Synthesis of 4,5-Dihydroisoxazole and Isoxazolin-5-ones

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The synthesis of 5-hydrazono-4,5-dihydroisoxazoles **3**, from *N'*-(3-imino-3-aryl-1-methyl-1-alquenyl) hydrazones **1** and hydroxylamine hydrochloride, is described. These 4,5-dihydroisoxazoles can be transformed into oximes **5** and isoxazolones **6** by treatment with reducing agents and ethyl chloroformate, respectively.

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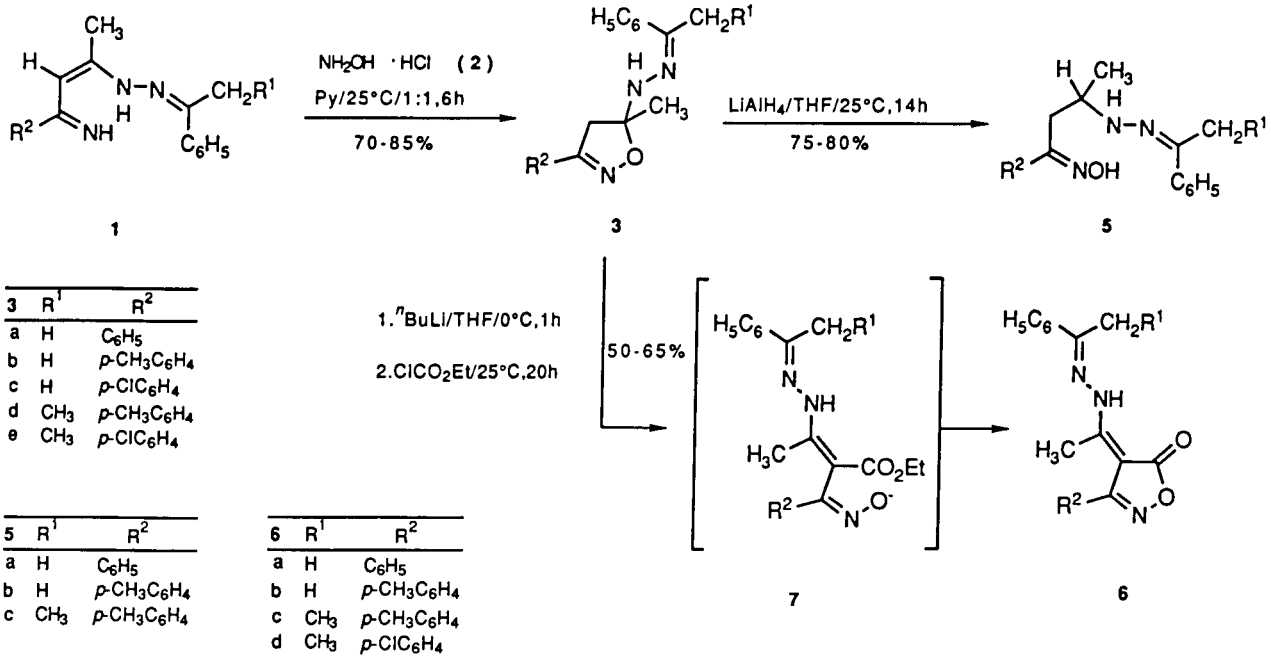
Heterocyclic compounds with a latent functionality have received a great deal of attention in organic synthesis [1]. Of these, the 4,5-dihydroisoxazole ring has become one of the most useful heterocyclic synthons, especially in the field of natural products [2] and pharmaceutically active heterocycles [3]. The great importance of these derivatives is mainly due to their ready transformation into a great variety of 1,3-difunctionalized compounds [4]. The important applications of the functionalized isoxazole ring at the C-4 and/or C-5 position [5] must also be emphasized.

In earlier papers, new procedures for the synthesis of isoxazoles and 4,5-dihydroisoxazoles by reaction of 1,3-diimines with hydroxylamine hydrochloride [6] were described. Moreover, hydrazone derivatives, obtained by the reaction of the appropriate ketazines and saturated nitriles [7], are suitable starting materials for the preparation of new heterocycles [7,8].

In this paper, the reaction of *N'*-(3-imino-3-aryl-1-methyl-1-alkenyl) hydrazones **1** with hydroxylamine hydrochloride leading to new 4,5-dihydroisoxazoles functionalized at the C-5 position is reported. The behaviour of these derivatives towards acids, reducing agents and ethyl chloroformate has also been investigated.

