

SYNTHESES OF TRIFLUOROMETHYLATED DIENE DERIVATIVES THROUGH THE
CLAISEN REARRANGEMENT OF TRIFLUOROMETHYLATED PROPARGYLIC AND
ALLYLIC ALCOHOLS

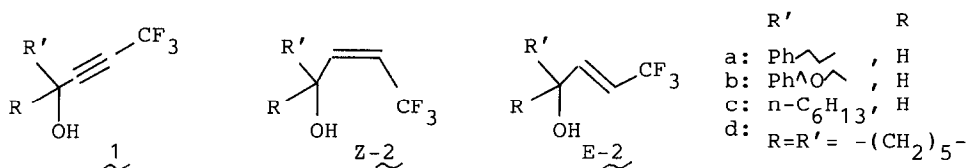
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Summary: 3-Trifluoromethyl-2Z,4E-dienoate (14) and the dienamide (10, 11) were prepared through the Claisen rearrangement of trifluoromethylated propargylic and allylic alcohols.

The synthesis of a functionalized molecule containing fluorine atom(s) or trifluoromethyl group is important since such a molecule can be applied to the synthesis of the fluorinated analogues of biologically active molecules.

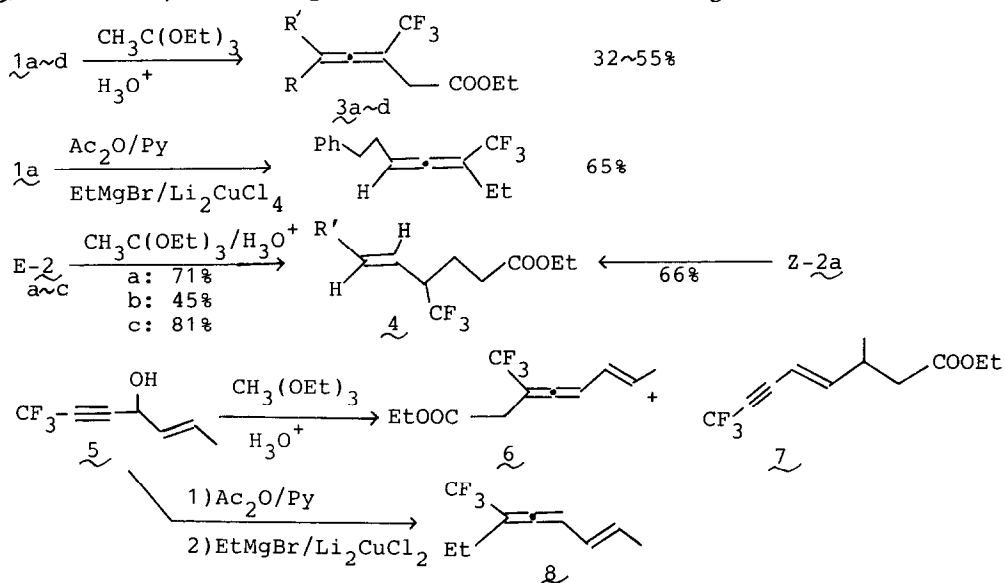
Recently, we reported that the hydrometallation and protonation of 1-alkyl-3(trifluoromethyl)propargylic alcohols (1) gave Z- and E-allylic alcohols (2) in a stereospecific manner.¹ In this communication, we describe the Claisen rearrangement of alcohols (1, 2) and certain reactions of the rearranged products to diene compound, which is a key intermediate of trifluoromethylated polyene possessing potentially biological activity.



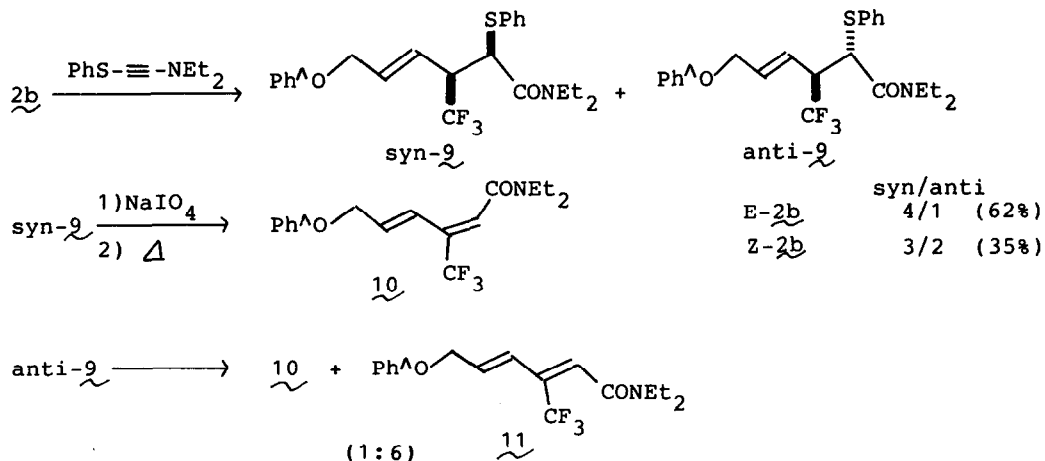
The Claisen rearrangement was carried out by heating a mixture of alcohols (1 or 2) and ethyl orthoacetate (large excess) at 130° in the presence of propionic acid (catalytic amount).²

