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Preliminary Note

Diels–Alder reactions of trifluoromethyl dienes obtained from ene reactions of trifluoromethyl carbonyl compounds

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Abstract

The ene reactions of trifluoromethyl carbonyl compounds give products which may be dehydrated to trifluoromethyl dienes; the Diels–Alder reaction of these have been investigated. The dienes from trifluoromethyl ketones hardly reacted, probably because the steric effect of the trifluoromethyl group prevents the diene from taking up a *cisoid* form Dienes obtained from the ene reaction of trifluoroacetaldehyde have one substituent at a terminal position and react with dienophiles to give trifluoromethylated cyclohexene derivatives.

Introduction

We have reported the ene reaction [1] of trifluoromethyl carbonyl compounds and its application [2] for syntheses of various types of trifluoromethyl compound. During this research, a trifluoromethyl group was found to have a much larger steric effect than previously believed in the biomedicinal field [3]. We have shown derivatization of trifluoromethyl homoallyl alcohols (the products of the ene reaction) to trifluoromethylated dienes and have discussed the steric effect of the trifluoromethyl group [3c]. We now report the Diels–Alder reaction of the trifluoromethyl dienes obtained above. The aim of this research was the synthesis of new trifluoromethyl compounds and a better understanding of the steric effect of a trifluoromethyl group.

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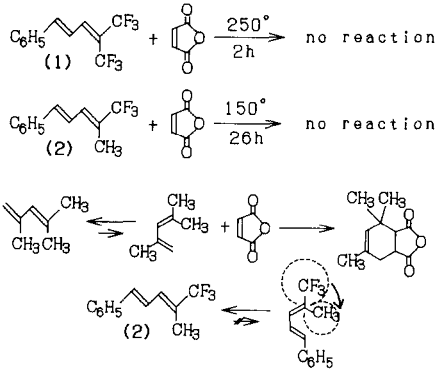
Results and discussion

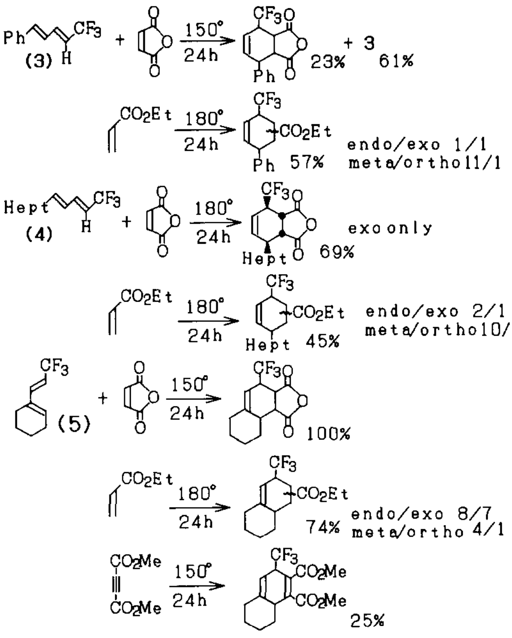
Dienes obtained from the ene reaction of trifluoromethyl ketones [2b] hardly reacted with dienophiles. Thus, 5,5,5-trifluoro-1-phenyl-4-(trifluoromethyl)-1,3-pentadiene (**1**) or 5,5,5-trifluoro-4-methyl-1-phenyl-1,3-pentadiene (**2**) did not react with maleic anhydride at all. This low reactivity might be explained by the strong electron-withdrawing effect of the trifluoromethyl group(s) or by the steric hindrance of the two substituents at the terminal position. As mentioned later, a diene with a trifluoromethyl group on the terminal position reacts with maleic anhydride. Thus, the electronic effect of a trifluoromethyl group is not strong enough to inhibit the Diels–Alder reaction of the diene. However, 2,4-dimethyl-1,3-pentadiene has been reported to react with maleic anhydride [4], which shows that the methyl group of **2** inhibits the reaction more strongly than that of 2,4-dimethyl-1,3-pentadiene. This may be explained as follows: the steric effect of the trifluoromethyl group is much larger than that of the methyl group; the methyl group of **2** is strongly pushed inside by the trifluoromethyl group; and **2** is more difficult to place in a *cisoid* form than 2,4-dimethyl-1,3-pentadiene. In other words, this result supports the large steric effect of a trifluoromethyl group discussed in previous reports [3].



Scheme 1.

Next, to evaluate the electronic effect of a trifluoromethyl group, we synthesized by the ene reaction of trifluoroacetaldehyde followed by dehydration, three dienes that had only a trifluoromethyl group on a terminal position. Thus, dehydration of the ene reaction product from allylbenzene gave 1-phenyl-5,5,5-trifluoro-1,3-pentadiene (**3**), from 1-octene 1,1,1-trifluoro-2,4-dodecadiene (**4**), and from methylenecyclohexane 1-(3,3,3-trifluoro-1-propenyl)cyclohexene (**5**). A solution of **3** and maleic anhydride in benzene was heated in a sealed tube at 150 °C to give an adduct in 23% yield, while **4** and **5** gave the corresponding adducts in 69%

and quantitative yields, respectively. These results show that the electronic effect of a trifluoromethyl group is not so strong as to inhibit the reaction completely, although the mixture must be heated to a higher temperature than for the reaction of non-trifluoromethylated dienes. The lower reactivity of **3** might be ascribed to the electronic effect of the phenyl group and the fact that a *transoid* form is much more stable than a *cisoid* form, through which the Diels–Alder reaction proceeds. This difference in stability is much smaller for **5**, which is the reason why **5** gave a much higher yield of the adduct than **3** and **4**. These results are summarized in Scheme 2, with results of the Diels–Alder reaction of **3**, **4** and **5** with other dienophiles.



