

Reactions of Isoxazoline and Isoxazole Derivatives with Hydrazine Hydrate†

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The reaction of *cis*- or *trans*-dialkyl-2-isoxazoline dicarboxylate (1a–d, 3a–d) and dialkyl isoxazole dicarboxylate (5a–d) with hydrazine hydrate afforded the corresponding *bis*-(hydrazinocarbonyl)-2-isoxazoline and isoxazole derivatives (2a–b, 4a–b and 6a–b) respectively. Short time reaction of di-*t*-butyl isoxazol dicarboxylate (5e–f) afforded the mono (hydrazinocarbonyl) derivatives (7e–f) which on prolonged heating with hydrazine hydrate afforded (6a–b). On the other hand when the same reaction is conducted with dibenzoylisoxazole (8a–b) and *trans*-dibenzoyl-2-isoxazoline (10a–b) the cyclized products, pyridazino isoxazole derivatives (9a–b, 11a–b), are formed.

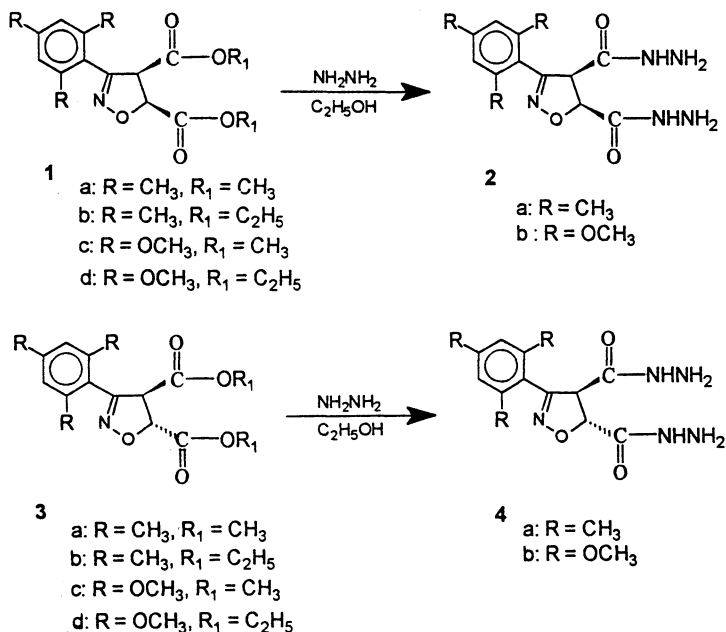
INTRODUCTION

The chemistry of nitrile oxide has attracted the attention of many chemists due to the importance that these reagents possess and to its pharmacologically active derivatives^{1,2}. The reaction of nitrile oxides with acetylenic and ethylenic compounds *via* 1,3-dipolar cycloaddition reactions are considered to be one of the most useful methods for the synthesis of isoxazole and isoxazoline derivatives^{1–6}. Recently it was reported by Abu-Orabi^{3,6} that the reaction of nitrile oxide with dibenzoylacetylene and *trans*-1,2-dibenzoylethylene afforded the corresponding isoxazole derivatives (8) and 2-isoxazoline derivatives (10). Fariana and coworkers⁷ have reported that the reaction of bromonitrile oxide and benzonitrile oxide with unsymmetrical acetylenic species can afford two regioisomers. Similar behaviours were reported by Chiarino and coworkers² on the reaction of bromonitrile oxide with ethyl propiolate. Furthermore, isoxazole and isoxazoline derivatives have been shown to be important precursors for the synthesis of pharmacologically active derivatives. Vyas and coworkers⁸ show that acivicin and bromoacivicin compounds which possess antitumor antibiotic activity, can be synthesized commercially *via* 1,3-dipolar cycloaddition reactions. Recently⁹ it was realized that some substituted isoxazole and isoxazoline derivatives have an anticorrosive effect.

