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Synthesis of fused [1,3]oxazines from 1,3-dichloro aceton, activated acetylenes and *N*-methyl imidazole

Anvar Mirzaei* and Hana Khanbabaei

Chemistry Department, Fculty of Science, Sanandaj Branch, Islamic Azad University, PO Box 618, Sanandaj, Iran.

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Abstract: The 1:1 intermediate generated by the addition of *N*-methyl imidazole to Activated acetylenes is trapped by 1,3-dichloroaceton to yield a new class of 1,3- oxazines heterocycles in good to excellent yields. The structures of these products were confirmed by NMR.

Keywords: 1,3-Oxazines, MCRs, Activated acetylenes, N-methyl imidazole.

Introduction

Organic synthesis like any other human activity aims at achieving ideality. An ideal synthesis is one that can be performed in the most efficient and facile manner with maximum conversion. In this respect multicomponent reactions (MCRs) come very close to the concept of an ideal synthesis [1-2]. MCRs are ordered pot reactions, where three or more starting materials react in a sequence of steps, until a final one, to give a final product which contains most of the portions of all the initial components [3-4] a MCR is thus a domino process by definition [5-6]. The development of novel MCRs is an intellectually challenging task since one has to consider not only the reactivity match of the starting materials but also the reactivities of the intermediate molecules generated *in situ*, their compatibility and their compartmentalization [7-8]

Nitrogen-oxygen heterocycles are of synthetic interest because they constitute an important class of natural and non-natural products, many of which exhibit useful biological activities [9]. Among these the interest in six membered systems containing one oxygen and one nitrogen atoms (positions 1, 3 or 1, 4) stems from the occurrence of oxazines in biologically activated compounds and natural products [10-11].

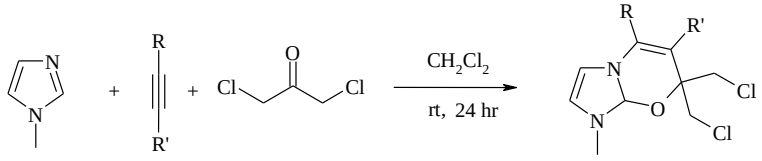
As part of our continuing interest in the construction of novel heterocycles [12-15], we now report the results of our studies involving the reactions of zwitterions derived from *N*-methyl imidazole (**1**) and Activated acetylenes (**2**) in the presence of 1,3-dichloroaceton (**3**), which constitutes a synthesis of new dialkyl 7,7-bis(chloromethyl)-1methyl-1,8a-dihydro-*7H*-imidazo[2,1-*b*][1,3-oxazine]-5,6-dicarboxylate derivatives (**4**) (Scheme **1**).

Results and discussion

The structures of compounds **4a–c** were deduced from their elemental analyses and their IR, ^{1}H NMR and ^{13}C NMR spectra. For example, the ^{1}H NMR spectrum of **4a** exhibited four singlets identified as N-methyl (δ 3.75 ppm), OMe (δ 3.87, 3.91 ppm), methine (δ 6.023) protons, along with doublet for the vinylic region. The ^{1}H-decoupled ^{13}C NMR spectrum of **4a** showed 13 distinct resonances, which confirmed the

*Corresponding author. Tel: (+98) 871 3288661, Fax: (+98) 871 3288662, E-mail: mirzaei.anvar@gmail.com

proposed structure. The IR spectrum of **4a** displayed characteristic hydroxy and aromatic bands. The ^{1}H NMR and ^{13}C NMR spectra of **4b-4c** were similar to those for **4a** except for the aromatic moieties, which exhibited characteristic resonances in appropriate regions of the spectrum.

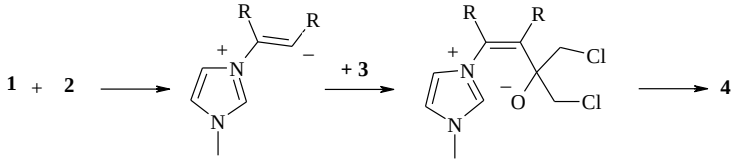


1 **2** **3**

4	R	R'	Yield %
a	CO_2Me	CO_2Me	76
b	CO_2Et	CO_2Et	68
c	$CO_2{}^{i}Pr$	$CO_2{}^{i}Pr$	59
d	H	CO_2Me	0

Scheme 1: Synthesis of new oxazines.

Although there is no experimental verification of this, a plausible rationalization may be advanced to explain the product formation. Presumably, the reaction involves the initial formation of a 1:1 zwitterionic intermediate [16-19] **5** drived from *N*-methyl imidazole and the activated acetylene **5**, reacts with **3** to produce **6**. Intermediate **6** undergoes cyclization to produce **4** (Scheme **2**).



5 **6**

Scheme 2: Proposed mechanism for the formation of products.

Conclusion

In summary, we have reported a transformation involving *N*-methyl imidazole and Activated acetylenes in the presence of 1,3-dichloroaceton, which affords a new route to the synthesis of completely new 1,3-oxazines. 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, Merck. M.p.: Electrothermal-9100 apparatus. IR Spectra: Shimadzu IR-460 spectrometer. ^{1}H-, ^{13}C- NMR spectra: Bruker DRX-300 AVANCE instrument; in $CDCl_3$ 300, 75 MHz, respectively; δ in ppm. Elemental analyses (C, H, N) were performed with a Heraeus CHNS-O-Rapid analyzer.

