## Synthesis of 3-isoxazolols revisited. Diketene and β-ketoesters as starting materials

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This paper is dedicated to Professor Paul de Mayo on the occasion of his 60th birthday

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3-Isoxazolols can be made in good yields from  $\beta$ -ketoesters or diketene and hydroxylamine, provided that pH is kept at about 10 throughout the reaction, and that the reaction mixture is quenched with an excess of strong mineral acid. This suppresses the formation of 5-isoxazolones, which are otherwise normally the main products of the reaction.

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On peut préparer les isoxazolols-3 avec de bons rendements en utilisant de l'hydroxylamine et des  $\beta$ -cétoesters ou dicétènes comme produits de départ à condition de maintenir le pH à environ 10 pendant toute la réaction et de piéger le mélange réactionnel avec un excès d'acide minéral fort. Cette précaution supprime la possibilité de formation des isoxazolones-5, qui sont autrement les produits principaux de la réaction.

#### [Traduit par le journal]

#### Introduction

In recent years much interest has been given to the 3-isoxazolol moiety, which is contained in a variety of physiologically active compounds. Thus the naturally occurring alkaloid muscimol 1 is an in vivo active mimetic of the neurotransmitter  $\gamma$ -aminobutyric acid (GABA) (1).



The synthetic analogue THIP, 2, is a very potent GABA receptor agonist and, as it is relatively nontoxic, it is of considerable pharmacological interest (1). The compound AMPA, 3, has been pointed out as an agonist of glutamic acid, and has powerful pharmacological effects after local injection into various brain areas of the rat (2). A rather simple molecule, 5-methyl-3-isoxazolol 4, has been commercialized under the names Tachigaren or Hymexazol. It is a soil fungicide and a growth promoter (3). Also the contact insecticide Karphos 5



contains the 3-isoxazolol moiety (4). A general and economical synthetic method for this interesting class of compounds is therefore desirable.

Although one of the most direct routes to 3-isoxazolols would appear to be the reaction of a  $\beta$ -ketoester (or diketene) with hydroxylamine, this method is unsuitable in most cases, largely because of preferential formation of 5-isoxazolones. This is particularly the case when 2-unsubstituted  $\beta$ -ketoesters are employed (5–8). Thus, it has been claimed that 4 cannot be prepared by direct condensation of hydroxylamine with acetoacetic esters or diketene (ref. 9, and references therein). As a consequence, these compounds are usually prepared from protected  $\beta$ -ketoesters or by entirely different methods (3, 9–11). Some 2-substituted  $\beta$ -ketoesters (e.g. ethyl 2-methylacetoacetate, **6**) have, however, been shown to yield 3-isoxazolols (5), although these were originally described as 5-isoxazolones (8). Jacquier *et al.* (12–14) made a detailed investigation of the reaction of  $\beta$ -ketoesters and hydroxylamine under alkaline conditions. They demonstrated that in the few cases where 3-isoxazolols were formed in substantial amounts (5, 15), their formation depended on rapid acidification of the reaction mixture with a large excess of concentrated hydro-chloric acid, whereas only 5-isoxazolones were formed upon slow acidification to pH 3–5. These authors suggested hydroxamic acids **7** and oximes **8** as discrete intermediates for 3-isoxazolols and 5-isoxazolones, respectively.



It seemed likely that the ratio of 7 to 8 and hence the total outcome of the reaction would be greatly influenced by the pH of the reaction mixture. The subject of the present paper is an investigation of the pH dependence of this reaction, which, combined with the "acidification brusque" of Jacquier *et al.*, ultimately led to a practical synthesis of 3-isoxazolols from  $\beta$ -ketoesters or diketene.

#### **Results and discussion**

Due to the economic importance of 4 and the availability and low price of methyl acetoacetate 9a, reaction of the latter with hydroxylamine was first investigated in detail. Addition of 9ato an aqueous solution of one equivalent of hydroxylamine hydrochloride, neutralized with 0.5 molar equivalents of sodium carbonate, and quenching the reaction mixture with a tenfold molar excess of concentrated hydrochloric acid gave 3-methyl-5-isoxazolone 10 as the main product. Only traces of 4 were detected.