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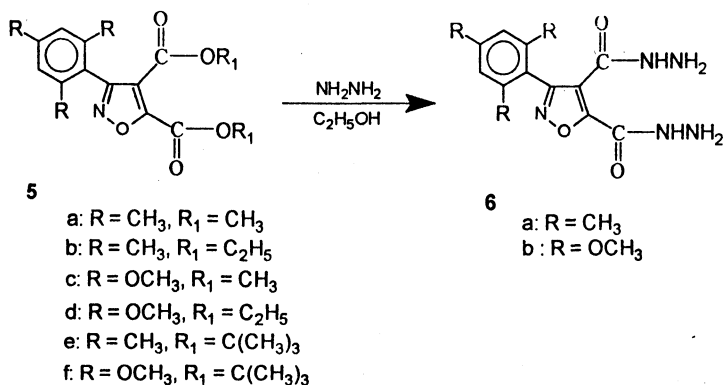
RESULTS AND DISCUSSION

Continuing with our previous work on isoxazole and 2-isoxazoline bearing an ester or benzoyl group, we have investigated the reaction of some of these derivatives with hydrazine hydrate. Thus the reactions of *cis*- or *trans*-dimethyl- or diethyl-3-aryl-4,5-dihydro-isoxazole dicarboxylate (1a-d), (3a-d) with excess of hydrazine hydrate in refluxing ethanol afforded in high yield the bis-(hydrazinocarbonyl) compounds (2a-b) and (4a-b) respectively (Scheme-1). The IR spectra of these products show the characteristic stretching frequencies in the following regions: 3300–3200 $\nu(\text{NH})$, 1650 $\nu(\text{C}=\text{O})$, 1600–1580 $\nu(\text{C}=\text{C})$, 1450–1440 $\nu(\text{C}=\text{N})$ and 1150–1100 cm^{-1} $\nu(\text{C}-\text{O})$. On the other hand, the $^1\text{H-NMR}$ spectra in d^6 -DMSO shows: the methyl groups of compounds (2a) and (4a) appeared as two singlets at 2.16–2.17 ppm integrating six protons due to the *ortho* methyl groups and at 2.22–2.24 ppm integrating three protons due to the *para* methyl. In similar manner the methoxy groups in compounds (2b) and (4b) appear at 3.71–3.73 ppm and 3.80 ppm respectively. The NH_2 protons in compounds (2a-b) appeared as a broad singlet at 4.10–4.37 ppm and for (4a-b) as two broad singlet at 3.80 ppm and 4.29 ppm. In similar manner the NH protons appear at 8.90–9.66 for compounds (2a-b) and at 9.14–9.35 ppm and 9.50–9.80 ppm for compounds (4a-b). The aromatic protons appear as a singlet in the range of 6.25–6.88 ppm; finally the two protons of isoxazoline ring H_4 and H_5 in compounds (2a-b) appear as two doublets at 4.50 and 5.05–5.17 ppm with $J = 11.7$ Hz, while in (4a-b) they appear as a doublet of doublet in the same region but with $J = 8.0$ –8.7 Hz.



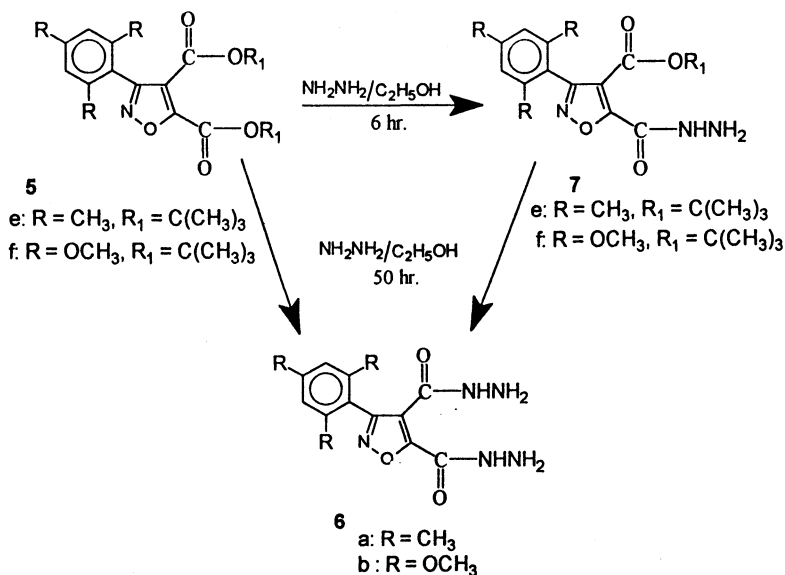
Scheme-1

Similarly, the bis-(hydrazinocarbonyl) compounds (6a–b) were produced from the reaction of dimethyl or diethyl-3-aryl-4,5-isoxazole dicarboxylate (5a–d) with hydrazine hydrate (Scheme-2). The IR spectra of compounds (6a–b) showed the



