Iranian Journal of Organic Chemistry Vol. 7, No. 3 (2015) 1613-1615

One pot three component synthesis of new amino furanyl derivatives via reaction of maleic anhydride, activated acetylenes and primary amine

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Received: May 2015; Revised: June 2015; Accepted: June 2015

Abstract: Primary amine reacts smoothly with maloeic anhydride in the presence of dialkyl acetylenedicarboxylates to produce tertiary amino furanyl derivatives in moderate to good yields.

Keywords: Amino furanyl, Primary amine, Activated acetylenes, Maleic anhydride.

Introduction

Nitrogen-containing compounds are ubiquitous in nature and many of them are biologically active. The nitrogen-containing units of these molecules play important roles in their bioactivity. For the synthesis of these nitrogen-containing building blocks, the Amine reactions is one of the most common and convenient routes. The science of organic synthesis is constantly enriched by the improvement of synthetic methodologies. The paradigms of organic synthesis have shifted from the traditional concept using only chemical yield to define efficiency to one in which the economic and ecological values are also considered [1-7].

Multi-component reactions (MCRs) have emerged as an efficient and powerful tool in modern synthetic organic chemistry due to their valued features such as atom economy, straightforward reaction design and the opportunity to construct target compounds by the of several diversity elements in a single chemical event. Typically, purification of products resulting from MCRs is also simple, since all the organic reagents employed are consumed and are incorporated into the target compound. MCRs, leading to interesting heterocyclic scaffolds, are particularly useful for the construction of diverse chemical libraries of 'drug like' molecules [8-9].

As part of our current studies on the development of new routes to new heterocyclic systems [10-14], in this letter we describe a simple and efficient synthesis of functionalized amino furanyl derivatives.

Results and discussion

The reaction of primary amine (**1**) with maleic anhydride (**2**) in the presence of dialkyl acetylenedicarboxylates (**3**) proceeded smoothly in toluene and was complete within 24 hours. The ^{1}H and ^{13}C NMR spectra of the crude products clearly indicated the formation of Dialkyl(Z)-2-[benzyl(2,5-dioxotetrahydro-3-furanyl)amonio]-2-butendioate (**4**) in 47– 73% yields (Scheme **1**).

The structures of compounds **4a-4c** were deduced from their elemental analyses and their IR, ^{1}H NMR, ^{13}C NMR. For example, the ^{1}H NMR spectrum of **4a** exhibited four singlets (δ= 2.25, 3.63, 3.85 and 3.96) identified as metyl, N-methyl and two methoxy protons, along with two doublets for the remaining

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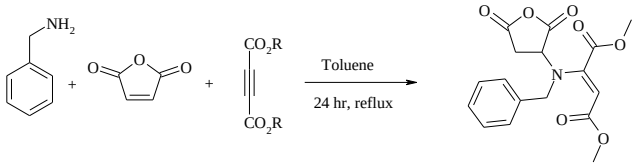
alkenes' protons. The ^{1}H-decoupled ^{13}C NMR spectrum of **4a** showed 13 distinct resonances which further confirmed the proposed structure. The IR spectrum of **4a** displayed characteristic ketone and ester carbonyl bands. The ^{1}H NMR and ^{13}C NMR spectra of **4b**–**4c** were similar to those for **4a** except for the ester moieties, which exhibited characteristic resonances in appropriate regions of the spectrum.



2, 4	R	Yield % of 4
a	Me	62
b	Et	53
c	^{i}Pro	39

Scheme 1: Synthesis of three-functionalized new amino furanyl derivatives.

A possible mechanism for the formation of **4** is shown in (**Scheme 3**). Presumably, the intermediate [15], formed from primary amine and the maleic anhydride, attacks **3** to furnish product **4**.

Scheme 3: Proposed mechanism for the formation of products.

Conclusion

In summary, we have reported a new procedure for the synthesis of biologically active tertiary amine derivatives *via* three component reaction of primary amine and maleic anhydride in the presence of activated acetylenes in moderate to good yield. The functionalized amine reported in this research may be considered as potentially useful intermediates because they possess atoms with different oxidation states. The present procedure has the advantage that not only is the reaction performed under neutral conditions, but also the reactants can be mixed without any prior activation or modification.

Experimental

General procedure:

All compounds were obtained from Fluka or Merck and were used without further purification. IR Spectra: Shimadzu IR-460 spectrometer. ^{1}H-, ^{13}C- NMR spectra: Bruker DRX- 500 AVANCE instrument; in $CDCl_3$ at 500, 125 MHz, respectively; δ in ppm. Elemental analyses (C, H, N) were performed with a Heraeus CHN-O-Rapid analyzer.

Typical procedure for preparation of (**4**):

To a stirred solution of **1** (2 mmol) in 3 mL tolune was added **2** (2 mmol) at rt and stirred for 1 hour. Then Activated acetylenes was added to reaction mixture and refluxed for 24 h. The solvent was removed under reduced pressure, and the residue was separated by silica gel (Merck 230–400 mesh) flash column chromatography using *n*-hexane–EtOAc (6:1) mixture as eluent to get pure product **4**.