When, however, the hydroxylamine hydrochloride solution was buffered with a twofold excess of sodium carbonate (ph 10-11) prior to the addition of 9a an approximately equimolar mixture of 4 and 10 resulted, whereas substituting the carbonate with bicarbonate (pH  $\sim 8$ ) led to the formation of 10 only.

We therefore investigated the dependence on pH of the for-



SCHEME 1

mation of 4 by running the reaction at constant pH values using a pH-stat with 2 N sodium hydroxide as the modifying reagent. In each case the reaction mixture was poured into a large excess of concentrated hydrochloric acid and the yield of 4 determined by hplc after continuous extraction with methylene chloride. The optimum pH for the formation of 4 was found to be 9-10, giving a yield of 70%. At pH 8.5 or 10.5 the yield is already reduced, at pH 8 it is below 40%, and at pH 11 it is below 50%.

At pH = 10, which is intermediate between the  $pK_a$  value of the hydroxylammonium ion (5.9) (10, 16) and hydroxylamine (13.7) (10) respectively, the dominant species is the neutral hydroxylamine molecule. This species has its nucleophilicity centered on the nitrogen atom (10), whose attack on 9a could lead to either the oxime 11a or the hydroxamic acid 12. Formation in alkaline solution of 10 via 11b is well documented (17, 18), and 11a could be isolated from the reaction buffered by bicarbonate upon extraction with methylene chloride prior to the acidification. When treated with concentrated hydrochloric acid 11a was transformed into 10 exclusively. Thus 11acannot be an intermediate in the formation of 4. Lowering the pH from 10, it therefore seems likely that enhanced oxime formation can account for the decrease in yield of 4. Around pH 10 the hydroxamic acid 12 could be suggested as the main intermediate, leading upon very rapid acidification to 4, whereas moving towards higher pH would cause an increasing participation of deprotonated hydroxylamine (NH<sub>2</sub>O<sup>-</sup>). This species has its nucleophilicity located mainly on the oxygen atom (10), which could lead to the formation of different intermediates incapable of forming 4. Our attempts to isolate the hydroxamic acid 12 have remained unsuccessful and, to our knowledge, only one hydroxamic acid of this type has been described (7, R = Ph, R' = CH<sub>3</sub> (14)).

Quenching of the reaction mixture with excess strong acid is crucial for obtaining high yields of 4. Diminution of the amounts of acid led to a decrease in the yield of 4 accompanied by an increase in the yield of 10. When the mixture from the reaction at pH 10 was brought to pH 2 by dropwise addition of concentrated hydrochloric acid, only approximately 1% 4 could be detected. Instead, a 85% yield of 10 was obtained, compared to the 70% yield of 4 obtained by rapid acidification.

Since the sum of these yields exceeds 100%, at least part of the mass of 4 and 10 must be derived from a common precursor. Our data do not allow definite assignment of a structure to this precursor, but if it were the hydroxamic acid 12, formation of 10 requires breaking of the C---N bond in 12. Thus hydrolysis of 12 would lead to acetoacetic acid 13, which under the Can. J. Chem. Downloaded from www.nrcresearchpress.com by NUS - CENTRAL LIBRARY on 06/03/13 For personal use only.

weakly acidic conditions could react with the liberated hydroxylamine to form an oxime 14 and, subsequently, 10. It is known that hydroxamic acids can be hydrolysed (19). The results of the different modes of acidification would thus reflect perturbations of the balance between cyclization and hydrolysis of 12.

The condensation product 15 (18, 20) between 10 and acetone is formed as a minor by-product in all the reactions. The acetone required for the formation of 15 can originate from several sources, e.g. via decarboxylation of 13. The reaction pathways discussed are depicted in Scheme 1. When ethyl acetoacetate 9b or diketene were used instead of 9a under optimum conditions for the formation of 4, almost identical yields were obtained (Table 1), whereas ethyl thiolacetoacetate 9c gave a mixture of 4 (15%) and 10 (40%), probably reflecting formation of 10 via the carbinolamine intermediate 16 (16), a pathway which is not operative for 9b (17). The reaction of 9b and ketene had similar pH profiles to that of 9a, with an optimum around pH 10.

