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Efficient synthesis of imidazo oxazine using electron deficient acetylenic compounds

Sayyed Jalal Shams-Najafi[a*], Faramarz Rostami-Charati[b] and Samaneh sadat Sharifi[c]

[a]*Department of Chemistry,Faculty of Sciences, Ferdowsi University of Mashhad, Mashhad 91779-1436, I.R. Iran*
[b]*Research Center for Conservation of Culture Relicst (RCCCR), Research institute of Cultural Heritage &Tourism, Tehran, Iran.*
[a]*Department of Chemistry,Faculty of Sciences, University of Sistan and Baluchestan, sistan and Balouchestan, Iran*

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Abstract: An efficient synthesis of imidazo oxazins is described using a reaction of activated dialkyl acetylenedicarboxylates with acid chloride and ethanol in the Presence of imidazole. In addition, for existing imidazol and oxazin core in the synthesized compounds, evaluation of antioxidant activity was performed by radical trapping by DPPH and reducing power of ferric ion experiments. As a result, synthesized compounds show low radical trapping by DPPH and good reducing ability of ferric ion. The current procedure has the benefits for instance excellent yield of reaction, green media and easy separation of product.

Keywords: Imidazole; Alkyl bromide; Activated acetylenic compounds; Dialkyl acetylenedicarboxylates.

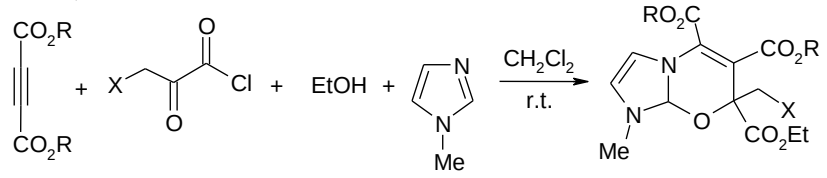
Introduction

Some heterocyclic compounds containing a imidazole ring in their structures offer important applications in pharmaceutical as well as in agrochemical chemistry [1, 2]. For example, ritonavir, an anti-HIV drug contains the thiazole moiety. These products, which have N and S atoms, are bridged easily with other molecules [3, 4] or can coordinate several metal ions. For example, they could be used to entrap mercury in the environment [5] and as a new inhibitor for copper [6]. In general, multi-component reactions (MCRs) are economically and environmentally very advantageous because multi-step syntheses produce considerable amounts of waste mainly due to complex isolation procedures often involving expensive, toxic and hazardous solvents after each step.

MCRs are perfectly suited for combinatorial library syntheses, thus are finding increasing use in the discovery process for new drugs and agrochemicals [7-13]. In recent years, the research into novel active organic substances and into the design of molecular electronic devices has attracted considerable interest [14, 15]. In this respect, several studies involved sulfur-containing compounds because they present good conduction in organic materials [16, 17] or are relevant biologically. Usually the compounds, which have antioxidant ability due to their reductive properties and chemical structure, remove the negative effect of free radicals and use as transitional metals chelators. Also, these compounds could be avoid or decrease many sicknesses such as cardiovascular, inflammatory bowel syndrome, cancer, ageing, and Alzheimer. Herein, we describe an efficient procedure for direct synthesis of imidazo oxazins. This involves a reaction of activated dialkyl acetylenedicarboxylates with with acid chloride

Corresponding author. Fax: +(98) 9123738148; E-mail: sj.shamsnajafi7148@gmail.com

and ethanol in the Presence of imidazole in $CH2Cl_2$ at room temperature (Scheme **1**).