Data:

*Dimethyl (Z)-2-[benzyl(2,5-dioxotetrahydro-3-furanyl)amonio]-2-butendioate (**4a**)*:

White powder, 0.21 g, yield 62%. IR (KBr) (ν_{max}/cm^{-1}): 1749, 1734, 1723, 1704, 1590, 1200, 929, 784, 699. Anal. Calcd for $C_{17}H_{17}NO_7$ (347.3): C, 58.79; H, 4.93; N, 4.03%. Found: C, 59.02; H, 5.01; N, 4.12%. ^{1}H NMR: δ 2.75 (1H, dd, ^{3}J = 16, 10 Hz, CH), 3.20 (1H, dd, ^{3}J = 16, 3 Hz, CH), 3.83 (3H, s, OMe), 3.90 (3H, s, OMe), 4.25 (1H, dd, ^{3}J = 10, 3 Hz CH), 4.85 (1H, s, N-CH_2), 7.06 – 7.21 (5 H, m, 5 CH) ppm. ^{13}C NMR: δ 35.4 (CH_2), 36.5 (N-CH_2), 46.4 (N-CH), 53.3 (OMe), 57.8 (OMe), 126.3 (2 CH), 127.2 (CH), 128.8 (2 CH), 129.1 (C), 116.6 (C), 127.4 (CH), 128.9 (C), 139.3 (C), 163.2 (C=O), 165.7 (C=O), 173.7 (C=O) ppm.

*Diethyl (Z)-2-[benzyl(2,5-dioxotetrahydro-3-furanyl)amonio]-2-butendioate (**4b**)*:

White powder, 0.20 g, yield 53%. IR (KBr) (ν_{max}/cm^{-1}): 1751, 1730, 1729, 1706, 1600, 1210, 949, 788, 689. Anal. Calcd for $C_{19}H_{21}NO_7$ (375.3): C, 60.80; H, 5.64; N, 3.73%. Found: C, 60.91; H, 5.73; N, 3.88%. ^{1}H NMR: δ 0.89 (3H, t, ^{3}J = 7.1 Hz, CH_3), 1.12 (3H, t, ^{3}J = 7.2 Hz, CH_3), 2.64 (1H, dd, ^{3}J = 14, 11 Hz, CH), 3.11 (1H, dd, ^{3}J = 14, 4 Hz, CH), 4.19-4.23 (4H, m, 2 O-CH_2), 4.27 (1H, dd, ^{3}J = 11, 4 Hz CH), 4.88 (1H, s, N-CH_2), 7.09 – 7.23 (5 H, m, 5 CH) ppm. ^{13}C NMR: δ 13.4 (CH_3), 14.1 (CH_3), 36.1 (CH_2), 36.9 (N-CH_2), 47.1 (N-CH), 63.4 (O-CH_2), 64.8 (O-CH_2), 125.4 (2 CH), 126.3 (CH), 128.9 (2 CH), 129.4 (C), 128.8 (C), 128.9 (CH), 129.2 (C), 139.3 (C), 163.6 (C=O), 166.9 (C=O), 175.7 (C=O) ppm.

*Diisopropyl (Z)-2-[benzyl(2,5-dioxotetrahydro-3-furanyl)amonio]-2-butendioate (**4c**)*:

White powder, 0.16 g, yield 39%. IR (KBr) (ν_{max}/cm^{-1}): 1751, 1730, 1729, 1706, 1600, 1210, 949, 788, 689. Anal. Calcd for $C_{21}H_{25}NO_7$ (403.4): C, 62.52; H, 6.25; N, 3.47%. Found: C, 52.71; H, 6.18; N, 3.57%. ^{1}H NMR: δ 1.25 (3 H, d, ^{3}J = 6.2 Hz, CH_3), 1.29 (3 H, d, ^{3}J = 7.1 Hz, CH_3), 1.32 (3 H, d, ^{3}J = 6.2 Hz, CH_3), 1.36

(3 H, d, ^{3}J = 7.1 Hz, CH_3), 2.66 (1H, dd, ^{3}J = 15, 10 Hz, CH), 3.18 (1H, dd, ^{3}J = 15, 5 Hz, CH), 4.37 (1H, dd, ^{3}J = 15, 5 Hz CH), 4.81 (1H, s, N-CH_2), 5.49 (1 H, m, CH), 6.33 (1 H, s, CH),6.97 – 7.18 (5 H, m, 5 CH) ppm. ^{13}C NMR: δ 21.8 (CH_3), 21.9 (CH_3), 22.4 (CH_3), 22.8 (CH_3), 37.2 (CH_2), 36.7 (N-CH_2), 47.8 (N-CH), 73.5 (O-CH), 77.2 (O-CH), 126.1 (2 CH), 126.7 (CH), 127.7 (CH), 128.7 (C), 129.3 (2 CH), 129.5 (C), 129.6 (C), 138.4 (C), 165.1 (C=O), 166.6 (C=O), 174.1 (C=O) ppm.

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