Chinese Chemical Letters Vol. 16, No. 10, pp 1293-1296, 2005 1293
http://www.imm.ac.cn/journal/ccl.html

Design and Synthesis of Novel Fluorine-containing Acrylates

Yan Chao WU, Chao WU, Xiao Mao ZOU, Fang Zhong HU, Hua Zheng YANG*

State Key Laboratory of Element-Organic Chemistry, Institute of Element-Organic Chemistry, Nankai University, Tianjin 300071

Abstract: A series of novel fluorine-containing acrylates **6a-6g** were synthesized *via* the condensation of ethyl cyanoacetate and trifluoroacetic anhydride, followed by chloridization and the coupling reaction with amines. These new compounds exhibited some biological activity as preliminary bioassay indicated. A plausible reaction mechanism was outlined and discussed.

Keywords: Fluorine-containing compound, acrylates, synthesis.

It has been known that introduction of fluorine atom in molecule may lead to significant influence on the biological and physical properties of compounds due to increase of membrane permeability, hydrophobic binding, stability against metabolic oxidation, *etc*[1]. Since fluorine is virtually absent in the living tissue, fluorine-containing compounds are expected to serve as important and useful bioactive compounds for medicinal chemistry and chemical biology[2]. Therefore the development of synthetic methods for fluorine-containing compounds has been an important field in both organofluorine chemistry and organic synthesis.

Acrylates representing an important class of organic compounds are widely used as important intermediates in organic synthesis due to the chemical versatility of the acrylate moiety, and are attracted considerable attention[3,4]. They display some biological and pharmaceutical activities too[5], for example, the compounds with general structure **1** (**Scheme 1**) revealed that cyanoacrylates are inhibitors of photosystem II (PSII) electron transport, which inhibit the growth of weeds by disrupting photosynthetic electron transport at a common binding domain on the 32 kD polypeptide of the PSII reaction center[6].

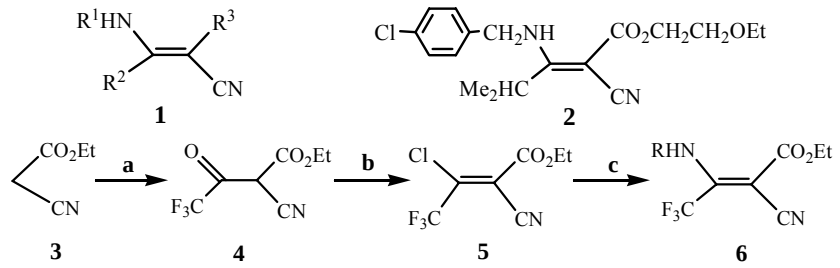
Among these cyanoacrylates, 3-(4-chlorobenzyl) amino-2-cyano-3-isobutylacrylate **2** (**Scheme 1**) exhibits the highest inhibitory activity of the Hill reaction[5]. Moreover, 3-aminoacrylates can also be hydrogenated into β-amino acids derivatives, which have extensive application in life sciences as components of biologically active peptides and small-molecule pharmaceuticals[7]. To the best of our knowledge, there are no reports involving the synthesis of 3-benzyl (or phenyl) amino-2-cyano-3-trifluoromethyl-acrylates. So we interested in the facile synthetic method for this kind of fluorine-

* E-mail: nk_yanghz@126.com

containing compounds. The condensation of ethyl cyanoacetate **3** and trifluoroacetic anhydride in the presence of triethylamine gave ethyl 2-cyano-4,4,4-trifluoro-3-oxobutanoate **4**, and ethyl 3-chloro-2-cyano-4,4,4-trifluorobut-2-enoate **5** was obtained by the chloridization of compound **4** with oxalyl chloride. The coupling reaction of compound **5** with benzyl (or phenyl) amines gave fluorine-containing acrylates **6a-6g** (**Scheme 1**).

Various benzyl (or phenyl) amines were examined to investigate the scope and limitation of this coupling reaction. As **Table 1** indicated, the yields were better when benzylamines bearing weak electron-withdrawing groups, such as halogen in comparison with unsubstituted benzylamine (entry 1-3), and high yields were obtained when 1-methylphenylamine or R-(+)-1-methylphenylamine was used (entry 4-5). Using 2-pyridylmethylamine (entry 6) caused decrease in the yield. High yields were obtained when phenylamines bearing strong electron-donating groups such as 4-chlorophenoxy (entry 7), but the reaction failed to give any product when phenylamines bearing strong electron-withdrawing groups such as nitro (entry 8). These results indicated that these coupling reactions highly depended upon the nature of the substituent of amines: These coupling reactions preferred to the benzylamines bearing weak electron-withdrawing groups or phenylamines bearing strong electron-donating groups.