Using the same reaction conditions, several  $\beta$ -ketoesters were reacted with hydroxylamine, and the results are found in Table 1. In several examples (4, 23, 26, 28, 38, and, presumably, 20) 3-isoxazolols, which were not previously accessible by this method, have been obtained, whereas in other examples (17, 34) substantial increases in the yield of 3-isoxazolols were obtained compared to those reported in the literature. Most of the 5-isoxazolones are unstable under our reaction and work-up conditions, so the yields given for these compounds must be interpreted with care.

Using 2-carbethoxycyclopentanone 40 as substrate, the reaction failed completely, and cyclopentanone oxime was the only product isolated. In spite of the apparent formation of 20 from 2-carbethoxycyclohexanone 19, all attempts to transform the structural analogue 41 into 42, a precursor of THIP 2 (22), failed. Only the 5-isoxazolone 43 was isolated. The previously unknown compound 28 seems well suited as a starting material for the synthesis of AMPA 3.



#### Experimental

Melting points were obtained with a Büchi 510 Melting Point Determinator and are uncorrected. The ir spectra were recorded on a Perkin–Elmer 177 grating spectrophotometer. The 60 mHz <sup>1</sup>Hmr spectra were obtained with a JEOL JNM-PMX 60 spectrometer. Peak positions are  $\delta$  values in ppm downfield from TMS. The uv spectra were recorded on a Shimadzu UV-240 spectrophotometer. The pHstat consisted of a Radiometer PHM 82 standard pH meter equipped with a titrator TTT 80 loaded with 2 *N* sodium hydroxide, a magnetic valve Type MNV I D, and a GK 2403 C electrode. The gc and hplc equipment was Hewlett-Packard 5840A and 1084B, respectively.

# Reaction of $\beta$ -ketoesters or diketene with hydroxylamine. General procedure

Hydroxylammonium chloride (0.20 mol) was dissolved in approximately 100 mL of 2 N sodium hydroxide to achieve a solution of pH 10.0. This solution was cooled to  $0-5^{\circ}$ C (20°C in the case of **30** and **33**) and vigorously stirred while the  $\beta$ -ketoester (0.20 mol) was added during 30 min, keeping pH at 10.0  $\pm$  0.2 by means of the pH-stat. Stirring was continued for about 30 min at pH 10. At this point approximately 100 mL of 2 N sodium hydroxide had been added. The mixture was then poured into 150 mL ice-cooled concentrated hydrochloric acid and the mixture left overnight at room temperature. In some cases the 3-isoxazolols crystallized from this mixture, but in most cases the products were isolated by continuous extraction with methylene chloride.

In the case of 9a, b or diketene as substrates, the pH dependence was determined using the general procedure, only varying the pH.

#### Methyl acetoacetate oxime 11a

To a solution of sodium bicarbonate (40 g) in 300 mL of water was added hydroxylammonium chloride (16 g, 0.23 mol) followed by methyl acetoacetate **9***a* (23 g, 0.20 mol). After 80 min the mixture was extracted with three 150-mL portions of methylene chloride. After drying and evaporation of the methylene chloride, the residue was bulb-to-bulb distilled at 150°C/0.05 Torr (1 Torr = 133.3 Pa) to give **11***a* (8.5 g) as a colourless oil; <sup>1</sup>Hmr (CDCl<sub>3</sub>)  $\delta$ : 1.97 (s, 3H), 3.27 (s, 2H), 3.72 (s, 3H), 9.6 (broad s, 1H). Anal. calcd. for C<sub>5</sub>H<sub>9</sub>NO<sub>3</sub>: C 45.80, H 6.92, N 10.68; found: C 45.96, H 6.78, N 10.86.

#### 4,5,6,7-Tetrahydro-1,2-benz-3-isoxazolol, 20 and 4,5,6,7-tetrahydro-2,1-benzisoxazolin-3-one, 21

The product from the standard procedure using 2-carbethoxycyclohexanone **19** as substrate was a crystalline solid (25.4 g), whose mp (90.5–93°C) did not change significantly after repeated recrystallization from MeOAc. From spectroscopic data, a 2:1 mixture of **20** and **21** may be proposed; uv (EtOH)  $\lambda_{max}$ : 218 and 256 nm; <sup>1</sup>Hmr (CDCl<sub>3</sub>)  $\delta$ : 1.3–3.0 (m, 8H), 3.1 (dd, 1H, **21**), 11.3 (s, 1H, **20**). Anal. calcd. for C<sub>7</sub>H<sub>9</sub>NO<sub>2</sub>: C 60.42, H 6.52, N 10.07, O 22.99; found: C 59.74, H 6.49, N 10.21, O 23.00.