Allene derivatives (3)³ were obtained in 32-55% yields from 1. An alternative route to allene derivatives was possible through the reaction of the acetate of 1a with the Grignard reagent in the presence of Li₂CuCl₄.⁴ The Claisen rearrangement of E-2 gave the γ,δ -unsaturated esters (4) in 45-81% yields under the same reaction conditions as described for 1. The stereochemistry (E-form of 4) revealed that the R' group in 2 preferentially occupies the equatorial position in the cyclic transition state.⁵ This was also the case in the rearrangement of Z-allylic alcohol (Z-2). The rearrangement of the compound (5) showed no selectivity in the direction of rearrangement, i.e., the

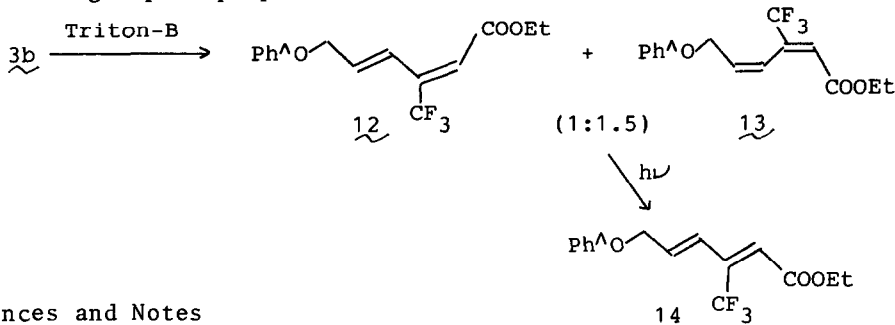
triene (6) and ene-yne (7) were obtained at nearly 1:1 ratio.⁶ On the other hand, the Grignard reaction of the acetate of 5 gave only the triene derivative (8) in a 43% yield along with the recovered starting material.



Although high selectivity in the Grignard reaction of the acetate of 5 seems quite probable, no selectivity in the Claisen rearrangement of 5 would be rather peculiar since the transition state leading to 7 is considered to be energetically more favorable than that leading to 6.⁷ The reaction of E-2b with the (phenylthio)ynamine⁸ in toluene gave the two diastereoisomers of the α -sulfenyl compound (9) in a 4:1 ratio (syn:anti) (62% yield). In the case of Z-2b, the ratio of syn:anti was 1.5:1 (35% yield).^{3,6} The structures of syn- and anti-9 were established by the following conversion to dienes (10,11) as has been discussed by Nakai.^{8,9} That is, removal of the α -sulfenyl group by oxidation (NaIO₄, aq. MeOH) followed by syn-elimination of sulfinic acid (CaCO₃, toluene, reflux) gave compounds 10 and 11. The dienamide obtained as only one product in a 70% yield from the syn-9 isomer was 10 (2E, 4E-isomer) and the products from the anti-9 isomer were 10 and 11 in a 1:6 ratio (67%).¹⁰ Preparation of trifluoromethylated diene-ester derivatives (12,13) was carried out by the base catalyzed isomerization of the allenic compound (3b) obtained above. The isomerization of allenic ester compounds to conjugated diene-esters has been reported in detail.¹¹ In our case, base catalyzed isomerization of 3b (Triton B, MeOH) gave 12 and 13 (2E, 4E and 2E, 4Z stereochemistry, respectively) in a 1:1.5 ratio.^{6,12}



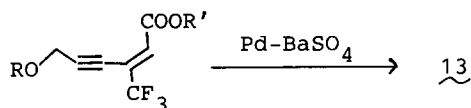
A new isomer (14) was obtained by irradiation of a mixture of 12 and 13 in acetone.¹³ The mixture consisted of a photostationary mixture of 12 and 14 (1:1.5 ratio).⁶ The structure of the new isomer (14) was proven to be 2Z,4E isomer.¹⁴ We are now investigating the conversion of the functional group to appropriate group to prepare the trifluoromethylated polyene.