When hydrazones **1** and hydroxylamine hydrochloride **2** (molar ratio 1:1) were allowed to react in pyridine at room temperature 5-hydrazono-4,5-dihydroisoxazoles **3** were always obtained in good yields (see Tables 1 and 2). Compounds **3** were converted into pyrazoles **4** by treatment with trifluoroacetic acid or 2*M* sulphuric acid. However, on treatment of **3** with bases, no reaction was observed.

Scheme



3	R^1	R^2
a	H	C_6H_5
b	H	*p*-$CH_3C_6H_4$
c	H	*p*-ClC_6H_4
d	CH_3	*p*-$CH_3C_6H_4$
e	CH_3	*p*-ClC_6H_4

5	R^1	R^2
a	H	C_6H_5
b	H	*p*-$CH_3C_6H_4$
c	CH_3	*p*-$CH_3C_6H_4$

6	R^1	R^2
a	H	C_6H_5
b	H	*p*-$CH_3C_6H_4$
c	CH_3	*p*-$CH_3C_6H_4$
d	CH_3	*p*-ClC_6H_4

Table 1

Compounds **3,5** and **6** Prepared

Product	Yield (%) [a]	Mp [b] (°C)	Molecular Formula	^{1}H-NMR [c] δ	^{13}C-NMR [c] δ	MS (70eV) m/z [d]
3a	73	131-132	$C_{18}H_{19}N_3O$ (293.4)	1.7 (s, 3H), 2.0 (s, 3H), 2.9-3.9 (dd, 2H), 6.1 (s, NH), 6.9-7.8 (m, 10 Ar-H)	11.7 (q), 24.1 (q), 43.0 (t), 98.3 (s), 125.4-138.7 (12 Ar-C), 144.8 (s), 156.7 (s)	293
3b	85	145-147	$C_{19}H_{21}N_3O$ (307.4)	1.8 (s, 3H), 2.0 (s, 3H), 2.3 (s, 3H), 2.8-4.1 (dd, 2H), 5.7 (s, NH), 6.8-7.7 (m, 9 Ar-H)	11.8 (q), 21.3 (q), 24.2 (q), 43.2 (t), 98.2 (t), 125.5-139.7 (12 Ar-C), 144.9 (s), 156.8 (s)	
3c	80	164-165	$C_{18}H_{18}ClN_3O$ (327.8)	1.7 (s, 3H), 2.0 (s, 3H), 2.9-4.1 (dd, 2H), 5.7 (s, NH), 6.9-7.8 (9 Ar-H)	11.7 (q), 24.1 (q), 42.8 (t), 98.6 (s), 125.4-138.7 (12 Ar-C), 145.1 (s), 155.8 (s)	
3d	83	111-112	$C_{20}H_{23}N_3O$ (321.4)	1.0 (t, 3H), 1.7 (s, 3H), 2.3 (s, 3H), 2.5 (q, 2H), 3.0-4.1 (dd, 2H), 5.7 (s, NH), 6.6-7.7 (m, 9 Ar-H)	8.4 (q), 17.1 (q), 19.8 (q), 22.7 (t), 41.6 (t), 96.8 (s), 124.0-138.2 (12 Ar-C), 147.6 (s), 155.3 (s)	321
3e	75	126-128	$C_{19}H_{20}ClN_3O$ (341.8)	1.1 (t, 3H), 1.8 (s, 3H), 2.6 (q, 2H), 3.0-4.1 (dd, 2H), 5.9 (s, NH), 7.0-7.8 (m, 9 Ar-H)	10.8 (q), 11.7 (q), 19.7 (t), 42.7 (t), 102.0 (s), 126.2-135.7 (12 Ar-C), 149.2 (s), 160.8 (s)	
5a	75	oil	$C_{18}H_{21}N_3O$ (295.4)	1.2 (d, 3H), 1.7 (s, 3H), 2.8-3.3 (m, 2H), 3.5-3.9 (m, 1H), 6.9-7.8 (m, 10 Ar-H)	11.1 (q), 20.1 (q), 32.0 (t), 53.2 (d), 124.6-139.0 (12 Ar-C), 142.0 (s), 156.1 (s)	
5b	80	oil	$C_{19}N_{21}N_3O$ (309.4)	1.4 (d, 3H), 1.9 (s, 3H), 2.4 (s, 3H), 2.4 (s, 3H), 2.8-3.5 (m, 2H), 3.7-4.1 (m, 1H), 7.0-8.0 (m, 9 Ar-H)	12.8 (q), 21.7 (q), 22.2 (q), 32.0 (t), 54.9 (d), 126.4-140.7 (12 Ar-C), 144.0 (s), 158.1 (s)	
5c	78	oil	$C_{20}H_{25}N_3O$ (323.4)	0.9 (t, 3H), 1.2 (d, 3H), 2.0-2.6 (q, 2H), 2.2 (s, 3H), 2.8-3.3 (m, 2H), 3.5-3.8 (m, 1H), 6.8-7.8 (m, 9 Ar-H)	9.1 (q), 18.2 (q), 20.4 (q), 20.6 (t), 31.9 (t), 53.3 (d), 123.3-138.3 (12 Ar-C), 148.9 (s), 156.1 (s)	
6a	60	175-177	$C_{19}H_{17}N_3O_2$ (739.6)	2.2 (s, 3H), 2.4 (s, 3H), 7.0-7.9 (m, 10 Ar-H), 10.8 (s, NH)	13.2 (q), 14.6 (q), 90.7 (s), 125.6-135.5 (12 Ar-C), 143.3 (s), 157.1 (s), 163.2 (s) 175.0 (s)	
6b	55	130-132	$C_{20}H_{19}N_3O_2$ (333.4)	2.2 (s, 3H), 2.3 (s, 3H), 2.4 (s, 3H), 6.7-7.9 (m, 9 Ar-H), 10.7 (s, NH)	13.2 (q), 14.5 (q), 20.8 (q), 90.2 (s), 124.9-136.9 (12 Ar-C), 140.0 (s), 157.1 (s), 162.7 (s), 175.4 (s)	333
6c	63	179-180	$C_{21}H_{21}N_3O_2$ (347.4)	1.3 (t, 3H), 2.2 (s, 3H), 2.4 (s, 3H), 2.8 (q, 2H), 7.0-7.8 (m, 9 Ar-H), 10.5 (s, NH)	10.1 (q), 15.2 (q), 20.8(q), 21.1 (t), 90.2 (s), 126.5-138.4 (12 Ar-C), 139.8 (s), 161.2 (s), 162.7 (s), 175.0 (s)	
6d	58	190-191	$C_{20}H_{18}ClN_3O_2$ (367.8)	1.3 (t, 3H), 2.2 (s, 3H), 2.9 (q, 2H), 7.2-7.9 (m, 9 Ar-H), 10.6 (s, NH)	9.7 (q), 14.9 (q), 21.3 (t), 89.6 (s), 126.3-136.4 (12 Ar-C), 160.9 (s), 161.7 (s), 175.1 (s)	