Typical procedure for preparation of **4a**:

A solution of 0.28 g of *N*-methyl imidazole (2.2 mmol) in 3 mL of solvent was added to a stirred solution of the Activated acetylenes (2 mmol) and 1,3-dichloroaceton (2 mmol) in 3 mL of solvent at room temperature. The reaction mixture was then allowed to stir for 24 h. The solvent was removed under reduced pressure, and the residue was purified by column chromatography (CC) (SiO_2 ; hexane/AcOEt 7 : 1) to afford the pure title compounds. **4a**.

Data:

*Dimethyl 7,7-bis(chloromethyl)-1methyl-1,8a-dihydro-7H-imidazo[2,1-b][1,3-oxazine]-5,6-dicarboxylate (**4a**):*

Pale yellow powder, 0.26 g, yield 76%. IR (KBr) (ν_{max}/cm^{-1}): 1736, 1714, 1435, 1263, 1010, 929, 765, 683. Anal. Calcd for $C_{13}H_{16}Cl_2N_2O_5$ (351.18): C, 44.46; H, 4.59; N, 7.98%. Found: C, 44.50; H, 4.68; N, 7.95%. ^{1}H NMR: δ 3.75 (3H, s, N-Me), 3.80-3,85 (3H,

m, 2 CH_2Cl) 3.87 (3H, s, OMe), 3.91 (3H, s, OMe), 6.02 (1H, s, CH), 7.13 (1H, d, ^3J=3.5 Hz, CH), 7.38 (1 H, ^3J=3.5 Hz, 1 CH) ppm. ^{13}C NMR: 37.7 (N-Me), 48.2 (CH_2Cl), 48.4 (CH_2Cl), 53.3 (OMe), 57.4 (OMe), 83.6 (C), 91.3 (CH), 115.6 (CH), 128.9 (C), 132.3 (CH), 142.3 (C), 163.5 (C=O), 164.9 (C=O) ppm.

*Diethyl 7,7-bis(chloromethyl)-1methyl-1,8a-dihydro-7H-imidazo[2,1-b][1,3-oxazine]-5,6-dicarboxylate (**4b**):*

Yellow powder, 0.26 g, yield 68%. IR (KBr) (ν_{max}/cm^{-1}): 1734, 1720, 1438, 1275, 1084, 949, 769, 670. Anal. Calcd for $C_{15}H_{20}Cl_2N_2O_5$ (379.23): C, 47.51; H, 5.32; N, 7.39%. Found: C, 47.64; H, 5.47; N, 7.51%. ^{1}H NMR: δ 1.12 (3H, d, J = 7.1, CH_3), 1.25 (3H, d, J = 6.9, CH_3), 3.64 (3H, s, N-Me), 3.76 (1H, d, J = 11.4, CH_2Cl), 3.81 (1H, d, J = 11.4, CH_2Cl), 3.89 (1H, d, J = 12.0, CH_2Cl), 4.01 (1H, d, J = 12.0, CH_2Cl), 4.12 (2H, t, J = 6.9, CH_3), 4.19 (2H, t, J = 7.1, CH_3), 5.89 (1H, s, CH), 7.02 (1H, d, ^3J=3.1 Hz, CH), 7.41 (1 H, ^3J=3.1 Hz, 1 CH) ppm. ^{13}C NMR: 13.9 (CH_3), 14.2 (CH_3), 38.1 (N-Me), 49.3 (CH_2Cl), 50.1 (CH_2Cl), 61.4 (O-CH_2), 62.3 (O-CH_2), 82.1 (C), 94.7 (CH), 116.9 (CH), 128.7 (C), 131.7 (CH), 140.2 (C), 164.6 (C=O), 164.8 (C=O) ppm.

*Diisopropyl 7,7-bis(chloromethyl)-1methyl-1,8a-dihydro-7H-imidazo[2,1-b][1,3-oxazine]-5,6-dicarboxylate (**4c**):*

Yellow powder, 0.24 g, yield 59%. IR (KBr) (ν_{max}/cm^{-1}): 1734, 1720, 1438, 1275, 1084, 949, 769, 670. Anal. Calcd for $C_{15}H_{20}Cl_2N_2O_5$ (407.29): C, 50.13; H, 5.94; N, 6.88%. Found: C, 50.19; H, 5.93; N, 6.79%. ^{1}H NMR: δ 1.26-1.34 (12H, m, 4CH_3), 3.69 (3H, s, N-Me), 3.70 (1H, d, J = 12.3, CH_2Cl), 3.76 (1H, d, J = 12.3, CH_2Cl), 3.98 (1H, d, J = 12.0, CH_2Cl), 4.13 (1H, d, J = 12.0, CH_2Cl), 5.02 (1H, m, CH), 5.16 (1H, m, CH), 5.87 (1H, s, CH), 6.67 (1H, d, ^3J=3.3 Hz, CH), 7.31 (1 H, ^3J=3.3 Hz, 1 CH) ppm. ^{13}C NMR: 21.1 (2CH_3), 21.9 (2CH_3), 38.3 (N-Me), 48.7 (CH_2Cl), 50.3 (CH_2Cl), 69.1 (O-CH), 69.9 (O-CH), 82.9 (C), 94.7 (CH), 116.1 (CH), 128.2 (C), 131.9 (CH), 141.3 (C), 162.4 (C=O), 165.1 (C=O) ppm.

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