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A novel synthetic route to ethyl 3-substituted-*trans*-2,3-difluoro-2-acrylates and their reactions with nucleophiles

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Abstract

Reaction of a variety of *trans*-1-trimethylsilyl-1,2-difluoroalkenes with ethyl chloroformate in the presence of potassium fluoride gave the corresponding ethyl 3-substituted-*trans*-2,3-difluoro-2-acrylates in good yields, which reacted with a variety of nucleophiles such as hydrazine hydrate, amidines and thiourea etc. in the presence of bases to afford the corresponding 4-fluoropyrazole, 5-fluoropyrimidine and 5-fluoro-2-uracil derivatives in good yields. © 2000 Elsevier Science Ltd. All rights reserved.

Much attention has been given to fluorinated organic compounds both in a theoretical and in a practical sense owing to the characteristic features of fluorine.[1] The introduction of fluorine into organic compounds often leads to enhanced biological activity. The preparation of alkenes fluorinated at selected positions is an important synthetic objective in this area.[2,3] Recently, stereoselective incorporation of a vinylic fluorine into bioactive organic molecules has been shown to increase biological potency compared with their non-fluorinated parent compounds.[4–7] However, methodology for introducing the 1,2-difluoroethylene unit (–CF=CF–) stereoselectively into organic compounds has not received much attention,[8–12] Recently, Burton described the preparation and palladium/CuI catalyzed stereospecific cross-coupling reaction of 1,2-difluorovinylstannanes with aryl iodides and vinyl halides.[13] We now report a novel synthetic route to a variety of ethyl 3-substituted-*trans*-2,3-difluoro-2-acrylates and their reactions with nucleophiles.

A modified literature procedure[11] was utilized to prepare *trans*-(2-alkyl- or 2-aryl-1,2-difluoroethenyl)trimethylsilanes. Trifluorovinyltrimethylsilane, prepared from trimethylsilyl chloride, chlorotrifluoroethylene and *n*-butyl lithium in THF, reacted with a variety of lithium reagents to afford the corresponding addition–elimination products (*trans*>98%) (Scheme 1).

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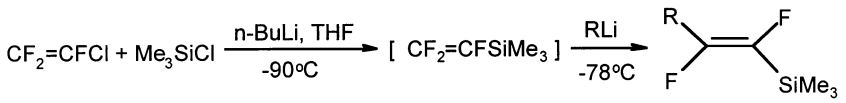
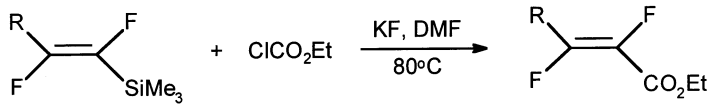


Scheme 1. R = *n*-Bu, *sec*-Bu, *n*-C_5H_{11}, *n*-C_6H_{13}, *n*-C_8H_{17}, Ph, *p*-MeOPh

Hiyama reported the fluoride ion-catalyzed generation and carbonyl addition of *trans*-2-substituted 1,2-difluoroethenyl carbanions from the corresponding *trans*-(2-substituted 1,2-difluoroethenyl)silanes.[14] In place of aldehydes, ethyl chloroformate reacted with *trans*-(2-alkyl- or 2-aryl-1,2-difluoroethenyl)trimethylsilanes in the presence of dry potassium fluoride (1.5–2.0 equiv.) in DMF at 80°C to afford the corresponding esters stereospecifically in good yields. Table 1 summarizes our preliminary results.

Table 1
Preparation of ethyl 3-substituted-*trans*-2,3-difluoro-2-acrylates



Entry	R	Yield(%)[a]
1	*sec*-Bu	62
2	*n*-Bu	66
3	Ph	72
4	*p*-MeOPh	81
5	*n*-C_5H_{11}	67
6	*n*-C_6H_{13}	76
7	*n*-C_8H_{17}	71

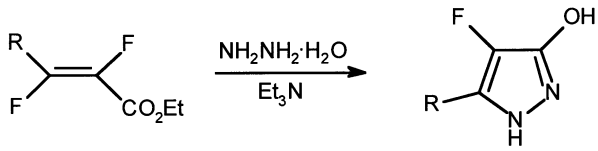
[a] Isolated yields based on the corresponding silanes.

