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3-Polyfluoroalkyl-substituted *E*-cinnamic acids: easy access via Perkin reaction

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Abstract—3-Polyfluoroalkyl-(*E*)-cinnamic acids being very useful building blocks were obtained by a simple and convenient one-step procedure. The Perkin type reaction of fluoroacyl-substituted arenes gives the titled compounds in good yields and excellent stereoselectivity independent on the electronic nature of substituents in the aromatic ring. In the case of fluoroalkyl–alkylketones only *O*-acylation occures under the same conditions.
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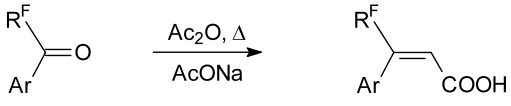
Replacement of hydrogen by the fluorine atoms often changes dramatically the physical and chemical properties of derived compounds, increasing their attractivity for diverse practical applications. Indeed, fluorinated substances have already become indispensable in many fields of modern agrochemistry, pharmaceutical industry and material sciences.[1] Therefore methods of the regio- and stereoselective synthesis of fluorinated compounds being at the same time efficient, economically realistic and suitable for scale up remain a significant challenge for organic chemists. Along with procedures for the direct fluorination or fluoroalkylation a building-block strategy is broadly applied. One of the important trifluoromethyl-containing 1,3-dielectrophilic building blocks is 3-trifluoromethylcinnamic acid. The wide use of this compound in the synthesis of biologically active compounds[2] is the reason of intensive search for satisfactory synthetic routes to acids of this type. The key point of the approaches mostly often applied involves the C^2–C^3 bond formation via well-known organic constructive transformations of fluorinated acetophenones: Wittig[2a] or Horner–Wadsworth–Emmons olefinations,[2b,c] Claisen condensation[3] and Reformatsky reaction.[4] These methodologies often have significant drawbacks: in many cases the stereoselectivity of condensation and yields of the product are low.

Table 1. Synthesis of *E*-cinnamic acids **2**



1 **2**

Entry	**1**, **2**	R^F	Ar	^{19}F NMR yield of **2** (%)	Isolated yield of **2** (%)	*E*:*Z* ratio[a]	Mp (°C) of **2**
1	**a**	CF_3	3-$CF_3C_6H_4$	82	75	91:9	76–77
2	**b**[6]	CF_3	4-ClC_6H_4	95	78	95:5	84–88
3	**c**	CF_3	Ph	93	67	93:7	95–97[b]
4	**d**	CF_3	4-MeC_6H_4	93	81	93:7	88–89
5	**e**	CF_2Cl	Ph	90	46	100:0	102–103

[a] Ratio of stereoisomers in reaction mixture, determined by ^{19}F NMR. The identification of *E*- and *Z*-forms was performed based on their ^1H[3] and ^{19}F[4,7] NMR data.
[b] Lit. 91–92°C.[3]

Keywords: Perkin reaction; condensation; fluorinated compounds; cinnamic acids; stereoselectivity.
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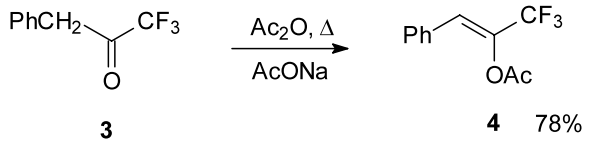

3 4 78%

Scheme 1. *O*-Acetylation of ketone **3**.

Beside that, to obtain the desired acid an additional synthetic step, namely the hydrolysis of the ester function, is necessary. In our search for novel fluorinated building blocks and their applications in organic synthesis,[5] we report here a simple and convenient one-step procedure to obtain 3-polyfluoroalkylated (*E*)-cinnamic acids.

The Perkin-type condensation of fluoroalkyl–arylketones **1** (1 equiv.) carried out in boiling acetic anhydride (15 equiv.) in the presence of anhydrous sodium acetate (2 equiv.) gave the acids **2** in good yields and stereoselectivity (90–100% *E*-isomer, Table 1). After usual aqueous work-up the analytically pure *E*-cinnamic acids **2** were easily isolated. Noteworthy, the yields and stereoselectivity of reaction do not depend on the nature of the substituent in the aryl group. To the best of our knowledge, this is the first example of a Perkin reaction involving a ketone substrate as the carbonyl component.