Scheme 1

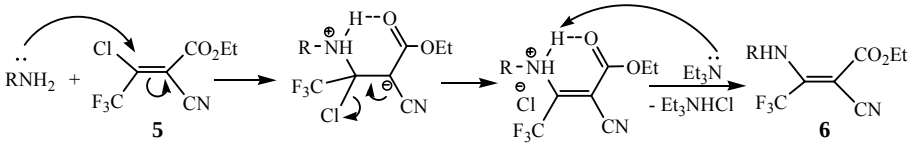


a. TFAA, Et_3N, CH_2Cl_2, 0°C; b. Oxalyl chloride, CH_2Cl_2, reflux; c. RNH_2, CH_2Cl_2, Et_3N.
6a. R = benzyl; **6b**. R = 4-fluorobenzyl; **6c**. R = 4-chlorobenzyl; **6d**. R = 1-phenylethyl;
6e. R = R- (+)-1-phenylethyl; **6f**. R = 2-pyridylmethyl; **6g**. R = 4-(4-chlorophenoxy) benzyl

Table 1 Synthesis of acrylates *via* coupling of compound **5** with benzyl (or phenyl) amines

Entry	R	Time(h)	Product	m.p. (°C)	Yield (%)
1	benzyl	12	**6a**	59-60	76.5
2	4-fluorobenzyl	10	**6b**	97-98	89.8
3	4-chlorobenzyl	10	**6c**	50-52	83.6
4	1-methylphenyl	8	**6d**	33-34	91.0
5	R- (+)-1-methylphenyl	8	**6e**	41-43	91.3
6	2-pyridinemethyl	12	**6f**	102-103	75.7
7	4-(4-chlorophenoxy)benzyl	12	**6g**	67-69	96.4
8	4-nitrobenzyl	24	-	-	0

Scheme 2 Proposed mechanism of the coupling reaction



A possible reaction mechanism is outlined in **Scheme 2**, according to the published paper[5]. These coupling reactions can be understood as a three-step process including β-amine addition, β-chlorine elimination and neutralization. *Syn*-products were formed predominantly, because of the chelation of oxygen to hydrogen in the transformation[5, 6]. The following reaction mechanism might be proposed: when benzylamines bearing strong electron-withdrawing groups such as nitro, the density of electron cloud of amines is thin and the nucleophilic ability is weak, so β-amine addition is difficult to take place. If the density of electron cloud of amines is too thick, its strong nucleophilic ability is disadvantageous for neutralization in the third step. So the moderate electron cloud density of amines is highly advantageous to these coupling reactions as illustrated in **Table 1**.

Preliminary bioassay test indicated these compounds exhibited some biological activities. Compound **6c** and **6d** against rape at 100 ppm are 62.3% and 64.8%, respectively. Compound **6b** and **6e** against barnyard grass at 100 ppm are 54.0% and 51.5%, respectively. Studies on other biological and pharmaceutical activities, structure modifications, as well as synthetic applications of this new strategy are in progress in our laboratory.

Acknowledgment

The project supported by the National Natural Science Foundation of China (No.20172031) and the Chinese Research Fund for the Doctoral Program of High Education.

