Synthetic Communications

ISSN: 0039-7911 (Print) 1532-2432 (Online) Journal homepage: http://www.tandfonline.com/loi/lsyc20

Efficient One Step Procedure for the Synthesis of α-Trifluoromethylated Arylacetates

In Howa Jeong , Tae Won Park & Bum Tae Kim

To cite this article: In Howa Jeong , Tae Won Park & Bum Tae Kim (1998) Efficient One Step Procedure for the Synthesis of α-Trifluoromethylated Arylacetates, Synthetic Communications, 28:11, 1981-1987, DOI: 10.1080/00397919808007172

To link to this article: http://dx.doi.org/10.1080/00397919808007172

Published online: 20 Aug 2006.

SYNTHETIC COMMUNICATIONS, 28(11), 1981-1987 (1998)

EFFICIENT ONE STEP PROCEDURE FOR THE SYNTHESIS OF α-TRIFLUOROMETHYLATED ARYLACETATES

In Howa Jeong,*[a] Tae Won Park,[a] and Bum Tae Kim[b]

[a]Department of Chemistry, Yonsei University, Wonju 220-710, Korea
[b]Korea Research Institute of Chemical Technology, Daejeon 305-606, Korea

Abstract : The reaction of β,β-difluoro-α–trifluoromethylstyrene derivatives **1** with 3 equiv. of sodium methoxide in acetonitrile at 25 ℃ afforded α-trifluoromethylated arylacetates **3** in good yields.

α-Trifluoromethylated arylacetates are very important intermediates for the preparation of biologically active compounds. For examples, panomifene,[1] a mammary-tumor inhibiting antiestrogen, and trifluoro-analog of ibuprofen and naproxen,[2] antiinflammatory agents, can be synthesized *via* α-trifluoromethylated arylacetates. Dehydrofluorination of α-trifluoromethylated arylacetates with base may provide 3,3-difluoroacrylates which are also very useful intermediates for the formation of 6,6-difluoroshikimic acid.[3]

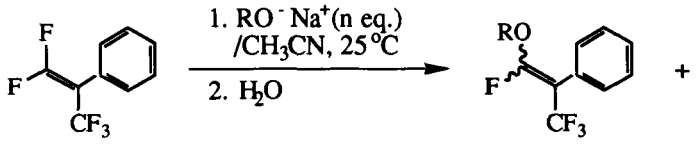
Although several synthetic methods for the preparation of α-trifluoromethylated arylacetates have been reported in the previous literatures, these methods suffer from low yields or multiple reaction steps. The first method involves the Wittig

*To whom correspondence should be addressed.

reaction of α,α,α-trifluoroacetophenone with phosphonium methoxymethylide followed by hydrolysis and oxidation, in which α-trifluoromethylated arylacetic acid was obtained in about 35% overall yield.[4] Middleton reported the practical procedure which is based on the addition-elimination of β,β-difluoro-α-trifluoromethylstyrene derivatives with sodium ethoxide followed by hydrolysis reaction.[2] The alkylation reaction of sodium diethyl phenylmalonate with dibromodifluoromethane, followed by bromine-fluorine exchange reaction afforded α-trifluoromethylated arylacetates in about 35% overall yield.[5] α-(Trifluoromethyl)styrene derivatives, which can be prepared from the palladium-catalyzed coupling reaction of trifluoroisopropenylzinc reagent with aryl halides, were allowed to react with borane followed by treatment with alkaline hydrogen and Jones oxidation to afford α-trifluoromethylated arylacetic acid.[6] In recent years, hydrogenation of α-hydroxy-α-(trifluoromethyl)arylacetate which can be prepared *via* α,α,α-trifluoro- acetophenone cyanohydrin provided α-trifluoromethylated arylacetates.[7] In this communication, we wish to describe about the addition-elimination of β,β-difluoro-α-trifluoromethylstyrene derivatives with sodium alkoxides as one pot procedure for the preparation of α-trifluoromethylated arylacetates.