This method is apparently not applicable to the synthesis of related 3-alkyl-3-polyfluoroalkylacrylic acids. Thus, treatment of ketone **3** with acetic anhydride under similar conditions led to the *Z*-configurated enol acetate **4** exclusively (Scheme 1).

In summary, 3-polyfluoroalkylated *E*-cinnamic acids, very useful building blocks, were obtained by a simple and convenient one-step procedure in good yields and excellent stereoselectivity. Condensation of fluoroacylarenes with acetic anhydride/sodium acetate system leading to the desired *E*-cinnamic acids represents the first example of Perkin type reaction with ketone as a carbonyl component. Further studies of the scope and applicability of this method to polyfluoroalkyl–(het)arylketones with R^F chains longer as CF_3 are presently under investigation in our group and will be published later.

References

1. (a) *Organofluorine Compounds in Medicinal Chemistry and Biomedical Applications*; Filler, R.; Kobayashi, Y.; Yagupolskii, L. M., Eds.; Elsevier: Amsterdam, 1993; (b) *Organofluorine Chemistry—Principles and Commercial Applications*; Banks, R. E.; Smart, B. E.; Tatlow, J. C., Eds.; Plenum Press: New York, 1994.
2. For example, see: (a) Portevin, B.; Benoist, A.; Rémond, G.; Hervé, Y.; Vincent, M.; Lepagnol, J.; De Nanteuil, G. *J. Med. Chem.* **1996**, *39*, 2379–2391; (b) Ohno, N.; Fukamiya, N.; Okano, M.; Tagahara, K.; Lee, K.-H. *Bioorg. Med. Chem.* **1997**, *5*, 1489–1495; (c) Carceller, E.; Merlos, M.; Giral, M.; Almansa, C.; Bartrolí, J.; García-Rafanell, J.; Forn, J. *J. Med. Chem.* **1993**, *36*, 2984–2997.
3. Sosnovskikh, V. Ya. *Zh. Org. Khim.* **1993**, *29*, 895–900 (*Russ. J. Org. Khim.* **1993**, *29*, 740–744).
4. Gong, Y.; Kato, K.; Kimoto, H. *J. Fluorine Chem.* **2000**, *105*, 169–173.
5. (a) Sevenard, D. V.; Khomutov, O. G.; Koryakova, O. V.; Sattarova, V. V.; Kodess, M. I.; Stelten, J.; Loop, I.; Lork, E.; Pashkevich, K. I.; Röschenthaler, G.-V. *Synthesis* **2000**, 1738–1748; (b) Sevenard, D. V.; Khomutov, O. G.; Kodess, M. I.; Pashkevich, K. I.; Loop, I.; Lork, E.; Röschenthaler, G.-V. *Can. J. Chem.* **2001**, *79*, 183–194; (c) Sevenard, D. V.; Sosnovskikh, V. Ya.; Schroeder, G.; Röschenthaler, G.-V. *Aust. J. Chem.* **2001**, *54*, 335–341; (d) Sevenard, D. V.; Kirsch, P.; Lork, E.; Röschenthaler, G.-V. *Tetrahedron Lett.* **2003**, *44*, 5995–5998.
6. *3-(4-Chlorophenyl)-4,4,4-trifluorobut-2-(E)-enoic acid (**2b**)*: Colorless prisms. ^{1}H NMR (200 MHz, $CDCl_3$, TMS) δ: 6.57 (q, 1H, C^{2}H, $^4J_{H-F}=1.2$ Hz), 7.19, 7.37 (AA′BB′-pattern, 4H, C_6H_4, $J_{AB}=J_{A'B'}=8.3$ Hz), 10.8 (br.s, 1H, COOH); ^{19}F NMR (188 MHz, $CDCl_3$, $CFCl_3$) δ: −68.23 s.
7. Shen, Y.; Gao, S. *J. Org. Chem.* **1993**, *58*, 4564–4566.