A Novel Base-Catalyzed Stereoselective Synthesis of Trifluoromethylated Dienedinitriles

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Abstract: The trifluoromethylated γ-cyano-β,γ-unsaturated nitrile 4 was prepared by the reaction of bromo(cyanomethyl)zinc with trifluorocacylated phosphonate 3 in 67% yield (E:Z = 60:40). The E- and Z-isomers obtained were easily separated by column chromatography. Treatment of a catalytic amount of t-BuOK (20 mol%) with a mixture of (Z)-4 and N-toluenesulfonylimines 5 gave trifluoromethylated dienedinitriles 6 in 68–83% yields.

Key words: trifluoromethylated dienedinitriles, γ-cyano-β,γ-unsaturated nitrile, trifluorocacylated phosphonate, organozinc reagent, stereoselective synthesis

1,5-Dinitriles are 1,5-bifunctional compounds, which are a useful class of substrates or precursors in aldol-type condensation and other annulation reactions.1 The cyano group is an important functional group in organic transformations and the cyano-containing compounds are useful intermediates for the synthesis of heterocyclic compounds.2 The trifluoromethylated heterocyclic compounds have been applied increasingly in the field of pharmaceuticals and agrochemicals,3 since the introduction of a trifluoromethyl group into organic compounds often dramatically changes their structure, stability, reactivity and biological activity of the resulting compounds.4 However, to the best of our knowledge a method for the synthesis of trifluoromethylated dienedinitriles has not been reported in the literature. Therefore, development of an efficient method for the synthesis of the title compounds would be valuable.

In our previous papers, the double olefination methodology was used to synthesize 3-trifluoromethyl (2Z,4E)-pentadienenitriles,5 and a stereocонтrolled method was used to synthesize (2E,4E)- or (2Z,4E)-pentadienenitriles.5 As part of our continuing investigation to explore new synthetic methodologies for carbon–carbon double bond formation,7 we report herein a novel base-catalyzed stereoselective methodology for the synthesis of trifluoromethylated (2Z,4Z)-4-cyanopentadieninitriles exclusively or predominately.

The phosphoryl-stabilized carbanion 2, generated from diethyl (1-cyanoethyl)phosphonate (1) and butyllithium in THF, was acylated by the addition of trifluoroacetic anhydride to give the trifluorocacylated phosphonate 3. The phosphonate 3 was reacted in situ with bromo(cyanomethyl)zinc with elimination of phosphonic acid anion to afford the trifluoromethylated γ-cyano-β,γ-unsaturated nitrile 4 in 67% yield (E:Z = 60:40) (Scheme 1). The E- and Z-isomers obtained were easily separated by column chromatography.

Scheme 1

19F NMR data reported for 4,4,4-trifluoro-3-phenylbut-2-enenitrile in the literature6 assert that the trifluoromethyl group cis with respect to the cyano group (Z-isomer) appears at −15.6 ppm, while that trans with respect to the cyano group (E-isomer) at −10.9 ppm (Figure 1). Based on these results, the CF3 group in compound 4 with the chemical shift at −13.4 ppm has been assigned as the E-isomer, and the one at −17.4 ppm as the Z-isomer.

Figure 1 Reported chemical shifts for CF3 in (E)- and (Z)-4,4,4-trifluoro-3-phenylbut-2-enenitrile

Compound (Z)-4 was used as the starting material for the synthesis of the title compounds. Treatment of a catalytic amount of t-BuOK (20 mol%) with a mixture of (Z)-4 and N-toluenesulfonylimines 5 gave trifluoromethylated dienedinitriles 6 in 68–83% yields (Scheme 2). The results are summarized in Table 1.

For the assignment of the configuration of the products 6, we performed an X-ray crystallographic analysis of compound 6e (major portion). The crystal structure shows that the cyano group is cis with respect to the trifluoromethyl group (2Z) and the other cyano group across the other
The double bond is also cis with respect to the 2-trifluoromethylphenyl group (4Z) (Figure 2). Hence, the configuration of products could be ascertained on the basis of the crystal structure.

The catalytic reaction mechanism may be rationalized as given in Scheme 3. The carbanion 7, generated from (Z)-4 and t-BuOK reacts with N-toluenesulfonylimine 5 to give the adduct 8. After hydrogen transfer, 8 affords 9. Elimination of p-toluenesulfonylamide anion from 9 furnishes the product 6. The p-toluenesulfonylamide anion abstracts a proton from (Z)-4 to give p-toluenesulfonylamide and regenerates the carbanion 7. Thus, the catalytic cycle is completed.

In conclusion, a novel base-catalyzed stereoselective route to trifluoromethylated (2Z,4Z)-4-cyanopentadieninitriles has been designed. It is noteworthy that the use of N-toluenesulfonylimines as substrates makes the reaction catalytic to prepare the conjugated alkene moiety. Thus, this methodology provides a simple and convenient synthesis of the title compounds from easily accessible starting materials. The title compounds are not easily available with existing synthetic methods.

