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# FACILE SYNTHESES OF FLUORINE-CONTAINING α,β-UNSATURATED ACIDS AND ESTERS FROM 2-TRIFLUOROMETHYLACRYLIC ACID

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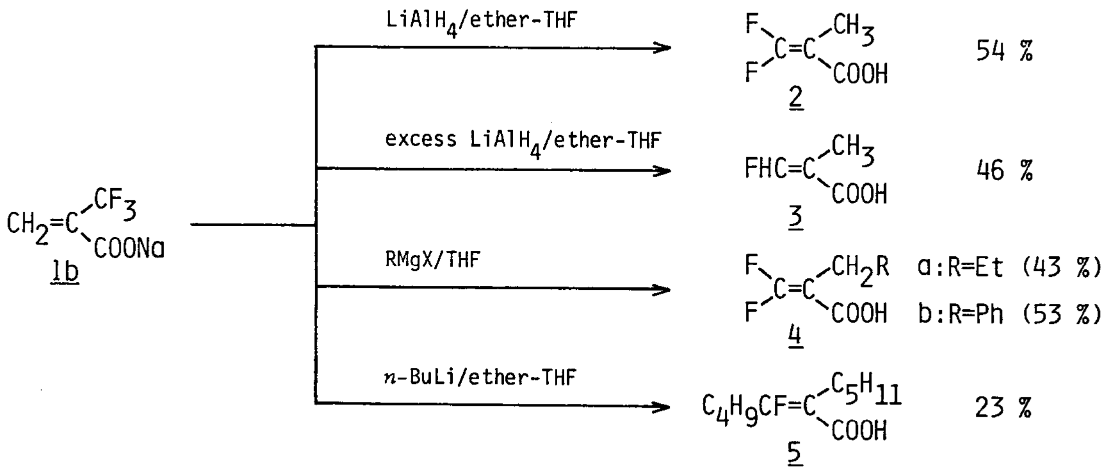
*Abstract: Various types of fluorine-containing* α,β-*unsaturated acids and their esters were synthesized from 2-trilfuoromethylacrylic acid as a sole starting material.*

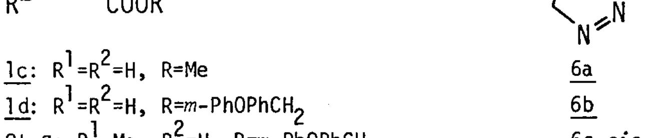
Recently, organofluorine compounds have attracted many attentions of investigators in various fields, such as medicine,$^{1)}$ herbicide,$^{2)}$ and polymer,$^{3)}$ for their unique physiological and physical properties. As building blocks for their syntheses, fluorine-containing α,β-unsaturated acids and esters should be one of the most hopeful candidates because of their facilities of functionalizations.$^{4)}$ Indeed, we have already shown that 5-fluorouracils$^{5)}$ and 5-trifluoromethyluracils,$^{6)}$ being well-known potent antitumor agents, can be readily synthesized from 2,3,3-trifluoro- and 2-trifluoromethyl-acrylic acids, respectively. However, difficulties for procurement of the desired α,β-unsaturated compounds have impeded the progress in this line. In this communication, we will describe convenient preparations of various types of fluorine-containing α,β-unsaturated acids and esters from a sole starting material, 2-trifluoromethylacrylic acid (**1a**).$^{6a)}$

Although soft nucleophiles such as ureas$^{6a)}$, alcohols, and amines easily add to carbon-carbon double bond of 2-trifluoromethylacrylic acid or ester to give the corresponding adducts, hard ones bring about $S_N2'$ type substitution