## 5-Isopropyl-3-isoxazolol, 23 and 3-isopropyl-5-isoxazolone, 24

The compound 23 crystallized spontaneously from the reaction mixture after acidification, yield 46%, mp (heptane)  $45-46^{\circ}$ C. Extraction of the filtrate gave a mixture of 23 and 24 in 21 and 16% yield, respectively (gc).

## 5-Propyl-3-isoxazolol, 26

The crude methylene chloride extract contained **26**, corresponding to a yield of 59% (gc). Crystallization from  $H_2O$  and heptane, successively, gave **26**, mp 43–44°C.

#### 4-(2-Hydroxyethyl)-5-methyl-3-isoxazolol, 28

The general procedure was followed, using 2-acetylbutyrolactone **27** as substrate, and, upon cooling the methylene chloride extract to 0°C, **28** crystallized in 48% yield, mp (MeOH) 167–169°C. The mother liquor contained **27**, 24% yield, and 5-hydroxy-2-pentanone, 24% yield (gc). Data of **28**: uv (EtOH)  $\lambda_{max}$  (log  $\epsilon$ ): 225 (3.1) nm; ir (KBr)  $\nu_{max}$ : 3180, 2940, 2810, 1660, 1520, 1390, 1350, 1330, 1245, and 1050 cm<sup>-1</sup>; <sup>1</sup>Hmr (CDCl<sub>3</sub> + DMSO-d<sub>6</sub>)  $\delta$ : 2.33 (s, 3H), 2.53 (t, J = 7.0 cps, 2H), 3.77 (t, J = 7.0 cps, 2H), 7–9 (broad signal, 2 × OH). *Anal.* calcd. for C<sub>6</sub>H<sub>9</sub>NO<sub>3</sub>: C 50.34, H 6.34, N 9.79; found: C 50.26, H 6.41, N 9.76.

## 5-tert-Butyl-3-isoxazolol, 38 and 3-tert-butyl-5-isoxazolone, 39

The crude product from the general procedure contained **38** and **39**, corresponding to yields of 73 and 22%, respectively, (nmr). Separation by fractional crystallization from aqueous methanol gave the pure compounds: **38**, mp 99–101°C; uv (EtOH)  $\lambda_{max}$  (log  $\epsilon$ ): 207 (3.8) nm; ir (KBr)  $\nu_{max}$ : 3400, 2960, 1615, 1530, 1455, 1365, 1345, and 1270 cm<sup>-1</sup>; <sup>1</sup>Hmr (DMSO- $d_6$ ) &: 1.25 (s, 9H), 5.65 (s, 1H), 10.5