References and Notes

1. L. Kuznetsova, M. I. Ungureanu, A. Pepe, *et al.*, *J. Fluorine Chem*., **2004**, *125*, 415.
2. S. C. O'Hagan, S. L. Cobb, J.T.G. Hamilton, D. Cormac, C.D. Murphy, *Nature,* **2002**, *416*, 279.
3. J. J. Kang, S. B. Fang, *Chin. Chem. Lett*., **2004**, *15*, 87.
4. T. Qiu, L. M. Tang, X. L. Tuo, D. S. Liu, *Chin. Chem. Lett*., **2004**, *15*, 931.
5. Q. Wang, H. Sun, H. Cao, M. Cheng, R. Huang, *J. Agric. Food Chem*., **2003**, *51*, 5030.
6. H. Liu, Y. Sha, H. Tan, H. Yang, *Sci. China Ser., B* **1999**, *42*, 326.
7. Y. Hsiao, N. R. Rivera, T. Rosner, *et al.*, *J. Am. Chem. Soc*., **2004**, *126*, 9918.
8. **5:** Yield: 58.1%; ^{1}H NMR (200MHz, $CDCl_3$, δ_{ppm}): 1.37 (t, 3H, *J* = 6.92 Hz), 4.39 (q, 2H, *J* = 6.92 Hz).
   6a: ^{1}H NMR (200MHz, $CDCl_3$, δ_{ppm}): 1.32 (t, 3H, *J* = 7.02 Hz), 4.26 (q, 2H, *J* = 7.02 Hz), 4.61 (d, 2H, *J* = 5.77 Hz), 7.25-7.37 (m, 5H), 10.05 (s, 1H); Anal. Calcd. for $C_{14}H_{13}F_3N_2O_2$: C, 56.38; H, 4.39; N, 9.39. Found: C, 56.26; H, 4.20; N, 9.45.
   6b: ^{1}H NMR (200MHz, $CDCl_3$, δ_{ppm}): 1.31 (t, 3H, *J* = 7.04 Hz), 4.21 (q, 2H, *J* = 7.04 Hz), 4.57 (d, 2H, *J* = 5.63 Hz), 7.07-7.84 (m, 4H), 10.04 (s, 1H); MS (EI): *m/z* 316 (M^+) (39%), 270 (5%), 203 (3%), 109 (100%), 83 (39%), 29 (20%); Anal. Calcd. for $C_{14}H_{12}F_4N_2O_2$: C, 53.17;

H, 3.82; N, 8.86. Found: C, 53.17; H, 4.02; N, 8.83.

6c: ^{1}H NMR (200MHz, $CDCl_3$, δ_{ppm}): 1.32 (t, 3H, *J* = 6.82 Hz), 4.24 (q, 2H, *J* = 6.82 Hz), 4.61 (d, 2H, *J* = 5.89 Hz), 7.21 (d, 2H, *J* = 8.54 Hz), 7.37 (d, 2H, *J* = 8.54 Hz), 10.40 (s, 1H); Anal. Calcd. for $C_{14}H_{12}ClF_3N_2O_2$: C, 50.54; H, 3.64; N, 8.42. Found: C, 50.58; H, 3.71; N, 8.34.

6d: ^{1}H NMR (200MHz, $CDCl_3$, δ_{ppm}): 1.34 (t, 3H, *J* = 7.35 Hz), 1.59 (d, 3H, *J* = 6.62 Hz), 4.28 (q, 2H, *J* = 7.35 Hz), 4.94 (m, 1H), 7.22-7.37 (m, 5H), 10.70 (s, 1H); Anal. Calcd. for $C_{15}H_{15}F_3N_2O_2$: C, 57.69; H, 4.84; N, 8.97. Found: C, 57.62; H, 4.64; N, 8.88.

6e: ^{1}H NMR (200MHz, $CDCl_3$, δ_{ppm}): 1.33 (t, 3H, *J* = 6.98 Hz), 1.59 (d, 3H, *J* = 6.65 Hz), 4.28 (q, 2H, *J* = 6.98 Hz), 4.93 (m, 1H), 7.21-7.37 (m, 5H), 10.70 (s, 1H); Anal. Calcd. for $C_{15}H_{15}F_3N_2O_2$: C, 57.69; H, 4.84; N, 8.97. Found: C, 57.74; H, 4.92; N, 8.97.

6f: ^{1}H NMR (200MHz, $CDCl_3$, δ_{ppm}): 1.35 (t, 3H, *J* = 6.91 Hz), 4.33 (q, 2H, *J* = 6.91 Hz), 4.87 (s, 2H), 7.24-8.68 (m, 4H), 11.02 (s, 1H); Anal. Calcd. for $C_{13}H_{12}F_3N_3O_2$: C, 52.18; H, 4.04; N, 14.04. Found: C, 51.95; H, 4.15; N, 14.10.

6g: ^{1}H NMR (200MHz, $CDCl_3$, δ_{ppm}): 1.37 (t, 3H, *J* = 7.01 Hz), 4.34 (q, 2H, *J* = 7.01 Hz), 7.34-7.93 (m, 8H), 11.05 (s, 1H); IR (KBr) 3027, 2215, 1671, 1614, 1540, 1502, 1382, 1249, 1226, 1195, 1157, 1082, 1021, 817, 787, 598, 490 cm^{-1}; Anal. Calcd. for $C_{19}H_{14}ClF_3N_2O_3$: C, 55.55; H, 3.44; N, 6.82. Found: C, 55.52; H, 3.57; N, 6.77.

Received 9 December, 2004