As α,β-unsaturated esters, ethyl 3-substituted-*trans*-2,3-difluoro-2-acrylates can undergo Michael addition reactions with nucleophiles such as thiophenol, sodium azide etc. followed by elimination of the β-fluorine to give addition–elimination products.[15] Consequently, a new synthetic route to monofluorinated heterocyclic compounds could be envisaged if reagents with two nucleophilic centers were employed.

Hydrazine monohydrate was selected first to react with ethyl 3-substituted-*trans*-2,3-difluoro-2-acrylates. In the presence of triethylamine, ethyl *trans*-2,3-difluoro-2-heptenoate reacted with a small excess of hydrazine monohydrate in ethanol at room temperature. The reaction was monitored by TLC and ^{19}F NMR. After the starting material disappeared, the reaction mixture was worked up and purified on a silica gel column to give the corresponding 3-hydroxy-4-fluoro-5-pentylpyrazole in a yield of 80%. The structure was confirmed by ^{1}H NMR, ^{19}F NMR, IR and HRMS. Table 2 summarizes the preliminary results.

Similarly, treatment of ethyl 3-substituted-*trans*-2,3-difluoro-2-acrylates with acetamidine hydrochloride and benzamidine hydrochloride, respectively, in the presence of potassium carbonate in 1,4-dioxane afforded the corresponding 5-fluoropyrimidine derivatives in good yield. The preliminary results are listed in Table 3.

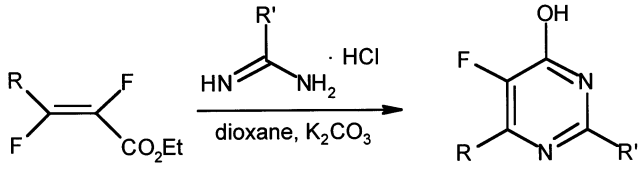
Table 2
Preparation of 4-fluoropyrazole derivatives



Entry	R	Yield(%)[a]
1	*sec*-Bu	76
2	*n*-Bu	75
3	*n*-C_5H_{11}	80
4	*n*-C_8H_{17}	78

[a] Isolated yield based on ethyl 3-substituted-*trans*-2,3-difluoro-2-acrylates.

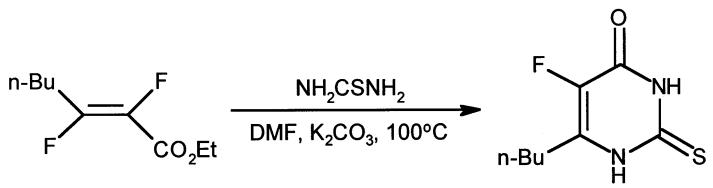
Table 3
Synthesis of 5-fluoropyrimidine derivatives



Entry	R	R′	Yield(%)[a]
1	*sec*-Bu	CH_3	87
2	*n*-C_5H_{11}	CH_3	85
3	*n*-C_6H_{13}	CH_3	76
4	Ph	CH_3	71
5	*p*-MeOPh	CH_3	92
6	*n*-C_8H_{17}	CH_3	89
7	*sec*-Bu	CH_3	84
8	*n*-Bu	Ph	89
9	*n*-C_5H_{11}	Ph	91
10	*n*-C_6H_{13}	Ph	83
11	Ph	Ph	88
12	*p*-MeOPh	Ph	81
13	*n*-C_8H_{17}	Ph	89
14	*sec*-Bu	Ph	93

[a] Isolated yields based on ethyl 3-substituted-*trans*-2,3-difluoro-2-acrylates.

When thiourea was employed in the above reaction, the corresponding 6-*n*-butyl-5-fluoro-2-thiouracil was obtained in 68% yield (Scheme 2).



Scheme 2.

In conclusion, we have developed a new and convenient method for the synthesis of ethyl 3-substituted-*trans*-2,3-difluoro-2-acrylates, which can further react with a variety of nucleophiles such as hydrazine hydrate, amidines and thiourea etc. to afford the corresponding 4-fluoropyrazole, 5-fluoropyrimidine and 5-fluoro-2-uracil derivatives in good yield.

