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Baylis–Hilman reaction for α,β-unsaturated trifluoromethyl ketones

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The reaction of β-substituted α,β-unsaturated CF_3 ketones with acrylonitrile under the conditions of the Baylis–Hilman reaction was found to proceed as 1,2-addition.

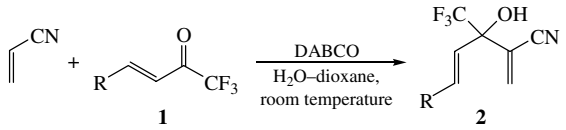
The trifluoromethyl group possesses unique stereoelectronic properties. Compounds containing the trifluoromethyl group present attractive targets for studying their chemical and physiological properties. Thus, the development of methods for the preparation of fluorine-containing compounds is of considerable current interest.[1]

Readily obtained α,β-unsaturated trifluoromethyl ketones[2,3] are perspective building blocks for the synthesis of both alicyclic and heterocyclic compounds containing the trifluoromethyl group. Note that, frequently, the reactions of these compounds proceed differently from their non-fluorinated analogues.[4,5]

The Baylis–Hilman reaction is a popular reaction for the formation of C–C bonds. It represents a two-component reaction involving coupling of α-position of activated alkenes (Michael acceptors) with electrophiles in the presence of tertiary amines. The presence of at least three functional groups (double bond, EWG and hydroxyl group) makes the reaction products very attractive objects for further transformations. There is a huge amount of works devoted to investigation of substrates, catalysts, reaction conditions and transformation of the products for Baylis–Hilman reaction.[6]

Ketones react too slow in this transformation and give low yields.[6] Only aromatic and aliphatic ketones with the carbonyl activated by the CF_3 group react for a satisfactory time and give good yields.[7,8] α,β-Unsaturated carbonyl compounds do not react, excepting α,β-unsaturated aldehydes[8] and conjugated cycloalkenones.[10] It is strange that α,β-unsaturated triflouromethyl ketones were not investigated at all, excepting the reaction of two acetylenic ketones containing CF_3 and perfluoropropyl groups.[8]

Here, we report the Baylis–Hilman reaction of β-substituted α,β-unsaturated trifluoromethyl ketones with aryl, alkoxy and dimetylamino substituents. As activated alkenes, methyl acrylate, ethyl acrylate, methyl vinyl ketone, acrolein, phenyl vinyl sulfone and acrylonitrile were studed. We took commonly applied 1,4-diazabicyclo[2,2,2]octane (DABCO) as the catalyst and a dioxane–water mixture as the solvent, which accelerated the reaction.[11] The above activated alkenes, except for acrylonitrile, showed the absence of reaction with α,β-unsaturated trifluoromethyl ketones during the period of several months. Only the polymerization of starting materials was observed. Positive results were obtained in the reaction with acrylonitrile. While using DABCO and acrylonitrile, the reaction proceeds as 1,2-addittion of the anion generated from activated acrylonitrile to the carbonyl group of the CF_3 ketone (Scheme 1). The 1,2-addition products of acrylonitrile were obtained in good yields. In the case of ketones containing EtO and Me_2N groups, only polymerization was observed and no target product was isolated.



1 **2**

Scheme 1 Reaction of α,β-unsaturated trifluoromethyl ketones with acrylonitrile.

α,β-Unsaturated trifluoromethyl ketones usually behave as Michael acceptors, and there are examples where the reaction with nucleophiles proceeds as 1,4-conjugated addition.[12] These compounds can also react as primary electrophiles in the Baylis–Hilman reaction. Their carbonyl group can serve as an electrophile, and they can react in the absence of any external anion generator to give the Baylis–Hilman adduct from two molecules of starting CF_3 enone. Nevertheless, no such adducts were isolated – the reaction with acrylonitrile proceeds chemoselectively to give the only product of cross-reaction.

Ketones having more electron-donating groups react more slowly, obviously, due to decreasing electrophilicity of the conjugated carbonyl group. Ketones having strong donating 3-indolyl and 3-(2-methylindolyl) substituents do not react for a period of

Table 1 Reaction products.

R	Product	Reaction time/h	Yield[a] (%)
Ph	**2a**	10	70
4-MeC_6H_4	**2b**	12	76
3-MeC_6H_4	**2c**	12	79
3-$MeOC_6H_4$	**2d**	15	59
2-thienyl	**2e**	12	66
2,5-$(MeO)_2C_6H_3$	**2f**	72	65
3-indolyl	—	—[b]	—
3-(2-methylindolyl)	—	—[b]	—
EtO	—	—[c]	—
Me_2N	—	—[c]	—

[a]Yields for isolated compounds are given. [b]No reaction observed. [c]No product was isolated.

half a year. Reaction times for the rest ketones at room temperature vary from 10 h to several days (Table 1).†

Thus, the above reactions present the first example of the participation of α,β-unsaturated trifluoromethyl ketones in the Baylis–Hilman reaction. The products are tertiary diallylic alcohols, which are very perspective compounds for further transformations.