[a] Yield after isolation and purification. [b] Uncorrected, measured with a Gallenkamp melting point apparatus. [c] The nmr spectra were obtained on a Varian FT-80 spectrometer with deuterated chloroform as the solvent and internal tetramethylsilane as the standard. [d] Recorded on a Hewlett-Packard 5897A spectrometer.

In the reaction of **3** with lithium aluminium hydride, it was found that the reduction took place through a similar pathway to the one observed in the case of the related 5-amino-4,5-dihydroisoxazoles [6b], yielding the corresponding γ-hydrazonooximes **5**. Three characteristic signals could be observed in the ^{13}C-nmr spectra -δ ≈ 175 (s), 54 (d) and 32 (t) ppm of these compounds, assigned to the oxime C-atom and the two saturated carbon atoms.

Similarly, the reaction between 4,5-dihydroisoxazoles **3** and ethyl chloroformate has been studied. Treatment of **3** with an excess of butyllithium and ethyl chloroformate yields new isoxazolin-5-ones **6**. Heterocycles **6** were characterized on the basis of their microanalyses and spectral data. All of them display absorptions in their ir spectra at $\nu \approx 3300$ (NH) and 1700 (C=O) cm^{-1}. The formation of

Table 2

Elemental Analyses for Compounds **3,5** and **6**

Product	Calcd.			Found		
	C	H	N	C	H	N
3a	73.69	6.53	14.32	73.43	6.46	14.56
3b	74.24	6.89	13.67	74.54	6.76	13.88
3c	65.95	5.53	12.32	65.72	5.36	12.65
3d	74.73	7.21	13.07	74.43	7.14	13.34
3e	66.76	5.90	12.30	66.43	6.01	12.16
5a	73.19	7.17	14.23	73.45	7.15	14.34
5b	73.75	7.49	13.58	73.64	7.60	13.31
5c	74.27	7.29	12.99	74.43	7.08	13.21
6a	71.46	5.37	13.16	71.65	5.29	13.37
6b	72.05	5.74	12.60	72.32	5.68	12.87
6c	72.60	6.10	12.10	72.41	6.23	12.24
6d	65.30	4.90	11.40	65.50	4.80	11.60

compounds **6** can be attributed to a condensation of the oxoanion with the ester carbonyl group (intermediate **7**, Scheme).

In conclusion, the reaction of hydrazonic derivatives **1** with hydroxylamine hydrochloride offers an easy high yield route to 5-hydrazono-4,5-dihydroisoxazoles **3**. These heterocycles **3** are suitable starting materials for the synthesis of oximes **5** and isoxazolin-5-ones **6**.