When β,β-difluoro-α-trifluoromethylstyrene **1a** was reacted with 1 equiv. of sodium methoxide in acetonitrile, only monosubstituted product **2a** was obtained in 87% yield. However, treatment of **1a** with 2 equiv. of sodium methoxide in acetonitrile afforded **2a** and α-trifluoromethylated arylacetate **3a** in 40% and 41% yields, respectively. The use of 3 equiv. of sodium methoxide under the same reaction condition completely provided **3a** in 75% yield. As a couple of minor products, compounds **4a** and **5a** were obtained in 5% and 3% yields, respectively. The use of large excess sodium methoxide(6 equiv.) resulted in the formation of only malonate **5a** in 79% yield. The reactions of **1a** with primary types of alkoxides(ethoxide, propoxide etc) also provided the similar results. The results for the reactions of **1a** with different types of alkoxides are shown in Table 1.

Table 1. Reactions of α-Trifluoromethyl-β,β-difluorostyrene **1a** with Alkoxides



1a **2a**

3a **4a** **5a**

R	n	Yield(%)[a]			
		2a	**3a**	**4a**	**5a**
CH_3	1	87	-	-	-
CH_3	2	40	41	-	-
CH_3	3	-	75	5	3
CH_3	6	-	-	-	79
C_2H_5	3	-	74	4	4
i-C_3H_7	3	63	5	-	-
t-C_4H_9	3	62	-	-	-

[a]Isolated yields.

A plausible mechanism for the formation of **3a** can be proposed as shown in Figure 1. Initial attack of sodium methoxide on **1a** resulted in the formation of **2a** *via* addition and β-defluorination. Dealkylation of **2a** by another 1 equiv. of sodium methoxide provided intermediate [I] which undergoes defluorination to give

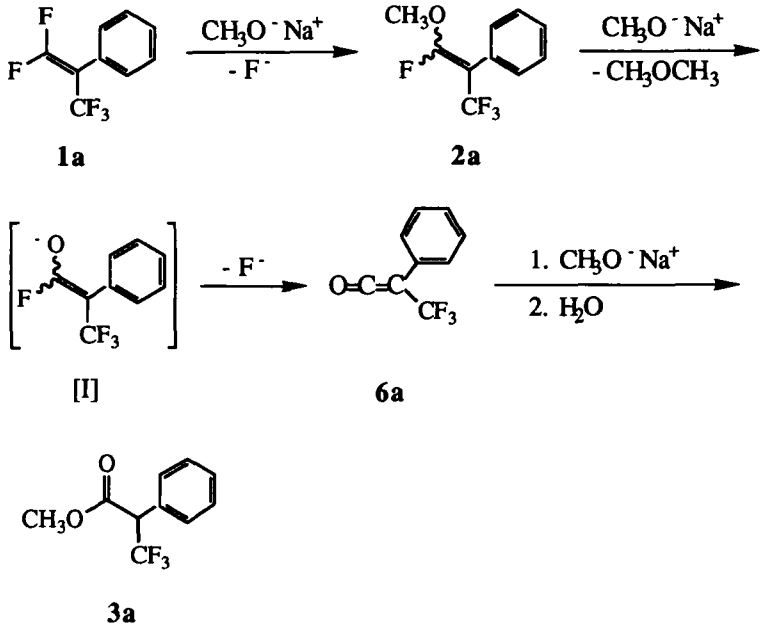
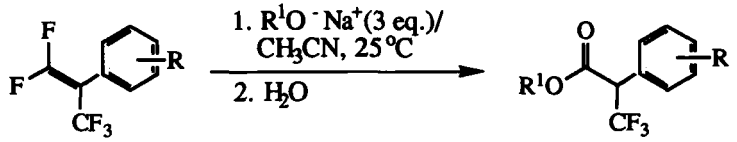


Figure 1. A Proposed Mechanism for the Formation of α-Trifluoromethylated Arylacetate **3a**

ketene **6a**. A similar dealkylation reaction of fluorinated vinyl ether with triethylamine has been reported in the previous literature.[8] The further reaction of **6a** with another 1 equiv. of sodium methoxide followed by quench with water quickly afforded **3a**. Although the direct isolation of **6a** from the raction mixture was failed, a large amount of methyl ether in GC-MS was detected, which may be a tool to prove dealkylation pathway. This dealkylation pathway may also be supported by the result for the reaction of **1a** with 3 equiv. of sodium *tert*-butoxide. In this reaction, *tert*-butyl group in fluorinated *tert*-butyl vinyl ether generated from the reaction of **1a** with 1 equiv. of sodium *tert*-butoxide can not be easily attacked by another equiv. of sodium *tert*-butoxide because a hindered, bulky *tert*-butyl group should prevent easy approach of *tert*-butoxide. When **1a** was reacted with 3 equiv.