Scheme-2

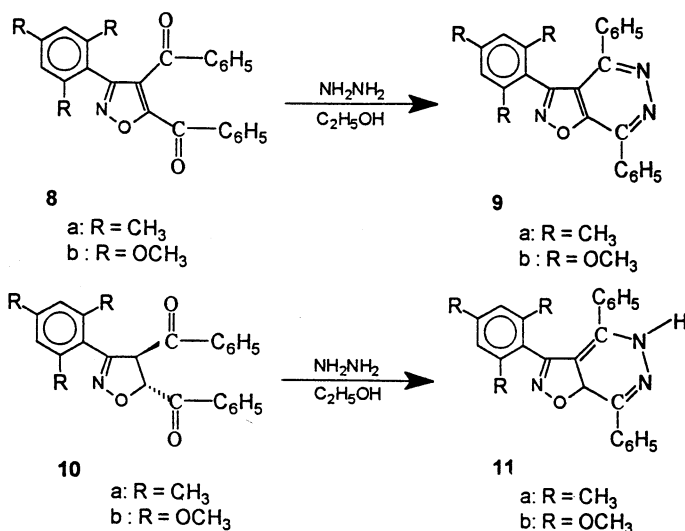
characteristic stretching bands at $3320\text{--}3250 \text{ v}(\text{NH})$, $1690\text{--}1650 \text{ v}(\text{C}=\text{O})$, $1600\text{--}1570 \text{ v}(\text{C}=\text{C})$, $1440 \text{ v}(\text{C}=\text{N})$ and $1150\text{--}1120 \text{ cm}^{-1} \text{ v}(\text{C}-\text{O})$. The $^1\text{H-NMR}$ spectra showed that the three methyl groups in compound (6a) appears as a two singlet at 2.06 ppm and 2.35 ppm corresponding to the *ortho* and *para* methyl groups respectively. In a similar manner the three methoxy groups in compound (6b) appear at 3.67 ppm and 3.85 ppm. The NH_2 protons appear as a broad singlet in the range of 4.11–4.50 ppm, while the NH protons appear in the range of 8.30–10.38 ppm. On the other hand, when either of compounds (5e) or



Scheme-3

(5f), the di-*t*-butyl ester, was treated with hydrazine in refluxing ethanol for about 6 h, it was realized from the spectral data that the mono-hydrazino derivatives (7e–f) were formed (Scheme-3). Their IR spectra showed the characteristic stretching bands at 3400–3100 $\nu(\text{NH})$, 1690, 1670 $\nu(\text{C}=\text{O})$, 1600–1570 $\nu(\text{C}=\text{C})$ and 1450–1440 cm^{-1} $\nu(\text{C}=\text{N})$. The $^1\text{H-NMR}$ spectra showed that nine protons of the tert-butyl group appeared as a singlet in the range of 1.20–1.27 ppm (Table-2). However when either the above reaction or the reactions of compounds (7e–f) with excess hydrazine was conducted for about 50 h, the bis-(hydrazino carbonyl) derivatives (6a–b) were obtained.

In the same manner, the two isoxazoles (8a) and (8b) when reacted with hydrazine hydrate afforded the isoxazolopyridazine fused ring; 3-(2,4,6-trimethylphenyl)-4,7-diphenylisoxazolo-[4,5,d] pyridazine (9a) and the 3-(2,4,6-trimethoxyphenyl) analogue (9b) respectively in good yields (Scheme-4).



Scheme-4

Similarly, the isoxazolodihydropyridazine fused rings; 3-(2,4,6-trimethylphenyl)-4,7-diphenylisoxazolo [4,5,d]-5,7a-dihydropyridazine (11a) and its trimethoxy analogue (11b) were produced from the corresponding 2-isoxazoline compounds (10a) and (10b) respectively.