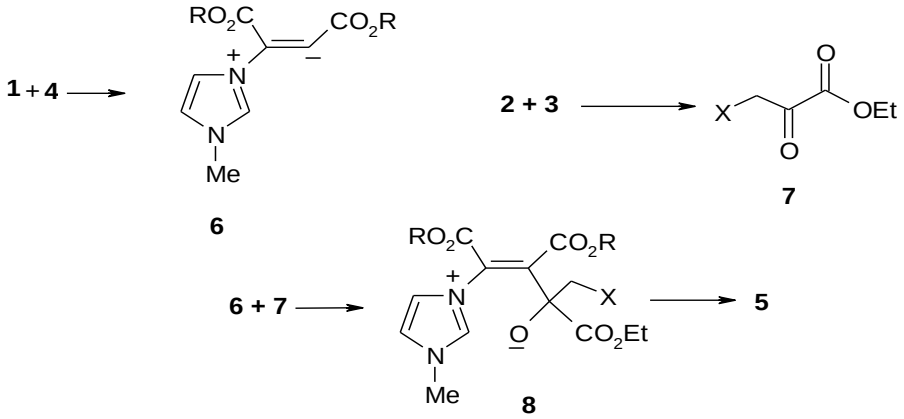
1 **2** **3** **4** **5**

1, 2, 5	R	X	Yield (%) of **5**
a	Me	Br	95
b	Et	Br	90
c	Me	H	87
d	Et	H	85

Scheme 1: Direct synthesis of imidazo oxazins

The reaction of **1** with **4** with acid chloride and ethanol **2, 3** led to imidazooxazin **5** in 95-85% yields (Scheme **1**). Structures of compounds **5a–d** were assigned by IR, ^{1}H NMR, ^{13}C NMR and mass spectral data. For example, the ^{1}H NMR spectrum of **5a** exhibited one triplet at 1.25 ($^3J_{HH}$ = 7.2) for methyl proton and two singlets at 3.68 and 3.89 for methoxy groups. Because of stereogenic center in these products, hydrogens of CH_2 and OCH_2 groups are diasterotopic, therefore, two doublets were observed at 4.09 ($^2J_{HH}$ = 10.9) and 4.17 ($^2J_{HH}$ = 10.9) for CH_2 group, one multiplet at 4.18-4.25 for OCH_2 moiety and one singlet at 6.60 ppm for CH groups. The carbonyl groups resonances in the ^{13}C NMR spectra of **5a** appear at 162.9, 164.1 and 167.5 ppm. The mass spectrum of **5a** displayed the molecular ion peak at *m*/*z* = 422.

A tentative mechanism for this transformation is proposed in Scheme **2**. It is conceivable that, the initial event is the formation of the 1:1 adducts **6** from the Reaction of activated dialkyl acetylenedicarboxylates **1** with imidazol **4** which is subsequently attacked by pyruvates **6**that is produced from the reaction of **2** and **3**. Intermediate **8** undergoes cyclization reaction to generate **5**.



Scheme 2: Tentative mechanism for synthesis of compounds **5**

Antioxidant ability evaluation of imidazol oxazin by utilizing of free radical of DPPH

Trapping of DPPH radical test is generally employed for the antioxidant capacity approval or strength of compounds for getting of selected imidazol oxazin free radical and investigation of percentage of inhibit oxidation of them in foods and biological structures. In these evaluation, antioxidant capacity of synthesized imidazol oxazin was determined by taking the hydrogen atom or one electron by DPPH radical and order of antioxidant ability of these compounds are basis of percentage of DPPH radical free trapping. The electron or hydrogen donating power of compounds **5a-5d** to the radical of DPPH determined the antioxidant ability of them. The radical of DPPH absorption was decreased from 517 nm when give one electron or hydrogen from antioxidant or a radical typs. In this work, the ability of imidazol oxazin **5a-5d** as antioxidant was evaluated relative to BHT and TBHQ as standard and prepared antioxidant with different concentrations. Overall, the power of DPPH trapping was obtained TBHQ>BHT>**5b**>**5a**>**5c**>**5d** (Figure **2**).

As seen in Figure 2, the novel prepared imidazol oxazin in all concentrations have a good activity relative to BHT and TBHQ. In between of prepared imidazol oxazin , comopound **5b** showed vrey good activity to radical trapping relative to BHT and TBHQ as standards antioxidant.

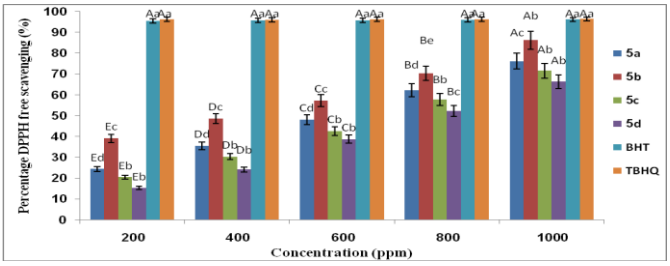


Figure 2. The activity of imidazol oxazine **5a-5d** for radical scavenging

The potential of synthesized imidazol oxazin by Ferric ions (Fe^{3+}) reducing

The reducing ferric ions (Fe^{3+}) ability of some synthesized imidazol oxazin such as **5a-5d** are calculated based on the quantity reducing of Fe^{3+}/ferricyanide to the Fe^{2+}/ ferrous at 700 nm [56]. As seen in Figure 3, compound **5b** was shown good ability of reducing than to BHT and TBHQ as standard antioxidants. The reducing activity trend of the samples was as follows: TBHQ>BHT>**5b**>**5d**>**5a**>**5c**. The outcomes are displayed in Figure 3.

