

Application of Sonogashira and Baylis–Hillman reactions with β -trifluoromethylated acroleins

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The reaction of alkynes with 2-phenyl-3-iodo-4,4-trifluorobut-2-enal in the presence of palladium (0) is reported (Sonogashira reaction). Moreover, 2-(hydroxytrifluoromethylalkenyl)cyclohexenones have been prepared by the reaction of cyclohexenone and β -trifluoromethylacroleins in the presence of *N*-methylimidazole catalysis.

Keywords: β -trifluoromethylenynes, palladium (0), cyclohexenone, *N*-methylimidazole catalysis, Baylis–Hillman adducts

Organofluorine compounds have found increasing use in the areas of agrochemicals, pharmaceuticals, polymers and new materials.^{1–5} The fluorine atom brings specific chemical and physical properties to molecules in the pharmaceutical field. Molecules containing CF_2 or CF_3 can offer a significant change in biological activity, compared to their non fluorinated analogues. For example, the enzyme inhibitory activity of trifluoromethylketones has been widely proved.⁶ The interest in molecules containing the CF_3 group entailed the development of new and efficient synthetic methodologies.

In particular, the formation of C–C bond and the transformation of functional groups are fundamental processes for organic synthesis. Recently, the catalysis by the transition metals and Baylis–Hillman reaction have been the focus of research.^{7–13}

In connection with our interest in the synthesis and the reactivity of trifluoromethylated Vilsmeier adducts,^{14,15} we considered the Sonogashira reaction with the acrolein **1** and the Baylis–Hillman reaction towards trifluoromethylated acroleins **5a–f**.^{17,18}

Palladium-catalysed coupling reaction; synthesis of trifluoromethylated enynes (3a–c): This reaction is useful for the preparation of biological polymers.¹⁹ It consists of introducing an sp^2 hybrid organic substratum to acetylenic one: (sp^2 - sp coupling). The utilisation of a co-catalysis (CuI) expedites the acetylenic substratum easing the reaction with the palladium complex (0). By utilising Sonogashira coupling, the reaction of the acrolein **1** with alkynes **2a–c** has given trifluoromethylated enynes **3a–c**; each one formed as a mixture of *Z* and *E* diastereomers. We have observed that the *E*:*Z* ratios of these compounds depend on the nature of the alkynes and can be determined by ^{19}F NMR spectroscopy. An anisotropic effect for the phenyl moiety on to the CF_3 group was observed in the case of the (*Z*)-**3** diastereomers (Scheme 1).

***N*-Methylimidazole-catalysed Baylis–Hillman reactions; synthesis of 2-(hydroxytrifluoromethylalkenyl)cyclohexenones from β -trifluoromethylated acroleins and cyclohexenone** The Baylis–Hillman reaction is a useful and general σ C–C bond-forming reaction providing a straight forward single-step

synthetic method to form densely functionalised precursors.^{20,21} Their versatility has made these multifunctionalised compounds valuable synthetic intermediates^{22,23} and has also stimulated their utilisation as substrates for chemical transformation mediated by palladium, especially for Heck reactions.^{24,25}

In continuation of our study on α -functionalisation of cyclic enones, we now report our results on the *N*-methylimidazole mediated Baylis–Hillman reaction between cyclic enones and trifluoromethylated acroleins **5a–f**. We have found the 2-(hydroxytrifluoromethylalkenyl)cyclohexenones **6a–f** (Scheme 2).

In conclusion, we describe in this work the synthesis of trifluoromethylated enynes **3a–c** by palladium catalysis coupling reaction. The products obtained can be precursors for the synthesis of biological heterocyclic such as Neocarzinstatine which has antitumor activity.²⁶

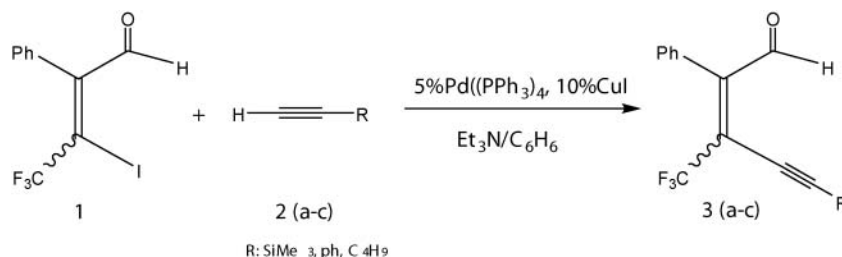
The Baylis–Hillman adducts **6–f** can be used as intermediates in the synthesis of natural products.²⁷ However, we have varied the operation conditions to ameliorate yields and to reduce the reaction time.

Experimental

All reactions progress was monitored by TLC analysis (Merck Kieselgel 60 F₂₅₄). All compounds were purified by chromatography column (Silica gel 60. 70–230 mesh ASTM). IR spectra were obtained on Perkin-Elmer Paragon 1000 PC. ^1H NMR spectra were recorded on a Bruker AC-300 (300 MHz) spectrometer using tetramethylsilane (TMS, δH , 0) as internal standard. ^{13}C NMR spectra were recorded on Bruker AC-300 (75 MHz) spectrometer with proton decoupling. For ^{19}F NMR spectra, C_6F_6 was used as reference and they were performed on a Bruker AC-300 (282.36 MHz). Mass spectra were carried out on a Hewlett-Packard model (70 eV) by the staff of the Faculty of Medicine, Department of Biochemistry, Monastir, Tunisia, under electronic impact (EI). Elemental analyses were performed by the microanalyses service of the Centre of Pharmaceutical Studies, Châtenay-Malabry. Coupling constants (*J* values) are given in Hertz and spin multiplicities are indicated by the following symbols: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet).

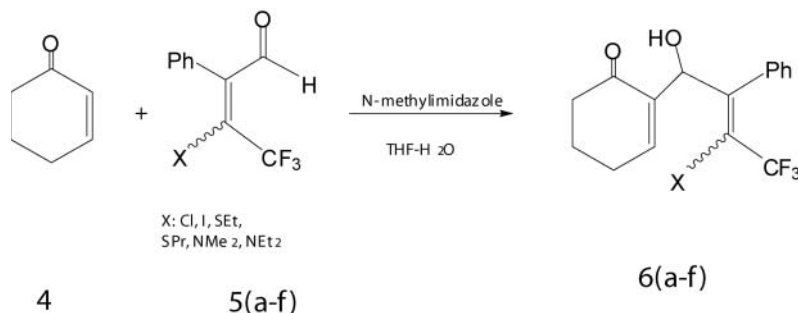
Typical procedure for the synthesis of compound 3a–c

To a solution of the acrolein **1** (3×10^{-4} mol) in the benzene, we are added under argon atmosphere and at room temperature, the $\text{Pd}^0(\text{PPh}_3)_4$



Scheme 1

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Scheme 2

(5%), CuI (10%), Et₃N (6 × 10⁻⁴ mol) and the alkynes **2a–c**). The mixture was stirred at room temperature the evolution of the reaction was followed by gaseous phase chromatography and quenched with NH₄Cl. The organic layer was separated and the aqueous phase was extracted with ether (3 × 15 mL) and dried over Na₂SO₄. The solvent was removed under reduced pressure. The product was purified by column chromatography, filled with silica gel and elution with ethyl ether-petroleum ether (20/80).

2-phenyl-3-trifluoromethyl-5-trimethylsilanylpent-2-en-4-ynal (3a): Colourless oil. Yield: 80%. IR ν (cm⁻¹): 1692 (CO); 1155–1148 (CF₃); ¹H NMR (400 MHz, CDCl₃): 0.2 (2s, 9H); 7.3 (m, 5H); 10 (q, 1H); 10.3 (s, 1H); ¹³C NMR (75.47 MHz, CDCl₃): 14.2–14.6 (2s, CH₃); 122.1–122.6 (2q, CF₃); 128–130.3 (m, C₆H₅); 192–191.7 (2s, CHO); ¹⁹F NMR (282.4 MHz; CDCl₃): E:Z= 5/95. δ_F: 109 (s, CF₃); 111 (s, CF₃). Anal Calcd for C₁₅H₁₅F₃O₂Si: C, 60.78; H, 5.10. Found: C, 60.72; H, 5.28%.

2,5-diphenyl-3-trifluoromethylpent-2-en-4-ynal (3b): Yellow oil. Yield: 85%. IR. ν (cm⁻¹): 1690 (CO); 1148–1185 (CF₃); ¹H NMR (400 MHz, CDCl₃): 7.5 (m, 10H); 10.3 (q, 1H); 10.6 (s, 1H); ¹³C NMR (75.47 MHz, CDCl₃): 122.8–122.3 (2q, CF₃); 128.15–131.5 (m, 2C₆H₅); 137 (CCF₃); 147.31 (C–C–CF₃); 192.6–191.83 (2s, CHO); ¹⁹F NMR (282.4 MHz; CDCl₃): E:Z= 13/87. δ_F: 103.5 (s, CF₃); 109 (s, CF₃). Anal Calcd for C₁₈H₁₅F₃O₂: C, 71.98; H, 3.69. Found C, 71.7; H, 3.28%.

2-phenyl-3-trifluoromethylnon-2-en-4-ynal (3c): Colourless oil. Yield: 78%. IR. ν (cm⁻¹): 1698 (CO); 1158.17–1134 (CF₃); ¹H NMR (400 MHz, CDCl₃): 0.7 (t, 3H); 1.4 (m, 4H); 2.1 (m, 2H); 7.3 (m, 5H); 10.4 (s, 1H); ¹³C NMR (75.47 MHz, CDCl₃): 13.58–14.8 (m, (CH₂)₂CH₃); 47.53–48.7 (2s, CH₂); (121.7; 122) (2q, CF₃); ¹J_{CF} = 282.7 Hz); 127.3–130.2 (m, C₆H₅); 134 (q, CCF₃); ²J_{CF} = 30.18 Hz); 145.22 (C–C–CF₃); (191.7; 190.6) (2s, CHO); ¹⁹F NMR (282.4 MHz; CDCl₃): E:Z = 10/90. δ_F: 108.8 (s, CF₃); 110.5 (s, CF₃). Anal Calcd for C₁₆H₁₅F₃O₂: C, 68.54; H, 5.39. Found C, 68.78; H, 5.43%.

Preparation of 2-(3-chloro-4,4,4-trifluoro-1-hydroxy-2-phenylbut-2-enyl)cyclohex-2-en-1-one (6a): A 50 mL round-bottomed flask was charged with cyclohexenone (0.48, 5mmol), 10 mmol of the acrolein **5a** 3mL of THF and 3mL of H₂O and N-methylimidazole (0.05g, 0.5mmol). The resulting mixture was stirred for 40 days at 60 °C. When the reaction, followed by TLC was finished, the mixture was acidified with aqueous HCl (1.5M) and extracted with methylenechloride. After the usual work up, chromatography of crude product on silica gel, using ether as eluent, gave pure 2-(3-chloro-4,4,4-trifluoro-1-hydroxy-2-phenylbut-2-enyl)cyclohex-2-en-1-one **6a**.

2-(3-chloro-4,4,4-trifluoro-1-hydroxy-2-phenylbut-2-enyl)cyclohex-2-en-1-one (6a): Yellow oil. Yield: 45%. 40 days. IR ν (cm⁻¹): 3397 (OH); 1686 (CO); ¹H NMR (400 MHz, CDCl₃): 1.2 (m, 6H); 4.1 (s, 1H); 4.9 (OH); 7.4 (m, 5H); 7.6 (m, 1H); ¹³C NMR (75.47 MHz, CDCl₃): 22.89; 26.31; 39.15; 61.23; 120.04; 127.4; 128.9; 127.53–130.5; 138.78; 147.84; 205. ¹⁹F NMR (282.4 MHz; CDCl₃): δ_F: 80.84; MS (m/z): 206 (30); 222 (45); 69 (78); 330 (25); 279 (36). Anal Calcd for C₁₆H₁₄F₃ClO₂: C, 58.07; H, 4.27. Found C, 58.23; H, 4.06%.

2-(4,4,4-trifluoro-1-hydroxy-3-iodo-2-phenylbut-2-enyl)cyclohex-2-en-1-one (6b): Yellow oil. Yield: 44%. 45 days. IR ν (cm⁻¹): 3383 (OH); 1672 (CO); ¹H NMR (400 MHz, CDCl₃): 1.3 (m, 6H); 3.9 (s, 1H); 4.3 (OH); 7.2 (m, 5H); 7.3 (m, 1H); ¹³C NMR (75.47 MHz, CDCl₃): 22.36; 25.69; 38.41; 61.07; 118.34; 125.98; 127.3; 127.21–130.1; 135.87; 146.71; 203. ¹⁹F NMR (282.4 MHz; CDCl₃): δ_F: 81.31. Anal Calcd for C₁₆H₁₄F₃IO₂: C, 45.49; H, 3.34. Found C, 45.53; H, 3.26%.

2-(3-ethylsulfanyl-4,4,4-trifluoro-1-hydroxy-2-phenylbut-2-enyl)cyclohex-2-en-1-one (6c): Colourless oil. Yield: 55%. 22 days. IR ν (cm⁻¹): 3406 (OH); 1669 (CO); 1167 (CF₃); ¹H NMR (400 MHz, CDCl₃): 0.85 (t, 3H); 2 (q, 2H); 2.38 (m, 6H); 6.1 (t, 1H); 3.9 (s, 1H); 4.6 (, OH); 7.3 (m, 5H); ¹³C NMR (75.47 MHz, CDCl₃): 14.15; 22.3; 26.22; 30.31; 37.78; 60.4; 127.40; 129.48; 136.91; 146.3; 200.65; ¹⁹F NMR (282.4 MHz; CDCl₃): δ_F: 106.84; MS (m/z): 356 (M⁺, 60); 231 (42); 126(31); 77(25); 61(30); 57(10). Anal Calcd for C₁₈H₁₉F₃O₂S: C, 60.65; H, 5.37. Found C, 60.52; H, 5.45%.

2-(4,4,4-trifluoro-1-hydroxy-2-phenyl-3-propylsulfanylbut-2-enyl)cyclohex-2-en-1-one (6d): Colourless oil. Yield: 50%. 28 days. IR ν (cm⁻¹): 3394 (OH); 1658 (CO); 1152 (CF₃); ¹H NMR (400 MHz, CDCl₃): 0.83 (t, 3H); 1.56 (m, 2H); 1.99 (t, 2H); 2.18 (m, 6H); 5.92 (t, 1H); 3.6 (s, 1H); 4.1 (OH); 7.1 (m, 5H); ¹³C NMR (75.47 MHz, CDCl₃): 14.12; 14.25; 21.88; 26.11; 30.28; 37.41; 60.1; 127.38; 128.78; 135.98; 144.8; 200.65; ¹⁹F NMR (282.4 MHz; CDCl₃): δ_F: 106.78. Anal Calcd for C₁₉H₂₁F₃O₂S: C, 61.59; H, 5.71. Found C, 61.59; H, 5.43%.

2-[3(dimethylamino)-4,4,4-trifluoro-1-hydroxy-2-phenylbut-2-enyl]cyclohex-en-1-one (6e): Colourless oil. Yield: 47%. 32 days. IR ν (cm⁻¹): 3547 (OH); 1690 (CO); 1163 (CF₃); ¹H NMR (400 MHz, CDCl₃): 2.09 (s, 6H); 2.6 (m, 6H); 4 (s, 1H); 5.8 (OH); 7.2 (t, 1H); 7.6 (m, 5H); ¹³C NMR (75.47 MHz, CDCl₃): 21.32; 26.43; 29.72; 43.02; 127.95; 129.23; 129.64; 129.89; 130.24; 131.28; 135.13; 172.06; ¹⁹F NMR (282.4 MHz; CDCl₃): δ_F: 80.93; MS (m/z): 339 (M⁺, 10); 282 (35); 224 (68); 97 (100). Anal Calcd for C₁₈H₂₀F₃N₂O₂: C, 63.68; H, 5.94; N = 4.13. Found C, 63.64; H, 5.73; N = 4.55%.

2-[3(diethylamino)-4,4,4-trifluoro-1-hydroxy-2-phenylbut-2-enyl]cyclohex-2-en-1-one (6f): Colourless oil. Yield: 45%. 30 days. IR ν (cm⁻¹): 3557 (OH); 1688 (CO); 1151 (CF₃); ¹H NMR (400 MHz, CDCl₃): 2 (t, 6H); 2.6 (q, 4H); 2.4 (m, 6H); 5.4 (OH); 3.9 (s, 1H); 6.1 (t, 1H); 7.4 (m, 5H); ¹³C NMR (75.47 MHz, CDCl₃): 13.58; 22.77; 25.69; 38.25; 47.53; 60.76; 128.49; 128.5; 128.47; 128.83; 131; 138.44; 146.77; 200.38; ¹⁹F NMR (282.4 MHz; CDCl₃): δ_F: 81; M S(m/z): 126 (60); 111 (29); 97 (44); 77 (78); 71 (18); 56 (40). Anal Calcd for C₂₀H₂₄F₃N₂O₂: C, 65.36; H, 6.59; N = 3.81. Found: C, 65.41; H, 6.52; N, 3.67%.

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