Table 2. Preparation of α-Trifluoromethylated Arylacetates 3



1 **3**

Compound No.	R	R^1	Yields(%)[a]
3b	H	C_2H_5	72
3d	H	*n*-C_4H_9	68
3e	3-CH_3	CH_3	66
3f	4-CH_3	CH_3	63
3g	3-CH_3O	CH_3	58
3h	4-CH_3O	CH_3	56
3i	4-F	CH_3	59
3j	4-Cl	CH_3	69
3k	3,5-Cl_2	CH_3	69
3l	4-Br	CH_3	70

[a]Isolated yields.

of sodium *tert*-butoxide, therefore, only monosubstituted product, fluorinated vinyl ether, was obtained in 62% yield. No α-trifluoromethylated arylacetate was detected, which indicates that dealkylation pathway of monosubstituted product was blocked.

The reactions of β,β-difluoro-α-trifluoromethylstyrene derivatives **1**, which have a variety of substituents on benzene ring, with 3 equiv. of sodium alkoxides

afforded α-trifluoromethylated arylacetates in good yields, which results are summarized in Table 2.

Experimental

Synthesis of methyl 2-phenyl-3,3,3-trifluoropropanoate (**3a**).

To a dry acetonitrile (10 ml) solution of methanol (0.100 g, 3.0 mmol) was added sodium hydride (120 mg, 60% dispersed in oil, 3.0 mmol) at room temperature, and the reaction mixture was stirred for 30 min. under argon atmosphere. 1-Trifluoromethyl-2,2-difluorostyrene (0.208 g, 1.0 mmol) was added by dropwise at -15 °C and the reaction mixture was stirred at -15 °C for 30 min. followed by warming to room temperature. The reaction mixture was poured on ice water and extracted with ethyl ether. The ethyl ether solution was dried and chromatographed on SiO_2 column. Elution with a mixture of hexane and ethyl acetate (9:1) provided methyl 2-phenyl-3,3,3-trifluoropropanoate (**3a**) (0.168 g, 77%). **3a**: oil; ^{1}H NMR ($CDCl_3$) δ 7.47-7.33(m, 5H), 4.43(q, J = 8.0 Hz, 1H), 3.73(s, 3H); ^{19}F NMR($CDCl_3$) δ -68.60 (d, J = 7.9 Hz, 3F); MS, m/z (relative intensity) 218(M^+, 27), 159(47), 140(24), 139(12), 109(100), 108(18), 105(61), 104(22), 89(16), 63(18), 59(80), 58(22); IR(neat) 3050, 2950, 1740, 1420, 1360, 1240, 1140, 1095, 950, 880, 830, 740, 680 cm^{-1}.

Acknowledgement. This work was supported by the Basic Science Research Institute Program, Ministry of Education(BSRI-97-3422) and the Ministry of Science and Technology.

References

1. Nemeth, G., Kapiller-Dezsofi, R., Lax, G. and Simig, G. *Tetrahedron* **1996**, 52, 12821.
2. Middleton, W. J. and Bingham, E. M. *J. Fluorine Chem.* **1983**, 22, 561.
3. Leory, J., Molines, H. and Wakselman, C. *J. Org. Chem.* **1987**, 52, 290.

4. Aaron, C., Dull, D., Schmiegel, J. L., Jaeger, D., Ohashi, Y. and Mosher, H. S. *J. Org. Chem.* **1967**, 32, 2797.
5. Everett, T. S., Purrington, S. T. and Bumgardner, C. L. *J. Org. Chem.* **1984**, 49, 3702.
6. Jiang, B. W. and Xu, Y. *J. Org. Chem.* **1991**, 56, 7336.
7. Nemeth, G., Rakoczy, E. and Simig, G. *J. Fluorine Chem.* **1996**, 76, 91.
8. Ishikawa, N. and Yokozawa, T. *Bull. Chem. Soc. Jpn.* **1983**, 56, 724.

(Received in Japan 4 November 1997)