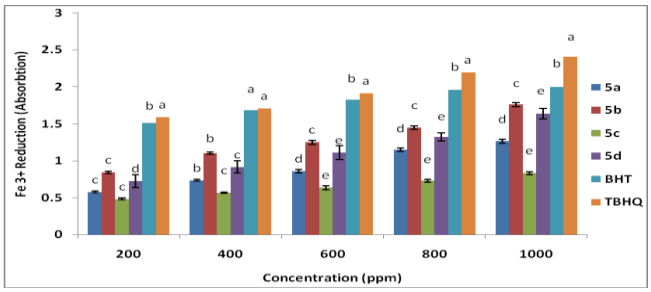


Figure 3. Antioxidant power of compounds **5a-5d** basis as ferric ions (Fe^{3+}) reducing.

Conclusion

In conclusion, the reaction of deficient acetylenic compounds with pyruvates in the presence of thiazol or benzothiazol led to imidazooxazins in excellent yields. The present procedure has the advantage that the reaction is performed under neutral conditions, and the starting material can be used without any activation or modification.

Experimental

All compounds in these reactions were obtained from Fluka and were used without further purification. M.p.: Electrothermal-9100 apparatus; uncorrected. IR Spectra: Shimadzu IR-460 spectrometer. ^{1}H and ^{13}C NMR spectra: Bruker DRX-500 AVANCE instrument; in $CDCl_3$ at 500.1 and 125.7 MHz, respectively; □ in ppm, *J* in Hz. EI-MS (70 eV): Finnigan-MAT-8430 mass spectrometer, in *m/z*. Elemental analyses (C, H, N) were performed with a Heraeus CHN-O-Rapid analyzer.

General Procedure for the Preparation of Compounds 5a-d:

Thiazol (2 mmol) were added to a mixture of pyruvates (2 mmol) and activated acetylenic ester (2 mmol) at room temperature. The reaction mixture was then stirred for 12 h to afford the pure compounds **5a-d**.

7-Ethyl 5,6-dimethyl 7-bromomethyl-7H-[1,3]imidazo[2,3-b][1,3]oxazin-5,6,7-tricarboxylate (5a):

Yellow oil, yield: 0.76 g (90%). IR (KBr): 1725, 1591, 1549, 1473, 1368, and 1015. ^{1}H NMR: 1.25 (3 H, *t*, $^3J_{HH}$ = 7.2, Me), 3.68 (3 H, s, OMe), 3.89 (3 H, s, OMe), 4.09 (1 H, *d*, $^2J_{HH}$ = 10.9, CH), 4.17 (1 H, *d*, $^2J_{HH}$ = 10.9, CH), 4.18-4.25 (2 H, *m*, OCH_2), 5.69 (1 H, *d*, $^3J_{HH}$ = 4.5, CH), 6.19 (1H, *d*, $^3J_{HH}$ = 4.5, CH), 6.60 (1 H, *s*, CH). ^{13}C NMR: 13.9 (Me), 31.8 (CH_2Br), 51.9 (OMe), 52.1 (OMe), 62.9 (OCH_2), 79.6

(C), 91.0 (CH), 102.7 (CH), 109.3 (C), 128.8 (CH), 141.7 (C), 162.9 (C=O), 164.1 (C=O), 167.5 (C=O). EI-MS: 422 (M^+, 10); 350 (20), 348 (20), 167 (25), 149 (60), 84 (100), 57 (62). Anal. Calcd for $C_{14}H_{16}BrNO_7S$ (422.24): C, 39.82; H, 3.82; N, 3.32; found: C, 39.80; H, 3.80; N, 3.31%.