Petroleum ether used had bp 60–90 °C. Bps and Mps are uncorrected. The IR spectra of liquid products were obtained as films and those of solid products as KBr disks on a Digilab FTS-20E spectrometer. 1H NMR spectra were recorded in CDCl₃ on a Bruker AM-300 (300 MHz) spectrometer (6 values in ppm from tetramethysilane, J-values are given in Hz). 19F NMR spectra were taken on a Varian EM-360 (60 MHz) spectrometer. [8 values from external trifluoroacetic acid (TFA), in CDCl₃, positive for upfield shifts]. Mass spectra were measured on a Finnigan GC-MS-4021 mass spectrometer.
Yield: 40%; bp 97 °C/0.2 mm Hg.

(E)- and (Z)-4-Cyano-3-trifluoromethylpent-3-enenitriles [(E)- and (Z)-4]

Treatment of phosphonate 1 (0.57 g, 3 mmol) with BuLi (3 mmol) at –78 °C in absolute THF (15 mL) gave the phosphoryl-stabilized carbanion 2, which was stirred at –78 °C for 0.5 h under N₂. Tri-fluoroacetic anhydride (0.63 g, 3 mmol) was added to the mixture in one portion. After stirring at –78 °C for 1 h, the reaction mixture was allowed to warm to 25 °C and the organozinc reagent [3 mmol, prepared from bromoacetonitrile (3 mmol, 0.36 g) and zinc powder (0.58 g, 9 mmol)] was added or bromoacetonitrile (0.36 g, 3 mmol) and zinc powder (0.58 g, 9 mmol) were added directly to the reaction mixture. The mixture was stirred for further 4 h and poured into H₂O (30 mL). The H₂O layer was extracted with Et₂O (3 × 15 mL) and dried (Na₂SO₄). Evaporation of the solvent gave a residue, which was purified by column chromatography by eluting with petroleum ether–EtOAc (98:2) to give the product 4. The E- and Z-isomers of 4 could be separated conveniently by column chromatography on silica gel. The component in the front was identified as E-isomer, while the one behind was the Z-isomer.

(E)-4

Yield: 40%; bp 97 °C/0.2 mm Hg.

IR (neat): 2980, 2260, 2230, 1650, 1340, 1210, 1150, 1010 cm⁻¹.

1H NMR (CDCl₃/TMS): δ = 3.36 (s, 2 H), 2.26 (q, J = 2.1 Hz, 3 H).

19F NMR (CDCl₃/TFA): δ = –17.4 (s, 3 F).

MS: m/z (%) = 175 (M⁺ + 1, 100), 154 (11), 147 (15), 128 (17), 105 (32), 78 (23), 69 (12).


Trifluoromethylated Dienes of General Procedure

A mixture of (Z)-4 (0.161 g, 0.93 mmol), N-p-toluenesulfonylimine 5 (0.94 mmol), KOBu-t (0.202 g, 0.18 mmol) and THF (15 mL) was stirred in a capped vessel under N₂ at 0 °C for 30 min. TLC showed that the reaction was complete. The mixture was poured into dil. HCl (2 M, 20 mL) and extracted with EtOAc (3 × 15 mL). The organic layer was combined, washed with H₂O (3 × 10 mL) and dried. Evaporation of the solvent gave a residue, which was purified by chromatography on silica gel by eluting with petroleum ether–EtOAc (95:5) to give the product 6.

(Z)-4

Yield: 27%; bp 87 °C/0.2 mm Hg.
(Z,4Z)-4-Cyano-3-trifluoromethyl-2-methyl-5-(4-nitrophene-nyl)pentadienenitrile [(Z,4Z)-6d]

Yield: 78%; oil.

IR (KBr): 2220, 1600, 1530, 1350, 1330, 1220, 1170, 1140 cm⁻¹.

1H NMR (CDCl₃/TMS): δ = 8.36 (dd, J = 7.0, 1.6 Hz, 2 H), 8.02 (dd, J = 8.7, 1.7 Hz, 2 H), 7.46 (s, 1 H), 2.37 (q, J = 2.2 Hz, 3 H).

19F NMR (CDCl₃/TFA): δ = −17.0 (s, 3 F).

MS: m/z (%) = 307 (M⁺, 18), 295 (25), 281 (31), 255 (99), 208 (26), 195 (10).


Found: C, 56.21; H, 2.17; N, 8.39.

Yield: 64%; mp 120–122 °C.

1H NMR (CDCl₃/TMS): δ = 7.98 (d, J = 7.6 Hz, 1 H), 7.82 (d, J = 7.6 Hz, 1 H), 7.74–7.62 (m, 2 H), 7.59 (s, 1 H), 2.28 (q, J = 1.9 Hz, 3 H).

19F NMR (CDCl₃/TFA): δ = −18.6 (s, 3 F), −16.0 (s, 3 F).

MS: m/z (%) = 331 (M⁺ + 1, 18), 315 (64), 295 (44), 261 (100), 234 (28), 214 (10).


Found: C, 61.57; H, 3.81; N, 9.59.

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References

(10) Crystallographic data of 6e have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication No. CCDC-208198(6e). Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk).