

Synthesis of fumarate derivatives using multicomponent reaction of thioles

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Abstract: The fumarate derivatives are obtained in good to excellent yields by proceeding through a simple, mild, and efficient procedure utilizing activated acetylenes, thioles and isocyanates in the presence of catalytic amount of Et₃N under solvent-free conditions.

Keywords: Fumarate, Activated acetylenes, Thioles, Solvent-free, Arylisocyanate.

Introduction

Multicomponent reactions (MCRs), with three or more reactants join in a one-pot procedure to afford a single product [1-3]. They are economically and environmentally useful because multi-step synthesis produces large amounts of trash frequently because of complex isolation actions frequently involving comfortable, toxic, and hazardous solvents after each step [4-7]. MCRs are absolutely suited for combinatorial library synthesis and increased utilize in the finding procedure for new drugs and agrochemicals [8]. They supply a dominant tool toward the one-pot synthesis of diverse and complex compounds as well as small and drug-like heterocycles [9]. Green chemistry move towards hold out significant potential not only for reduction of byproducts, waste produced, and lowering of energy but also in the expansion of new methodologies toward before exclusive materials, using existing technologies [10]. Between existing part of chemistry, medicinal and pharmaceutical chemistry are possibly developed for greening [11]. With propargylic esters yield of reactions is low (Scheme 1).

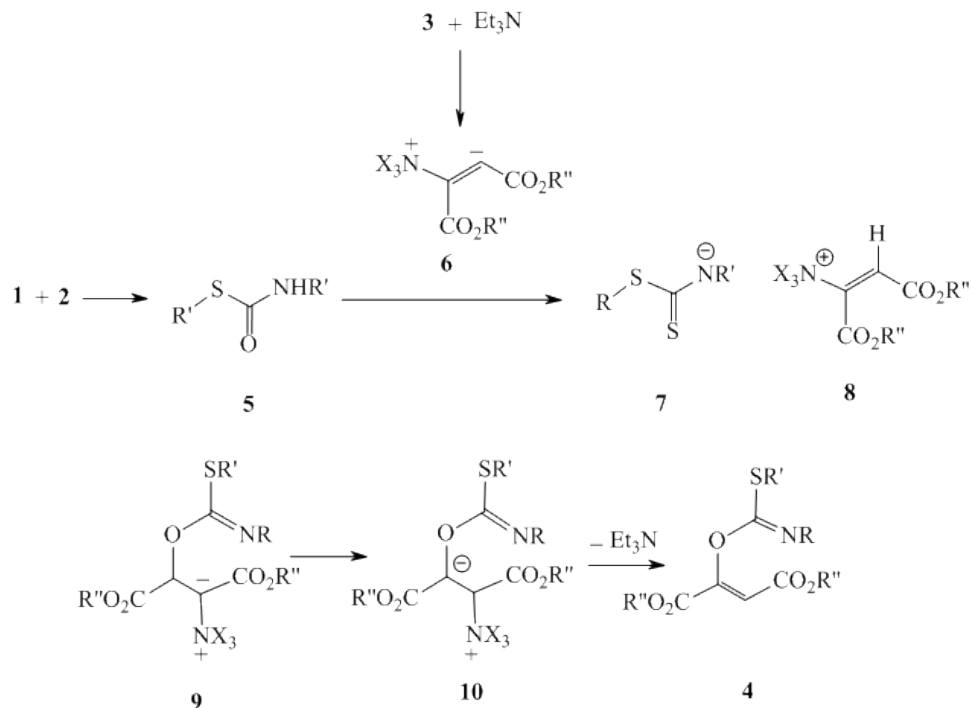
Hence, we investigated a simple three-component reaction between activated acetylenic compounds, temperature which afforded fumarate derivatives **4** in good isolated yields.

Results and discussion

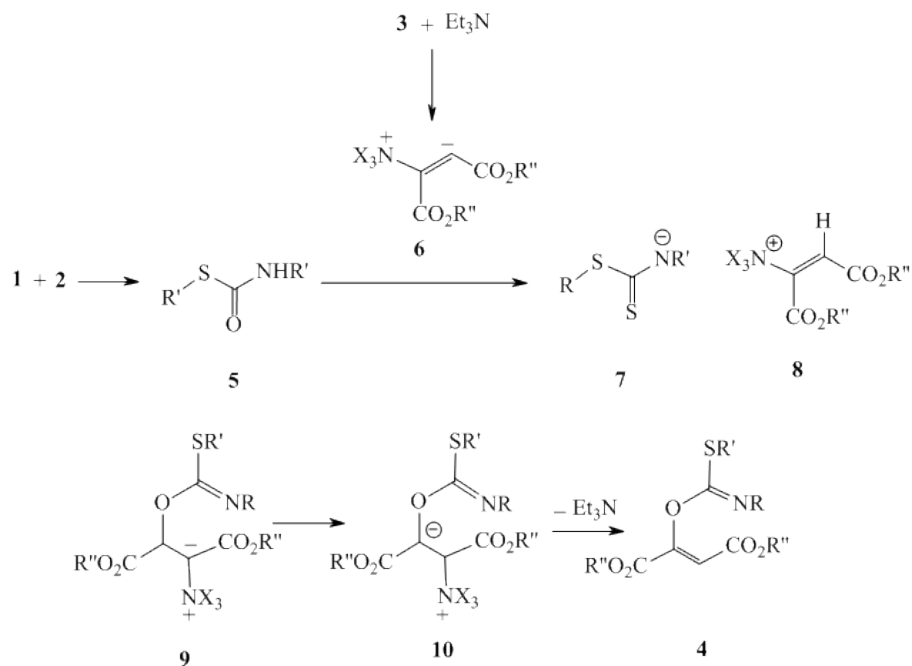
The ¹H NMR spectrum of **4a** displayed signals for vicinal methine protons at $\delta = 4.78$ and 4.92 , which appeared as two set of doublets with ³J_{HH} values of 12.4 Hz. The methoxy groups showed two separate singlet at $\delta = 3.78$ and 3.85 . Observation of ³J_{HH} = 12.4 Hz for the vicinal methine protons in **4a** indicates the dominance of anti arrangement. The carbonyl groups resonances in the ¹³C NMR spectra of **4a** are appeared at 172.5 (C=O), 173.7 (C=O) ppm. Also the mass spectra of **4a** displayed the molecular ion peak in the appropriate m/z values. A proposed mechanism for the formation of compound **4** is shown in Scheme 2. Apparently, the zwitterionic intermediate **6** which formed from the reaction of Et₃N(X₃N) and electron deficient acetylenic ester **3** is protonated by the intermediate **5** that was generated in situ from the reaction of thioles **2** and isocyanate **1**, produce intermediates **7** and **8**. Nucleophilic attack of the conjugate base **7** on intermediate **8** leads to adduct **9**

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which undergo proton shifts to afford new zwitterionic **10**. Finally, intramolecular cyclization of **10** produces compound **4**.



Scheme 1: Reaction of activated acetylenes, isocyanates and thioles



Scheme 2: Proposed mechanism for the formation of **4**.

Conclusion

In conclusion, we found that the reaction of activated acetylenic compounds with isocyanates and thioles in the presence of Et₃N leads to a facile synthesis of some functionalized fumarates under solvent-free conditions without using any catalyst.

Experimental

All chemicals used in this work were prepared from Fluka (Buchs, Switzerland) and were used without further purification. Electrothermal 9100 apparatus is employed for measuring of melting points of products. Elemental analyses for C, H, and N were performed with Heraeus CHN–O–Rapid analyzer. Mass spectra were recorded on a FINNIGAN-MAT 8430 spectrometer operating at an ionization potential of 70 eV. Measurement of IR spectra was performed by Shimadzu IR-460 spectrometer. ¹H, and ¹³C NMR spectra were evaluated with a BRUKER DRX-500 AVANCE spectrometer at 500.1 and 125.8 MHz, respectively. ¹H, and ¹³C, spectra were obtained for solutions in CDCl₃ using TMS as internal standard or 85% H₃PO₄ as external standard.

General procedure for preparation of compounds 4:

To a magnetically stirred mixture of activated acetylenes **3** (2 mmol) and Et₃N was added mixture of isocyanates **1** and thioles **2** (2 mmol) at room temperature. The reaction mixture was then stirred. After completion of the reaction [TLC (AcOEt/hexane 1:7) monitoring], 15 mL H₂O was poured into the reaction mixture. The solid residue was filtered and washed by cold diethyl ether to afforded pure compounds **4**.

Dimethyl 2-(methylimino)-3-phenyl-fumarate-4,5-dicarboxylate (4a):

Yellow powder, m.p. 156-158°C, yield: 0.46 g (75%). IR (KBr) (ν_{max}/cm⁻¹): 1745, 1738, 1698, 1657, 1574, 1467, 1382, 1215 cm⁻¹. Anal. Calcd for C₁₄H₁₆N₂O₄S (308.35): C, 54.53; H, 5.23; N, 9.08. Found: C, 54.62; H, 5.34; N, 9.23%. ¹H NMR (500 MHz, CDCl₃): δ 2.83 (3 H, s, NMe), 3.78 (3 H, s, MeO), 3.85 (3 H, s, MeO), 4.78 (1 H, d, ³J = 12.4, CH), 4.92 (1 H, d, ³J = 12.4, CH), 7.23 (1 H, t, ³J = 7.4, CH), 7.35 (2 H, d, ³J = 7.6, 2 CH), 7.54 (2 H, t, ³J = 7.6, 2 CH) ppm. ¹³C NMR (125.7 MHz, CDCl₃): δ 34.6 (NMe), 42.7 (CH), 51.6 (MeO), 52.4 (MeO), 58.4 (CH), 122.8 (CH), 128.3 (2 CH), 129.6 (2 CH), 139.8 (C), 163.4 (C=N), 172.5 (C=O), 173.7 (C=O) ppm. MS, *m/z* (%): 308 (M⁺, 15), 277 (86), 77 (64), 31 (100).

Dimethyl 2-(ethylimino)-3-(4-methoxyphenyl)-fumarate-4,5-dicarboxylate (4b):

Pale yellow powder, m.p. 168-170 °C, yield: 0.59 g (87%). IR (KBr) (ν_{max}/cm⁻¹): 1742, 1736, 1686, 1632, 1525, 1487, 1325, 1219 cm⁻¹. Anal. Calcd for C₁₆H₂₀N₂O₅S (352.41): C, 54.53; H, 5.72; N, 7.95. Found: C, 54.64; H, 5.80; N, 8.10%. ¹H NMR (500 MHz, CDCl₃): δ 1.24 (3H, t, ³J = 7.3, CH₃), 3.27 (2 H, q, ³J = 7.3, CH₂), 3.70 (3 H, s, MeO), 3.76 (3 H, s, MeO), 3.87 (3 H, s, MeO), 4.75 (1 H, d, ³J = 12.2, CH), 4.87 (1 H, d, ³J = 12.2, CH), 7.14 (2 H, d, ³J = 7.8, 2 CH), 7.28 (2 H, d, ³J = 7.6, 2 CH) ppm. ¹³C NMR (125.7 MHz, CDCl₃): δ 14.2 (CH₃), 41.5 (CH₂), 43.7 (CH), 51.5 (MeO), 52.6 (MeO), 55.4 (MeO), 59.3 (CH), 111.2 (2 CH), 130.3 (2 CH), 134.8 (C), 154.2 (C), 160.7 (C=N), 171.8 (C=O), 172.6 (C=O) ppm. MS, *m/z* (%): 352 (M⁺, 10), 321 (64), 108 (96), 31 (100).

Diethyl 2-(buthylimino)-3-(4-methoxyphenyl)-fumarate-4,5-dicarboxylate (4c):

White powder, m.p. 162-164 °C, yield: 0.70 g (83%). IR (KBr) (ν_{max}/cm⁻¹): 1740, 1738, 1687, 1645, 1438, 1357, 1256 cm⁻¹. Anal. Calcd for C₂₀H₂₈N₂O₅S (408.51): C, 58.80; H, 6.91; N, 6.86. Found: C, 58.92; H, 6.98; N, 6.90%. ¹H NMR (500 MHz, CDCl₃): δ 1.19 (3H, t, ³J = 7.2, CH₃), 1.22 (3H, t, ³J = 7.4, CH₃), 1.28 (3H, t, ³J = 7.3, CH₃), 1.68 (2 H, q, ³J = 7.3, CH₂), 1.78 (2 H, m, CH₂), 2.83 (2 H, t, ³J = 6.8, NCH₂), 3.75 (3 H, s, MeO), 4.12 (2 H, q, ³J = 7.3, CH₂O), 4.23 (2 H, q, ³J = 7.3, CH₂O), 4.62 (1 H, d, ³J = 11.7, CH), 5.02 (1 H, d, ³J = 11.7, CH), 7.12 (2 H, d, ³J = 7.6, 2 CH), 7.32 (2 H, d, ³J = 7.6, 2 CH) ppm. ¹³C NMR (125.7 MHz, CDCl₃): δ 13.3 (CH₃), 13.8 (CH₃), 14.3 (CH₃), 21.4 (CH₂), 32.5 (CH₂), 43.6 (CH), 54.8 (MeO), 59.5 (CH), 61.2 (CH₂O), 62.0 (CH₂O), 62.7 (NCH₂), 114.5 (2 CH), 130.8 (2 CH), 135.4 (C), 156.7 (C), 161.2 (C=N), 172.3 (C=O), 174.2 (C=O) ppm. MS, *m/z* (%): 408 (M⁺, 8), 363 (84), 108 (68), 45 (100).

Diethyl 2-(tert-butyylimino)-3-(4-methylphenyl)-fumarate-4,5-dicarboxylate (4d):

yellow powder, m.p. 164-166 °C, yield: 0.59 g (75%). IR (KBr) (ν_{max}/cm⁻¹): 1736, 1732, 1694, 1587, 1467, 1346, 1238 cm⁻¹. Anal. Calcd for C₂₀H₂₈N₂O₄S (392.51): C, 61.20; H, 7.19; N, 7.14. Found: C, 61.32; H, 7.25; N, 7.22%. ¹H NMR (500 MHz, CDCl₃): δ 1.25 (3H, t, ³J = 7.4, CH₃), 1.32 (3H, t, ³J = 7.4, CH₃), 1.35 (9H, s, Me₃C), 2.28 (3 H, s, CH₃), 4.15 (2 H, q, ³J = 7.4, CH₂O), 4.28 (2 H, q, ³J = 7.4, CH₂O), 4.73 (1 H, d, ³J = 11.5, CH), 4.96 (1 H, d, ³J = 11.5, CH), 7.24 (2 H, d, ³J = 7.5, 2 CH), 7.36 (2 H, d, ³J = 7.6, 2 CH)

ppm. ^{13}C NMR (125.7 MHz, CDCl_3): δ 13.8 (CH_3), 14.2 (CH_3), 22.4 (CH_3), 28.7 (Me_3C), 44.3 (CH), 48.7 (Me_3C), 58.7 (CH), 61.4 (CH_2O), 62.3 (CH_2O), 129.4 (2 CH), 130.2 (C), 131.4 (2 CH), 140.7 (C), 160.4 ($\text{C}=\text{N}$), 172.5 ($\text{C}=\text{O}$), 175.3 ($\text{C}=\text{O}$) ppm. MS, m/z (%): 392 (M^+ , 20), 377 (84), 91 (84), 45 (100).

Dimethyl 2-(methylimino)-3-(4-bromophenyl)-fumarate-4,5-dicarboxylate (4e):

Yellow crystals, m.p. 183-185 °C, yield: 0.62 g (80%). IR (KBr) ($\nu_{\text{max}}/\text{cm}^{-1}$): 1737, 1732, 1695, 1587, 1485, 1436, 1342, 1225 cm^{-1} . Anal. Calcd for $\text{C}_{14}\text{H}_{15}\text{BrN}_2\text{O}_4\text{S}$ (387.25): C, 43.42; H, 3.90; N, 7.23. Found: C, 43.53; H, 3.95; N, 7.32%. ^1H NMR (500 MHz, CDCl_3): δ 3.12 (3H, s, NMe), 3.75 (3 H, s, MeO), 3.82 (3 H, s, MeO), 4.83 (1 H, d, $^3J = 11.8$, CH), 4.92 (1 H, d, $^3J = 11.8$, CH), 7.10 (2 H, d, $^3J = 7.8$, 2 CH), 7.54 (2 H, d, $^3J = 7.8$, 2 CH) ppm. ^{13}C NMR (125.7 MHz, CDCl_3): δ 34.5 (NCH₃), 44.2 (CH), 51.2 (MeO), 51.8 (MeO), 60.3 (CH), 116.7 (C), 129.7 (2 CH), 132.6 (2 CH), 139.4 (C), 162.3 (C=N), 172.4 (C=O), 173.8 (C=O) ppm. MS, m/z (%): 387 (M^+ , 15), 356 (78), 156 (64), 31 (100).

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