The IR spectra of compounds (9a–b) and (11a–b) show the characteristic stretching bands at 3400–3100 $\nu(\text{NH})$; for compounds (11a) and (11b), 1610–1580 $\nu(\text{C}=\text{C})$, 1440 $\nu(\text{C}=\text{N})$ and 1140–1120 cm^{-1} $\nu(\text{C}-\text{O})$ bonds. The $^1\text{H-NMR}$ spectra showed the three methyl groups of compounds (9a) and (11a) as two singlets in the range 1.86–2.26 ppm and the three methoxy groups in compounds (9b) and (11b) as two singlets at 3.45–3.81 ppm. The protons of the aryl groups at 6.08–6.86 ppm, and the ten protons of the two phenyl groups as a multiplet at 7.06–8.58 ppm. H-7a in compounds (11a) and (11b) appears as a sharp singlet at 8.42 and 8.00 ppm

respectively. The NH protons of (11a) and (11b) appear as two broad singlets at 12.01 and 11.67 ppm respectively. The formation of the isoxazolopyridazine compounds (9a–b) can be easily explained while for compounds (11a–b), a racemisation at C7a is required: a mechanism which still needs to be explained.

EXPERIMENTAL

All chemicals and solvents used in this work were purchased from Aldrich and Fluka chemical companies and were used without any further purification. Isoxazole and 2-isoxazoline derivatives (1a–d), (3a–d), (5a–f), (8a–b) and (10a–b) were prepared according to the published methods^{1,3,4}.

¹H-NMR spectra were recorded on WP 80 SY spectrometer using tetramethylsilane as an internal standard and the chemical shifts were recorded in ppm. IR spectra were measured using Pye-Unicam SP-300 spectrometer as KBr disk. Melting points were measured on electrothermal melting point apparatus and were uncorrected. Elemental analyses were performed at M.H.W. Laboratories, Phoenix, Arizona, USA.

Preparation of bis-(hydrazinocarbonyl) compounds (2a–b), (4a–b) and (6a–b)

General procedure: To a solution of 1.0 g of the corresponding isoxazole dicarboxylate derivatives in 80 mL ethanol was added an excess amount of

TABLE-1
PHYSICAL DATA OF THE SYNTHESIZED COMPOUNDS

Compound	Reflux time (h)	Yield (%)	m.p. (°C)	m.f.	% Analysis calculated (found)		
					C	H	N
2a	6	67	119–120	C ₁₄ H ₁₉ N ₅ O ₃	55.08 (55.13)	6.23 (6.45)	22.95 (23.12)
2b	6	53	180–181	C ₁₄ H ₁₉ N ₅ O ₆	47.59 (47.50)	5.38 (5.34)	19.83 (20.00)
4a	3	47	222–223	C ₁₄ H ₁₉ N ₅ O ₃	55.08 (54.96)	6.23 (6.12)	22.95 (22.86)
4b	6	67	178–180	C ₁₄ H ₁₉ N ₅ O ₆	47.59 (47.65)	5.38 (5.51)	19.83 (20.10)
6a	6	70	125–126	C ₁₄ H ₁₇ N ₅ O ₃	55.44 (55.56)	5.61 (5.51)	23.10 (23.00)
6b	2	60	180–181	C ₁₄ H ₁₇ N ₅ O ₆	47.86 (47.96)	4.84 (5.00)	19.94 (19.92)
7e	6	92	168–170	C ₁₈ H ₂₃ N ₃ O ₄	62.61 (62.49)	6.67 (6.80)	12.17 (11.92)
7f	6	88	167–168	C ₁₈ H ₂₃ N ₃ O ₇	54.96 (55.16)	5.85 (5.81)	10.69 (10.57)
9a	3	70	180–181	C ₂₆ H ₂₁ N ₃ O	79.80 (79.69)	5.40 (5.50)	10.70 (10.53)
9b	3	70	192–193	C ₂₆ H ₂₁ N ₃ O ₄	71.07 (71.17)	4.78 (5.00)	9.57 (9.42)
11a	3	74	126–127	C ₂₆ H ₂₃ N ₃ O	79.39 (79.38)	5.85 (5.95)	10.69 (10.72)
11b	3	76	118–119	C ₂₆ H ₂₃ N ₃ O ₄	70.75 (70.91)	5.22 (5.17)	9.52 (9.70)

hydrazine hydrate. The mixture was refluxed for the required time. Evaporating the solvent under vacuum afforded a solid product which was recrystallized from a mixture of methanol-petroleum ether (60–80°C) to give the corresponding bis-(hydrazinocarbonyl) compound. (Tables 1 and 2 for physical and spectra data.)

