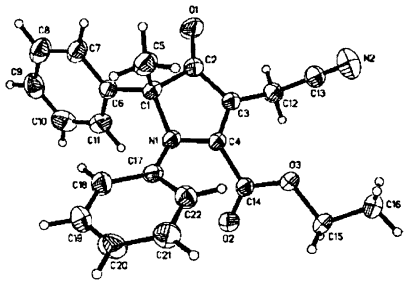


Figure 1.

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 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 dihyropyrrole **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.

Acknowledgment. The authors thank the National Natural Science Foundation of China (NNSFC) (Nos. 20072049 and 20032010) and the Innovation Foundation of Chinese Academy of Sciences for financial support. We thank Nicole J. Bernshaw (CCS, University of Utah) for a critical reading of the manuscript.

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.

OL0275670

(16) Davies, Huw, M. L.; Ahmed, G.; Churchill, M. R. *J. Am. Chem. Soc.* **1996**, *118*, 10774.

(17) (a) Sharts, C. M.; Sheppard, W. A. In *Organic Fluorine Chemistry*; W. A. Benjiamim, Inc.: New York, 1969. (b) Cottrell, T. L. In *The Strengths of Chemical Bonds*, 2nd ed.; Butterloorths Scientific Publications: London, 1958.

(18) (a) Shi, G. Q.; Cai, W. *J. Org. Chem.* **1995**, *60*, 6289. (b) Tdannley, R. L.; Taborsky, R. C. *J. Org. Chem.* **1957**, *22*, 77. (c) Barr, D. A.; Haszeldine, R. N. *J. Chem. Soc.* **1956**, 3416, 3428. (d) Bauks, R. E.; Chang, W. M.; Hazseldine, R. N. *J. Chem. Soc.* **1962**, 3407.