Scheme 2.

A typical experiment was as follows. A solution of 5,5,5-trifluoro-1-phenyl-1,3-pentadiene (96 mg, 0.48 mmol) and maleic anhydride (64 mg, 0.65 mmol) in benzene (5 ml) was heated in a sealed tube at 150 °C for 24 h, then the tube was cooled and opened. The content was extracted with Et_2O. After evaporation of the solvent, the residue was separated by column chromatography (Florisil, *n*-hexane–CH_2Cl_2 1:1–CH_2Cl_2) to give the starting diene (58.6 mg, 61%) and 3-phenyl-6-(trifluoromethyl)-4-cyclohexene-1,2-dicarboxylic anhydride (33.3 mg, 22.5%).

Characteristic points of these reactions are as follows. The reaction of compounds **3**–**5** with maleic anhydride gave only *exo*-adducts while reaction with acrylic ester gave *endo*- and *exo*-isomers. Reaction with ethyl acrylate gave adducts that have the trifluoromethyl group and the ethoxycarbonyl group in the *meta*-position preferentially to the *ortho* position, while the Diels–Alder reaction of dienes substituted with electron-withdrawing groups with acrylic acid derivatives have been reported to give *ortho*-isomers selectively [5]. This regioselectivity might be explained by a large steric effect or a special electronic effect of the trifluoromethyl group.

Spectral data

All the new compounds gave satisfactory spectral data including high-resolution mass spectra. The stereochemistries were determined based on NOE correlation on two-dimensional ^{1}H NMR. These will be discussed in the full paper. ^{19}F NMR spectra of the Diels–Alder adducts in Scheme 2 are as follows.

3-Phenyl-6-(trifluoromethyl)-4-cyclohexene-1,2-dicarboxylic anhydride: colorless needles; ^{19}F NMR ($CDCl_3$) ppm (benzotrifluoride as an internal standard; high field is taken as plus): −3.39 (d, $J = 9.9$ Hz). *t*-3-Heptyl-*t*-6-(trifluoromethyl)-4-cyclohexene-*r*-1,*c*-2-dicarboxylic anhydride: viscous oil: 3.57 (d, $J = 9.8$ Hz). Ethyl *t*-2-heptyl-*t*-5-(trifluoromethyl)-3-cyclohexene-*r*-1-carboxylate: colorless oil; 9.06 (d, $J = 9.5$ Hz). Ethyl *t*-5-heptyl-*t*-2-(trifluoromethyl)-3-cyclohexene-*r*-1-carboxylate: 8.37 (d, $J = 9.9$ Hz). Ethyl *c*-2-heptyl-*c*-5-(trifluoromethyl)-3-cyclohexene-*r*-1-carboxylate: colorless oil; 10.69 (d, $J = 9.1$ Hz). Ethyl *c*-5-heptyl-*c*-2-(trifluoromethyl)-3-cyclohexene-*r*-1-carboxylate: colorless oil; 2.67 (d, $J =$ 8.7 Hz). Ethyl *t*-2-phenyl-*t*-5-(trifluoromethyl)-3-cyclohexene-*r*-1-carboxylate: colorless oil; 8.67 (d, $J = 9.5$ Hz), 8.05 (d, $J = 9.1$ Hz) 11:1. Ethyl *c*-2-phenyl-*c*-5-(trifluoromethyl)-3-cyclohexene-*r*-1-carboxylate: colorless oil; 10.34 (d, $J = 8.7$ Hz), 2.39 (d, $J = 8.7$ Hz) 13:1. 3-(Trifluoromethyl)-bicyclo[4.4.0]decene-4,5-dicarboxylic anhydride: viscous oil; 3.78 (d, $J =$ 9.5 Hz). Ethyl *r*-3-(trifluoromethyl)-*c*-6-bicyclo[4.4.0]dec-1-ene-*c*-4-carboxylate: 2.67 (d, $J = 9.3$ Hz). Ethyl *r*-3-(trifluoromethyl)-*c*-6-bicyclo[4.4.0]-dec-1-ene-*t*-4-carboxylate: 8.02 (d, $J = 9.3$ Hz). Ethyl *r*-3-(trifluoromethyl)-*c*-6-bicyclo[4.4.0]-dec-1-ene-*t*-5-carboxylate: 8.21 (d, $J = 9.8$ Hz). Ethyl *r*-3-(trifluoromethyl)-*c*-6-bicyclo[4.4.0]-dec-1-ene-*c*-5-carboxylate: 10.70 (d, $J =$ 8.8 Hz). Dimethyl 3-(trifluoromethyl)bicyclo[4.4.0]deca-1,4-diene-4,5-dicarboxylate: 7.53 ((d, $J = 7.5$ Hz).

Conclusions

Trifluoromethylated dienes obtained from the ene reaction of trifluoroacetaldehyde undergo the Diels–Alder reaction with dienophiles to give trifluoromethylated cyclohexene derivatives. This reaction provides another useful application of the ene reaction of trifluoromethyl carbonyl compounds. 1-(3,3,3-Trifluoro-1-propenyl) cyclohexene is the most reactive since it can take a *cisoid* form much more easily than the other dienes.

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