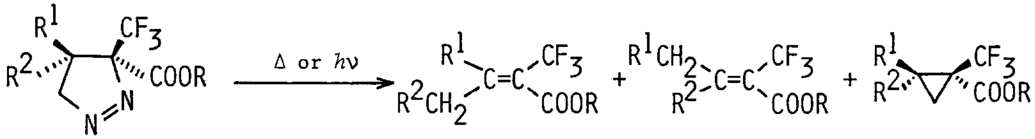
reactions. Thus, 3,3-difluoroacrylic acid (**2**) was synthesized in 54 % yield from sodium 2-trifluoromethylacrylate (**1b**) on using 1/4 molar equivalent of lithium aluminum hydride in ether at -78°C. Compound **2** could undergo further reduction by the action of excess of $LiAlH_4$ giving 3-fluoromethacrylic acid (**3**) in 46 % yield from **1b**, probably proceeding *via* the addition-elimination mechanism. Similarly, the reaction of **1b** with Grignard reagent such as ethylmagnesium bromide or phenylmagnesium chloride gave 2-propyl- or 2-benzyl-3,3-difluoroacrylic acid (**4a** or **4b**) in 43 % or 53 % yield, respectively. While, 2-pentyl-3-fluoro-2-heptenoic acid (5) was a main product (23 %) even when one equivalent of butyllithium was used. This shows that butyllithium reacts more easily with initially formed sodium 2-pentyl-3,3-difluoroacrylate than with **1b**.

In the course of our study for the preparation of methyl 2-trifluoromethylacrylate by the reaction of acid **1a** with diazomethane, we found that the addition of 2 equivalents of diazomethane was required until color of yellow in the reaction mixture did not fade out any longer, and thus 1-pyrazoline derivative **6a** was obtained in 93 % isolated yield. It is confirmed by the detailed studies on the reaction course that one equivalent of diazomethane reacts first with carboxylic acid function of compound **1a** to form methyl 2-trifluoromethylacrylate (**1c**), which can be isolated in 76 % yield, followed by undergoing 1,3-dipolar cycloaddition of an additional diazomethane to carbon-carbon double bond of **1c**. Accordingly, *m*-phenoxybenzyl ester (**6b**) of 1-pyrazoline can be prepared form *m*-phenoxybenzyl 2-trifluoromethylacrylate (**1d**) and 1 equivalent of diazomethane, and other 4-substituted ones were also done from the corresponding acrylates (**8b, c,** and **f**) (*vide infra*) quantitatively, except for 4,4-dimethyl-1-pyrazoline **6d** (conv. 69 %, yield 56 %). However, our attempt to get 5-substituted 1-pyrazoline derivative by the reaction of **1d** with *p*-chlorophenyldiazomethane resulted in the formation of a mixture of olefins, (*E*)-4-(*p*-chlorophenyl)-2-trifluoromethyl-3-butenoate (**7**), and (*E*)- and (*Z*)-4-(*p*-chlorophenyl)-2-trifluoromethyl-2-butenoates (**8f**-*E* and *Z*), in a ratio of 50:17:33.



| | |
|---|---|
| 1c: $R^1=R^2=H$, R=Me | 6a |
| 1d: $R^1=R^2=H$, R=*m*-$PhOPhCH_2$ | 6b |
| 8b-*Z*: $R^1=Me$, $R^2=H$, R=*m*-$PhOPhCH_2$ | 6c-*cis* |
| 8b-*E*: $R^1=H$, $R^2=Me$, R=*m*-$PhOPhCH_2$ | 6c-*trans* |
| 8c: $R^1=R^2=Me$, R=*m*-$PhOPhCH_2$ | 6d |
| 8f-*Z*: $R^1$=*p*-Cl-$PhCH_2$, $R^2=H$, R=*m*-$PhOPhCH_2$ | 6e-*cis* |
| 8f-*E*: $R^1=H$, $R^2$=*p*-Cl-$PhCH_2$, R=*m*=$PhOPhCH_2$ | 6e-*trans* |

Next, we have investigated thermal and photochemical decompositions of 1-pyrazolines **6a**-**e** obtained here (Table 1). Thermolysis of 4-unsubstituted 1-pyrazolines **6a** and **6b** in refluxing toluene gave 2-trifluoromethyl-2-butenoates (**8a** and **b**) in 93 to 98 % yields, and no formation of cyclopropane derivatives (Type C) was detected. *E*/*Z* ratios of **8a** and **8b** are found to be 86/14 and 70/30, respectively, indicating that methylene inserts more readily into C-H bond *trans* (Type A) than *cis* (Type B) to trifluoromethyl group. In the reaction of 4-Me substituted 1-pyrazolines (**6c**-*cis* and *trans*), dramatic change of the products according to the stereochemistry of starting compounds was