Acknowledgements

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References

1. (a) In *Biochemical Aspects of Fluorine Chemistry*; Filler, R.; Kobayashi, Y., Eds.; Elsevier Biomedical Press and Kodansha Ltd: Tokyo, 1982. (b) Welch, J. T. *Tetrahedron* **1987**, *43*, 3123. (c) In *Selective Fluorination in Organic and Bioorganic Chemistry*; Welch, J. T., Ed.; ACS Symposium Series, 1991; No. 456.
2. (a) Sun, W. C.; Ng, C. S.; Prestwich, G. D. *J. Org. Chem.* **1992**, *57*, 132 and references cited therein. (b) Masnyk, M.; Fried, J.; Roelofs, W. *Tetrahedron Lett.* **1989**, *30*, 3243. (c) Kwok, P. Y.; Muellner, F. W.; Chen, C. K.; Fried, J. *J. Am. Chem. Soc.* **1987**, *109*, 3684.
3. (a) Briggs, G. C.; Cayley, G. R.; Dawson, G. W.; Griffiths, D. C.; Macaulay, E. D. M.; Pickett, J. A.; Pile, M. M.; Wadhams, L. J.; Woodcock, C. M. *Pestic. Sci.* **1986**, *17*, 441. (b) Buist, P. H.; Findlay, J. M.; Leger, G.; Pon, R. A. *Tetrahedron* **1987**, *28*, 3891.
4. (a) Camps, F.; Coll, J.; Fabrias, G.; Guerrero, A. *Tetrahedron* **1984**, *40*, 2871. (b) Camps, F.; Fabrias, G.; Guerrero, A. *Tetrahedron Lett.* **1986**, *42*, 3623.
5. (a) Taguchi, T.; Takigawa, T.; Kobayashi, Y.; Tanaka, Y.; Jubiz, W.; Briggo, R. G. *Chem. Pharm. Bull.* **1987**, *37*, 1666. (b) Ducep, J.-B.; Nave, J. F.; Zimmermann, P. R. *Bioorg. Med. Chem.* **1994**, *2*, 213.
6. (a) McCarthy, J. R.; Mattews, D. P.; Stemerick, D. M.; Huber, E. W.; Bey, P.; Lippert, B. J.; Snyder, R. D.; Sunkara, P. S. *J. Am. Chem. Soc.* **1991**, *113*, 7439 and references cited therein. (b) Mattews, D. P.; Miller, S. C.; Jarri, E. T.; Sabol, J. S.; McCarthy, J. R. *Tetrahedron Lett.* **1993**, *34*, 3057.
7. (a) Eddarir, S.; Francesch, C.; Mestdagh, H.; Rolando, C. *Tetrahedron Lett.* **1990**, *31*, 4449. (b) Eddarir, S.; Mestdagh, H.; Rolando, C. *Tetrahedron Lett.* **1991**, *32*, 69.
8. (a) Normant, J. F. *J. Organomet. Chem.* **1990**, *400*, 19 and references cited therein. (b) Tellier, F.; Sauvetre, R.; Normant, J.-F. *J. Organomet. Chem.* **1989**, *364*, 17.
9. (a) Xue, L.; Lu, L.; Pederson, S.; Liu, Q.; Narske, R.; Burton, D. J. *Tetrahedron Lett.* **1996**, *37*, 1921. (b) Xue, L.; Lu, L.; Pederson, S.; Liu, Q.; Narske, R.; Burton, D. J. *J. Org. Chem.* **1997**, *62*, 1064.
10. (a) Asato, A. E.; Liu, R. S. H. *Tetrahedron Lett.* **1986**, *27*, 3337. (b) Bildstein, S.; Ducep, J.-B.; Jacob, D.; Zimmermann, P. R. *Tetrahedron Lett.* **1996**, *37*, 4941.
11. Martinet, P.; Sauvetre, R.; Normant, J. F. *Bull. Soc. Chim. Fr.* **1990**, 86.
12. Kuroboshi, M.; Yamada, N.; Takebe, Y.; Hiyama, T. *Tetrahedron Lett.* **1995**, *36*, 6271.
13. Lu, L; Burton, D. J. *Tetrahedron Lett.* **1997**, *38*, 7673 and references cited therein.
14. Fujita, M.; Obayashi, M.; Hiyama, T. *Tetrahedron* **1988**, *44*, 4135.
15. Zhang, Q. S.; Lu, L., to be published.