TABLE-2
SPECTRAL DATA OF THE SYNTHESIZED COMPOUNDS

Compound	IR (KBr), cm^{-1}	$^1\text{H-NMR}$ ($\text{d}^6\text{-DMSO}$)
2a	3260, 1650, 1600, 1450	2.17 (s, 6H), 2.24 (s, 3H), 4.37 (bs, 4H, NH_2), 4.49 (d, 1H, $J = 10.6$ Hz), 5.17 (d, 1H, $J = 10.6$ Hz), 6.88 (s, 2H), 9.35 (bs, 1H, NH), 9.66 (bs, 1H, NH)
2b	3300–3200, 1655, 1600, 1580	3.73 (s, 6H), 3.80 (s, 3H), 4.10 (bs, 4H, NH_2), 4.50 (d, 1H, $J = 11.7$ Hz), 5.05 (d, 1H, $J = 11.7$ Hz), 6.25 (s, 2H), 8.90 (bs, 2H, NH)
4a	3240, 1650, 1600, 1450	2.16 (s, 6H), 2.23 (s, 3H), 3.80 (bs, 4H, NH_2), 4.48 (d, 1H, $J = 8.0$ Hz), 5.15 (d, 1H, $J = 8.0$ Hz), 6.86 (s, 2H), 9.00 (bs, 2H, NH)
4b	3300, 1650, 1600, 1450	3.7 (s, 6H), 3.80 (s, 3H), 4.29 (bs, 4H, NH_2), 4.50 (d, 1H, $J = 8.7$ Hz), 5.05 (d, 1H, $J = 8.7$ Hz), 6.23 (s, 2H), 9.14 (bs, 1H, NH), 9.50 (bs, 1H, NH)
6a	3320, 1650, 1600, 1450	2.06 (s, 6H), 2.35 (s, 3H), 4.11 (bs, 4H, NH_2), 7.00 (s, 2H), 8.53 (bs, 1H, NH), 10.83 (bs, 1H, NH)
6b	3320–3140, 1650, 1600, 1450	3.67 (s, 6H), 3.83 (s, 3H), 4.50 (bs, 4H, NH_2), 6.30 (s, 2H), 10.0 (bs, 2H, NH)
7e	3320, 3140, 1650, 1590, 1440, 1130	1.20 (s, 9H), 2.00 (s, 6H), 2.30 (s, 3H), 4.90 (bs, 2H, NH_2), 7.00 (s, 2H), 10.30 (bs, 1H, NH)
7f	3240–3100, 1690, 1670, 1600, 1440, 1120	1.27 (s, 9H), 3.70 (s, 6H), 3.83 (s, 3H), 4.76 (bs, 2H, NH_2), 6.35 (s, 2H), 16.33 (bs, 1H, NH)
9a	1600, 1450	1.86 (s, 6H), 2.26 (s, 3H), 6.86 (s, 2H), 7.06–8.58 (m, 10H)
9b	1610, 1600, 1450, 1145	3.47 (s, 6H), 3.81 (s, 3H), 6.16 (s, 2H), 7.31–8.54 (m, 10H)
11a	3400–3040, 1610, 1450, 1140	1.86 (s, 6H), 2.13 (s, 3H), 6.66 (s, 2H), 7.38–8.30 (m, 10H), 8.42 (s, 1H), 12.01 (s, 1H)
11b	3200, 1600, 1450, 1120	3.45 (s, 6H), 3.72 (s, 3H), 6.08 (s, 2H), 7.46–7.90 (m, 8H), 8.0 (s, 1H), 8.05–8.16 (m, 2H), 11.67 (s, 1H)

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