6a-e Type A Type B Type C

Table 1. Thermolysis and Photolysis of 1-Pyrazolines (6a-e)

| Compound | $R^1$ | $R^2$ | R | Conditions | Yield (%) | Product and selectivity (%) of Types A, B, and C | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | Type A | Type B | Type C |
| 6a | H | H | Me | toluene/reflux, 1 h | 93 | 8a-*E*<br>(86) | 8a-*Z*<br>(14) | |
| 6b | H | H | PB[a] | toluene/reflux, 1 h | 98 | 8b-*E*<br>(70) | 8b-*Z*<br>(30) | |
| | | | | *h*ν (benzene), 45 h | 90 | 8b-*E*<br>(27) | 8b-*Z*<br>(32) | 9a<br>(41) |
| 6c-*cis* | Me | H | PB[a] | xylene/reflux, 4 h | 86 | 8c<br>(100) | | |
| | | | | *h*ν (benzene), 44 h | 90 | 8c<br>(9) | 8d-*Z*<br>(27) | 9b-*cis*<br>(64) |
| 6c-*trans* | H | Me | PB[a] | xylene/reflux, 4 h | 89 | 8d-*E*<br>(24) | 8c<br>(35) | 9b-*trans*<br>(41) |
| | | | | *h*ν (benzene), 47 h | 93 | 8d-*E*<br>(44) | 8c<br>(5) | 9b-*trans*<br>(51) |
| 6d | Me | Me | PB[a] | xylene/reflux, 10 h | 41<br>(conv. 54 %) | 8e-*E*<br>(54) | | 9c<br>(46) |
| 6e-*cis* | CB[b] | H | PB[a] | *h*ν (benzene), 24 h | 95 | | 8g-Z<br>(23) | 9d-*cis*<br>(77) |
| 6e-*trans* | H | CB[b] | PB[a] | *h*ν (benzene), 47 h | 75 | 8g-*E*<br>(28) | | 9d-*trans*<br>(72) |

[a] PB=*m*-PhOPh$CH_2$. [b] CB=*p*-Cl-Ph$CH_2$.

observed. Thermolysis of *cis* isomer affords 3-methyl-2-trifluoromethyl-2-butenoate **8c** (Type A) in 86 % yield as single product, while that of *trans* one giving a mixture of cyclopropane carboxylate **9b**-*trans* (Type C) and α,β-unsaturated esters (**8c** and **8d**-*E*) (Types B and A) in the ratio of 41:35:24. The insertion of methylene into *trans* C-C bond (54 % selectivity) and the formation of cyclopropane ring (46 % selectivity) also took place in the thermal reaction of 4,4-dimethyl derivative **6d**. These results show us that the facility of methylene insertions at 4-position is in the order of *trans* C-H > *cis* C-H > *trans* C-C >> *cis* C-C under these thermal conditions, and that the presence of the substituent at 4-*trans* position of 1-pyrazolines brings about the competitive cyclopropanation reaction (Type C).

On the other hand, Type C reaction is a main pathway in photolytic decomposition of all of these 1-pyrazolines (**6a-e**). Thus, cyclopropane carboxylates (**9a-d**) were obtained in 41 to 77 % selectivities by external irradiation in benzene solution through Pyrex filter using high-pressure Hg lamp (450 W). It was found that bulkiness at 4-position increases the selectivity of Type C. Moreover, the reversed selectivities of methylene insertions (Type A *vs*. Type B) were observed in the photolysis of compounds **6b**, **6c**-*cis* and *trans*. And methylene inserts more readily into C-C bond than C-H bond. Therefor, the order of the facilities of methylene insertions under these photolytic conditions turns out to be *trans* C-C > *cis* C-C > *cis* C-H > *trans* C-H bond.

As shown here, we have demonstrated that 2-trifluoromethylacrylic acid is a quite useful building block for the synthesis of a variety of fluorine-containing α,β-unsaturated carbonyl compounds, and further functionalizations of these compounds are now in progress.

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