References and Notes

- 1) Y. Hanzawa, K. Kawagoe, N. Tanahashi and Y. Kobayashi, *Tetrahedron Lett.*, **25**, 4749 (1984).
- 2) An attempted Claisen rearrangement of CF₃-propargylic alcohol having bulky substituent in R' of 1 was reported to be unsuccessful. B. A. Pawson, K. K. Chan, J. DeNoble, R. J. Han, V. Piermattie, A. C. Speciman, S. Srisethnil, P. W. Trown, O. Bohoslawec, L. J. Machlin and E. Gabriel, *J. Med. Chem.*, **22**, 1059 (1979).
- 3) All new compounds were identified by their IR, NMR and mass spectra.
- 4) a) P. Vermeer, J. Meijer and L. Brandsma, *Rec. Trav. Chim.*, **94**, 112 (1975). b) J. Luche, E. Barreiro, J. M. Dollat and P. Crabbe, *Tetrahedron Lett.*, 4615 (1975). c) P. Crabbe, E. Barreiro, J. M. Dollat and J. Luche, *Chem. Commun.*, 183 (1976). d) F. Delbecq and J. Gore, *Angew. Chem. Int. Ed. Engl.*, **15**, 496 (1976). e) J. L. Moreau and M. Gaudemar, *J. Organometal. Chem.*, **108**, 159 (1976). f) M. Montury, B. Psaume and J. Gore, *Tetrahedron Lett.*, **21**, 163 (1980).
- 5) a) S. J. Roads and N. R. Raulins, *Organic Reactions*, **22**, 1 (1975). b) T. Nakai, K. Mikami and N. Sayo, *J. Synth. Org. Chem. Japan*, **41**, 100 (1983).

- 6) The ratio was determined by capillary GC (OV-101, 25m) and the integration of ^{19}F -NMR signals.
- 7) J. Labovitz, C. A. Henric and V. L. Corbin, *Tetrahedron Lett.*, 691 (1975).
- 8) T. Nakai, H. Setoi and Y. Kageyama, *Tetrahedron Lett.*, 22, 4097 (1981).
- 9) Further structural evidence for 9 was obtained by the iodolactonization of the α -sulfinyl derivatives derived from 9; only the α -sulfinyl syn-isomer gave iodolactone derivative. The anti-isomer gave no product under the same reaction conditions due to the steric congestion of the substituents in the five membered lactone. These results and discussion will be reported elsewhere.
- 10) The geometry of trisubstituted double bond was determined by nmr spectra. The γ -hydrogen of 10 (δ , 6.7) is shifted to down field compared to that of 11 (δ , 6.2).
- 11) a) C. A. Henric, W. E. Willy, D. R. McKean, E. Baggiolini and J. B. Sidall, *J. Org. Chem.*, 40, 8 (1975). b) R. A. Amos and J. A. Katsenelenbogen, *J. Org. Chem.*, 43, 555 (1978). c) S. Tsuboi, T. Masuda, H. Makino and A. Takeda, *Tetrahedron Lett.*, 23, 209 (1982).
- 12) $^1\text{H-NMR}(\text{CDCl}_3)$ δ , 12: 1.29(t, $J=7.1$ Hz, CH_2CH_3) 4.17-4.25 (m, CH_2CH_3 and $\text{OCH}_2\text{CH}=\text{CH}$), 4.56 (s, PhCH_2O), 6.25 (s, $\text{C}=\text{CHCO}_2\text{Et}$), 6.37 (bd, $J=16.8$ Hz, $\text{OCH}_2\text{CH}=\text{CH}$ -), 7.35 (bs, Ar-H), 7.48 (d, $J=16.8$ Hz, $=\text{CHCH}=\text{CHCO}_2\text{Et}$). 13: 1.26 (t, $J=7.1$ Hz, CH_2CH_3), 3.99 (d, $J=3.9$ Hz, $\text{OCH}_2\text{CH}=\text{CH}$ -), 4.17 (q, $J=7.1$ Hz, CH_2CH_3), 4.45 (s, PhCH_2O), 6.14 (bs, $\text{CH}=\text{CH}-\text{CCF}_3=\text{CH}$), 6.42 (s, $\text{CCF}_3=\text{CHCO}_2\text{Et}$), 7.30 (bs, Ar-H). An alternative synthesis of 13 was carried out by the partial reduction of acetylenic compound.



- 13) Rayonet photochemical reactor (RPR-100, 3000Å) was used.
- 14) $^1\text{H-NMR}(\text{CDCl}_3)$ δ , 14: 1.31(t, $J=7.1$ Hz, CH_2CH_3), 4.13 (bs, $\text{OCH}_2\text{CH}=\text{CH}$ -), 4.25 (q, $J=7.1$ Hz, CH_2CH_3), 4.55 (s, PhCH_2O), 6.23 (s, $\text{CCF}_3=\text{CHCO}_2\text{Et}$), 6.25 (bs, $\text{CH}=\text{CH}-\text{CCF}_3=\text{C}$ -), 7.35 (bs, Ar-H). 14 was isomerized very easily to 12, with catalytic amount of I_2 . On the other hand, 13 did not give any isomerized products under the same conditions. These facts mean the γ - δ double bond of 14 must be E-form. This speculation was confirmed by the chemical conversion of analogues compound (15) obtained in a same way with 14 to 16 whose structure was clearly assigned by nmr spectrum.