7-Ethyl 5,6-diethyl 7-bromomethyl-7H-[1,3]imidazo[2,3-b][1,3]oxazin-5,6,7-tricarboxylate (5b):

Yellow Oil, yield: 0.76 g (85%). IR (KBr): 1732, 1685, 1583, 1504, 1453 and 1384. ^{1}H NMR: 1.22 (3 H, *t*, $^3J_{HH}$ = 7.2, Me), 1.28 (3 H, *t*, $^3J_{HH}$ = 7.2, Me), 1.35 (3 H, *t*, $^3J_{HH}$ = 7.2, Me), 4.12 (1 H, *d*, $^2J_{HH}$ = 10.5, CH), 4.18 (1 H, *d*, $^2J_{HH}$ = 10.5, CH), 4.19-4.23 (4 H, *m*, 2 OCH_2), 4.29-4.37 (2 H, *m*, OCH_2), 5.71 (1H, *d*, $^3J_{HH}$ = 4.6, CH), 6.20 (1H, *d*, $^3J_{HH}$ = 4.6, CH), 6.62 (1 H, *s*, CH). ^{13}C NMR: 13.8 (Me), 13.9 (Me), 14.0 (Me), 35.7 (CH_2Br), 61.0 (OCH_2), 62.4 (OCH_2), 62.7 (OCH_2), 78.4 (C), 90.9 (CH), 102.5 (CH), 113.4 (C), 121.4 (CH), 142.0 (C), 162.4 (C=O), 163.6 (C=O), 167.6 (C=O). EI-MS: 450 (M^+, 5); 377 (24), 375 (24), 370 (68), 231 (45), 229 (45), 84 (100), 73 (60). Anal. Calcd for $C_{16}H_{20}BrNO_7S$ (450.30): C, 42.68; H, 4.48; N, 3.11; found: C, 42.70; H, 4.50; N, 3.10%.

7-Ethyl 5,6-dimethyl 7-methyl-7H-[1,3]imidazo[2,3-b][1,3]oxazin-5,6,7-tricarboxylate (4c):

Yellow Oil, yield: 0.58 g (85%). IR (KBr): 1716, 1687, 1429, 1364, 1199 and 1103. ^{1}H NMR: 1.17 (3 H, *t*, $^3J_{HH}$ = 7.2, Me), 1.75 (3 H, s, Me), 3.65 (3 H, *s*, OCH_3), 3.82 (3 H, *s*, OCH_3), 4.12-4.17 (2 H, *m*, OCH_2), 5.61 (1 H, *d*, $^3J_{HH}$ = 4.6, CH), 6.11 (1 H, *d*, $^3J_{HH}$ = 4.6, CH), 6.52 (1 H, *s*, CH). ^{13}C NMR: 13.6 (Me), 23.6 (Me), 51.7 (OCH_3), 53.0 (OCH_3), 61.9 (OCH_2), 89.9 (C), 90.7 (CH), 101.3 (CH), 112.7 (C), 121.4 (CH), 138.4 (C), 163.1 (C=O), 164.5 (C=O), 169.8 (C=O). EI-MS: 343 (M^+, 10); 270 (85); 306 (66); 292(64), 284 (60);275 (85), 84 (100); 59 (67). Anal. Calcd for $C_{14}H_{17}NO_7S$ (343.35): C, 48.97; H, 4.99; N, 4.08; found: C, 48.95; H, 4.92; N, 4.02%.

7-Ethyl 5,6-diethyl 7-methyl-7H-[1,3]imidazo[2,3-b][1,3]oxazin-5,6,7-tricarboxylate (4d):

Yellow Oil, yield: 0.59 g (80%). IR (KBr): 1716, 1686, 1461, 1360, 1312 and 1025. ^{1}H NMR: 1.16 (3 H, *t*, $^3J_{HH}$ = 7.2, Me), 1.19 (3 H, *t*, $^3J_{HH}$ = 7.2, Me), 1.27 (3 H, *t*, $^3J_{HH}$ = 7.2, Me), 1.71 (3 H, s, Me), 4.00-4.18 (4 H, *m*, 2 OCH_2), 4.20-4.32 (2 H, *m*, OCH_2), 5.58 (1 H, *d*, $^3J_{HH}$ = 4.6, CH), 6.07 (1 H, *d*, $^3J_{HH}$ = 4.6, CH), 6.52 (1 H, *s*, CH). ^{13}C NMR: 13.8 (Me), 13.9 (Me), 14.0 (Me), 23.8 (Me), 60.8 (OCH_2), 61.7 (OCH_2), 62.5 (OCH_2), 78.2 (C), 90.7 (CH), 101.3 (CH), 112.5 (C), 121.6 (CH), 138.8 (C), 162.8 (C=O), 163.9 (C=O), 170.0 (C=O). EI-MS: 371 (M^+, 15); 298 (85); 225 (66); 292(64), 275 (85), 84 (100); 45 (84). Anal. Calcd for $C_{16}H_{21}NO_7S$ (371.41): C, 51.74; H, 5.70; N, 3.77; found: C, 51.70; H, 5.68; N, 3.71%.

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