EXPERIMENTAL

Commercial reagents were purchased from Aldrich Chemical Co. Reactions conducted under inert atmosphere were done so after several cycles of evacuation and argon purging. The THF was dried with potassium by reflux. Microanalyses were performed on a Perkin-Elmer Model 240. TMS was employed as the internal reference in the nmr spectra.

3-Phenyl-5-methyl(α-methylbenzylidenehydrazino)-4,5-dihydroisoxazole (**3a**).

To a solution of acetophenone 3-imino-1-methyl-3-phenylprop-1-enylhydrazone (**1a**) (2.63 g, 10 mmoles) in pyridine (50 ml), hydroxylamine hydrochloride (0.7 g, 10 mmoles) is added. After stirring for 6 hours at room temperature, the mixture is treated with 2*M* sulphuric acid (150 ml) and extracted with ether (3 x 50 ml). The dried organic layer is evaporated and the residue recrystallized from hexane/chloroform to afford **3a**, 2.14 g (73%), mp 131-132°; ir: ν NH 3340, ν C=N 1600; ^{1}H nmr (deuteriochloroform): δ 1.7 (s, 3H), 2.0 (s, 3H), 2.9-3.9 (dd, 2H), 6.1 (s, NH), 6.9-7.8 (m, $10H_{ar}$); ^{13}C nmr (deuteriochloroform): δ 11.7 (q), 24.1 (q), 43.0 (t), 98.3 (s), 125.4-138.7 (12 C-Ar), 144.8 (s), 156.7 (s); ms: m/z 293 (M^+).

Anal. Calcd. for $C_{18}H_{19}N_3O$: C, 73.69; H, 6.53; N, 14.32. Found: C, 73.43; H, 6.46; N, 14.56.

Buten-1-one [1-Phenyl-3-(α-methylbenzylidenehydrazino)] Oxime (**5a**).

A solution of (**3a**) (1.47 g, 5 mmoles) in dry tetrahydrofuran (30 ml) is added under argon to a stirred suspension of lithium aluminium hydride (40 mmoles) in dry tetrahydrofuran (20 ml). After stirring for 14 hours, the solution is treated with a mixture of water (10 ml) and 0.1*M* sodium hydroxide and extracted with three 50 ml portions of ether. The combined organic layers are dried over anhydrous sodium sulfate, filtered and evaporated to yield an oil **5a**, 1.11 g (75%); ^{1}H nmr (deuteriochloroform): δ 1.2 (d, 3H), 1.7 (s, 3H), 2.8-3.3 (m, 2H), 3.5-3.9 (m, 1H), 6.9-7.8 (m, $10H_{ar}$); ^{13}C nmr (deuteriochloroform): δ 11.1 (q), 20.1 (q), 32.0 (t), 53.2 (d), 124.6-139.0 (12 C-Ar), 142.0 (s), 156.1 (s).

Anal. Calcd. for $C_{18}H_{21}N_3O$: C, 73.19; H, 7.17; N, 14.23. Found: C, 73.45; H, 7.15; N, 14.34.

4-(2,3-Diaza-4-phenyl-1-methylpent-3-enylidene)-3-*p*-tolylisoxazolin-5-one (**6b**).

A solution of (**3b**) (3.07 g, 10 mmoles) in dry tetrahydrofuran (60 ml) is added under argon to an ethereal solution of *n*-butyllithium (30 mmoles) at 0°. After stirring for 1 hour, ethyl chloroformate (0.9 ml, 10 mmoles) is added dropwise. The solution is allowed to warm to room temperature and stirred for 20 hours. The mixture is then slowly poured into ice cooled water and extracted with ether (3 x 50 ml). The dried organic layer is evaporated and the residue recrystallized from hexane/chloroform to afford **6b**, 1.83 g (55%), mp 130-132°; ir: ν NH 3450, ν CO 1690, ν C=N 1610; ^{1}H nmr (deuteriochloroform): δ 2.2 (s, 3H), 2.3 (s, 3H), 2.4 (s, 3H), 6.7-7.9 (m, $9H_{ar}$), 10.7 (s, NH); ^{13}C nmr (deuteriochloroform): δ 13.2 (q), 14.5 (q), 20.8 (q), 90.2 (s), 124.9-136.9 (12 C-Ar), 140.0 (s), 157.1 (s), 162.7 (s), 175.4 (s); ms: m/z 333 (M^+).

Anal. Calcd. for $C_{20}H_{19}N_3O_2$: C, 72.05; H, 5.74; N, 12.60. Found: C, 72.32; H, 5.68; N, 12.87.

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