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† *Typical procedure for the Baylis–Hilman adducts of α,β-unsaturated trifluoromethyl ketones with acrylonitrile*. A mixture of 4-aryl-1,1,1-trifluorobut-3-en-2-one (3 mmol), 1,4-diazabicyclo[2,2,2]octane (DABCO) (6 mmol) and acrylonitrile (6 mmol) was dissolved in a mixture of dioxane (4 ml) and water (4 ml). The emulsion was stirred for several hours until the absence of the ketone (TLC monitoring, hexane–ethyl acetate, 3:1). The solution was diluted with water (20 ml) and extracted with methylene chloride (4×10 ml). Combined organic fractions were passed through a thin layer of silica gel. After solvent evaporation, the product of analytical purity grade was obtained.

*(4*E*)-3-Hydroxy-2-methylene-5-phenyl-3-(trifluoromethyl)pent-4-enenitrile* **2a**: white solid, yield 70%, mp 91–92 °C. IR (ν/cm^{-1}): 1620 (Ph–C=C), 1655 (C=C–CN), 2255 (CN), 3420 (OH). ^{1}H NMR ($CDCl_3$) δ: 3.72 (br. s, 1H, OH), 6.30 (br. s, 1H, =CH_2), 6.47 (br. s, 1H, =CH_2), 6.48 (d, 1H, CH, *J* 16.0 Hz), 6.98 (d, 1H, CH, *J* 16.0 Hz), 7.29–7.39 (m, 3H, Ph), 7.39–7.46 (m, 2H, Ph). ^{13}C NMR ($CDCl_3$) δ: 75.8 (q, *C*–CF_3, *J* 30.0 Hz), 115.7 (CN), 121.0 (Ph–*C*H), 121.5 (=CH_2), 123.5 (q, CF_3, *J* 286.9 Hz), 134.6 (*C*H–C–OH), 135.7 (*C*–CN), 127.1, 128.8, 129.2, 135.2 (Ph). Found (%): C, 61.68; H, 4.15. Calc. for $C_{13}H_{10}F_3NO$ (%): C, 61.66; H, 3.98.

*(4*E*)-3-Hydroxy-2-methylene-5-(4-methylphenyl)-3-(trifluoromethyl)-pent-4-enenitrile* **2b**: white solid, yield 76%, mp 76–77 °C. IR (ν, cm^{-1}): 1615 (4-MeC_6H_4–C=C), 1655 (C=C–CN), 2250 (CN), 3430 (OH). ^{1}H NMR ($CDCl_3$) δ: 2.35 (s, 3H, Me), 3.90 (br. s, 1H, OH), 6.22 (br. s, 1H, =CH_2), 6.38 (br. s, 1H, =CH_2), 6.43 (d, 1H, CH, *J* 16.0 Hz), 6.90 (d, 1H, CH, *J* 16.0 Hz), 7.12 (d, 1H, 4-MeC_6H_4, *J* 8.1 Hz), 7.28 (d, 1H, *J* 8.1 Hz). ^{13}C NMR ($CDCl_3$) δ: 21.0 (Me), 75.8 (q, *C*–CF_3, *J* 30.0 Hz), 115.8 (CN), 126.9, 129.4, 135.4, 139.2 (4-MeC_6H_4), 120.3 (=CH_2), 121.0 (4-MeC_6H_4–*C*H), 123.6 (q, CF_3, *J* 286.9 Hz), 131.9 (*C*H–C–OH), 135.6 (*C*–CN). Found (%): C, 62.53; H, 4.67. Calc. for $C_{14}H_{12}F_3NO$ (%): C, 62.92; H, 4.53.

*(4*E*)-3-Hydroxy-2-methylene-5-(3-methylphenyl)-3-(trifluoromethyl)-pent-4-enenitrile* **2c**: white solid, yield 79%, mp 58–59 °C. IR (ν/cm^{-1}): 1610 (3-MeC_6H_4–C=C), 1660 (C=C–CN), 2255 (CN), 3400 (OH). ^{1}H NMR ($CDCl_3$) δ: 2.39 (s, 3H, Me), 4.18 (br. s, 1H, OH), 6.44 (br. s, 1H, =CH_2), 6.46 (d, 1H, CH, *J* 16.0 Hz), 6.48 (br. s, 1H, =CH_2), 6.88 (dd, 1H, 3-MeC_6H_4, *J* 8.1 Hz, *J* 1.8 Hz), 6.90–6.97 (m, 1H, 3-MeC_6H_4), 6.94 (d, 1H, CH, *J* 16.0 Hz), 7.02 (d, 1H, 3-MeC_6H_4, *J* 7.8 Hz), 7.26 (t, 1H, 3-MeC_6H_4, *J* 7.8 Hz). ^{13}C NMR ($CDCl_3$) δ: 21.0 (Me), 75.8 (q, *C*–CF_3, *J* 30.0 Hz), 115.8 (CN), 120.9 (3-MeC_6H_4–*C*H), 121.1 (=CH_2), 123.6 (q, CF_3, *J* 286.9 Hz), 124.2, 127.6, 128.6, 129.9, 135.8, 138.4 (3-MeC_6H_4), 134.6 (*C*H–C–OH), 135.4 (*C*–CN). Found (%): C, 62.71; H, 4.54. Calc. for $C_{14}H_{12}F_3NO$ (%): C, 62.92; H, 4.53.

*(4*E*)-3-Hydroxy-2-methylene-5-(3-methoxyphenyl)-3-(trifluoromethyl)-pent-4-enenitrile* **2d**: yield 59%, white solid, mp 58–59 °C. IR (ν/cm^{-1}): 1610 (3-$MeOC_6H_4$–C=C), 1660 (C=C–CN), 2260 (CN), 3410 (OH). ^{1}H NMR ($CDCl_3$) δ: 3.83 (s, 3H, OMe), 4.18 (br. s, 1H, OH), 6.33 (br. s, 1H, =CH_2), 6.49 (d, 1H, CH, *J* 16.0 Hz), 6.51 (br. s, 1H, =CH_2), 6.91 (dd, 1H, 3-$MeOC_6H_4$, *J* 8.1 Hz, *J* 1.8 Hz), 6.96–6.98 (m, 1H, 3-$MeOC_6H_4$), 6.97 (d, 1H, CH, *J* 16.0 Hz), 7.29 (d, 1H, 3-$MeOC_6H_4$, *J* 7.8 Hz). ^{13}C NMR ($CDCl_3$) δ: 55.2 (OMe), 75.7 (q, *C*–CF_3, *J* 30.0 Hz), 112.5, 114.7, 128.6, 119.7, 129.7, 135.5, 159.6 (3-$MeOC_6H_4$), 115.7 (CN), 120.8 (3-$MeOC_6H_4$–*C*H), 121.8 (=CH_2), 123.5 (q, CF_3, *J* 286.9 Hz), 135.5 (*C*H–C–OH), 136.0 (*C*–CN). Found (%): C, 59.24; H, 4.14. Calc. for $C_{14}H_{12}F_3NO_2$ (%): C, 59.37; H, 4.27.

*(4*E*)-3-Hydroxy-2-methylene-5-(2-thienyl)-3-(trifluoromethyl)pent-4-enenitrile* **2e**: yield 66%, white solid, mp 56–57 °C. IR (ν/cm^{-1}): 1615 (2-Th–C=C), 1645 (C=C–CN), 2250 (CN), 3390 (OH). ^{1}H NMR ($CDCl_3$) δ: 4.12 (br. s, 1H, OH), 6.30 (d, 1H, CH, *J* 15.9 Hz), 6.50 (br. s, 1H, =CH_2), 6.54 (br. s, 1H, =CH_2), 7.04 (dd, 1H, 2-Th, *J* 4.8 Hz, *J* 3.5 Hz), 7.12 (d, 1H, CH, *J* 15.9 Hz), 7.13 (d, 1H, 2-Th, *J* 3.5 Hz), 7.31 (d, 1H, 2-Th). ^{13}C NMR ($CDCl_3$) δ: 75.8 (q, *C*–CF_3, *J* 30.0 Hz), 115.6 (CN), 120.2 (=CH_2), 120.7 (2-Th–*C*H), 123.5 (q, CF_3, *J* 286.9 Hz), 126.5, 127.7, 128.4, 139.4 (2-Th), 128.9 (*C*H–C–OH), 135.6 (*C*–CN). Found (%): C, 50.75; H, 2.98. Calc. for $C_{11}H_8F_3NOS$ (%): C, 50.96; H, 3.11.

*(4*E*)-3-Hydroxy-2-methylene-5-(2,5-dimethoxyphenyl)-3-(trifluoromethyl)-pent-4-enenitrile* **2f**: yield 65%, white solid, mp 54–55 °C. IR (ν/cm^{-1}): 1610 [2,5-$(MeO)_2C_6H_3$–C=C], 1650 (C=C–CN), 2250 (CN), 3430 (OH). ^{1}H NMR ($CDCl_3$) δ: 3.80 (s, 3H, OMe), 3.81 (s, 3H, OMe), 4.24 (br. s, 1H, OH), 6.33 (br. s, 1H, =CH_2), 6.52 (br. s, 1H, =CH_2), 6.59 (d, 1H, CH, *J* 16.0 Hz), 6.80–6.90 [m, 2H, 2,5-$(MeO)_2C_6H_3$], 6.99 [d, 1H, 2,5-$(MeO)_2C_6H_3$, *J* 2.8 Hz]; 7.26 (d, 1H, CH, *J* 16.0 Hz). ^{13}C NMR ($CDCl_3$) δ: 55.7 (OMe), 56.0 (OMe), 75.9 (q, *C*–CF_3, *J* 30.0 Hz), 112.5, 113.0, 115.3, 129.9, 130.6, 151.7, 153.3 [2,5-$(MeO)_2C_6H_3$], 115.8 (CN), 121.0 [2,5-$(MeO)_2C_6H_3$–*C*H], 122.4 (=CH_2), 123.6 (q, CF_3, *J* 286.9 Hz), 124.3 (*C*H–C–OH), 135.3 (*C*–CN). Found (%): C, 57.30; H, 4.41. Calc. for $C_{15}H_{14}F_3NO_3$ (%): C, 57.51; H, 4.50.