| β-Ketoesters      | RCOCHR' COOR"  |                 |                               |          | 3-Isoxazololes R'OH<br>R O'N |         |                               |              | 5-Isoxazolones |                        |         |                    |              |
|-------------------|--|-----------------|-------------------------------|----------|------------------------------|---------|-------------------------------|--------------|----------------|------------------------|---------|--------------------|--------------|
|                   |  |                 |                               |          | Yield (%)                    |         | Melting point (°C)            |              |                | Yield (%)              |         | Melting point (°C) |              |
| Compound          | R  | R'              | R"                            | Compound | Found                        | (lit.)  | Found                         | (lit.)       | Compound       | Found                  | (lit.)  | Found              | (lit.)       |
| <u>9a</u>         | CH <sub>3</sub>  | н               | CH <sub>3</sub>               | 4        | 70"                          |         | 85.5-86                       | 86-87 (3)    | 10             |                        |         | <br>Oil            |              |
| <b>9</b> b        | CH <sub>3</sub>  | Н               | $C_2H_5$                      | 4        | 61"                          | 0(13)   |                               |              | 10             |                        | 65 (13) | Oil                |              |
| 6                 | CH3  | CH <sub>3</sub> | $C_2H_5$                      | 17       | 80 <sup>.</sup>              | 40 (13) | 122–124<br>(H <sub>2</sub> O) | 123–124 (11) | 18             |                        | 55 (13) |                    | 49-51 (15)   |
|                   |  |                 |                               |          | See                          |         |                               |              |                | See                    |         |                    |              |
| 19                | $-C_4H_8$  | · (ring)        | C <sub>2</sub> H <sub>5</sub> | 20       | experimental                 | 0 (13)  |                               | 130 (11)     | 21             | experimental           | 85 (13) |                    | 66 (13)      |
| 22                | iso-C <sub>3</sub> H <sub>7</sub>                                  | Ĥ               | $C_2H_5$                      | 23       | 67°                          | 0 (13)  | 45-46                         | 41-42 (11)   | 24             | 16                     | 50 (13) |                    | Oil          |
| 25                | $n-C_3H_7$   | Н               | $C_2H_5$                      | 26       | 59°                          |         | 43-44                         | 41 - 41.5(3) |                |                        |         |                    |              |
| 27                | CH <sub>3</sub>  | $-C_2H_4$       | — (ring)                      | 28       | 484                          |         | 167-169                       |              | 29             |                        | 70 (21) |                    | 113-114 (21) |
| 30                | CH <sub>3</sub>  | C₂H₅            | C <sub>2</sub> H <sub>5</sub> | 31       | 32°                          | 35 (13) |                               |              | 32             | 56'                    | 50 (13) |                    |              |
| 33                | Ph   | Н               | C <sub>2</sub> H <sub>5</sub> | 34       | Trace"                       | 0 (13)  |                               |              | 35             | 88"                    | 75 (13) |                    |              |
| 36                | Ph   | Н               | $CH_3$                        | 34       | 49"                          |         |                               |              | 35             | 40"                    |         |                    |              |
| 37                | <i>tert-</i> C₄H <sub>9</sub>                                      | Н               | CH <sub>3</sub>               | 38       | 73*                          | 0 (5)   | 99-101                        |              | 39             | 22 <sup><i>b</i></sup> |         | 106-107            | 107-108 (5)  |
| 40                | $-C_3H_6$  | (ring)          | $C_2H_5$                      |          | 0                            |         |                               |              |                | 0                      |         |                    |              |
| <b>9</b> <i>c</i> | CH <sub>3</sub> COCH <sub>2</sub> COSC <sub>2</sub> H <sub>5</sub> |                 |                               | 4        | 15°                          |         |                               |              | 10             | 40                     |         |                    |              |
|                   | Diketene   |                 |                               | 4        | 71"                          |         |                               |              |                |                        |         |                    |              |

## TABLE 1. 3-Isoxazololes and 5-isoxazolones from $\beta$ -ketoesters

"By hplc. <sup>»</sup>By nmr.

<sup>c</sup> By gc. <sup>d</sup> Isolated yield.

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(broad singlet, 1H). *Anal.* calcd. for  $C_7H_{11}NO_2$ : C 59.56, H 7.86, N 9.92; found: C 59.17, H 7.83, N 9.83. Compound **39**, mp 106–107°C (lit. (5) mp 107–108°C); <sup>1</sup>Hmr (CDCl<sub>3</sub>)  $\delta$ : 1.28 (s, 9H), 3.57 (s, 2H).

## Methyl 3-hydroxy-4,5,6,7-tetrahydroisoxazolol[3,4-c]pyridine-6carboxylate, 43

Reaction of ethyl 1-methoxycarbonyl-3-oxopiperidine-4-carboxylate, **41**, with hydroxylamine by the standard procedure yielded 76% of **43** in which traces of methyl 3-hydroxy-4,5,6,7-tetrahydroisoxazolol[5,4-*c*]pyridine-6-carboxylate, **42** (22) was detected by tlc. The compound **43** was identical (tlc, ir, uv, mp and mixture mp) with an authentic sample generously supplied by P. Krogsgaard-Larsen; mp (MeOH) 140–142°C (dec.); uv (EtOH)  $\lambda_{max}$  (log  $\epsilon$ ): 260 (3.9) nm; ir (KBr)  $\nu_{max}$ : 3090, 1725, 1685, 1625, 1615 (sh), 1475, 1440, 1410, and 1425 cm<sup>-1</sup>; <sup>1</sup>Hmr (CDCl<sub>3</sub> + DMSO-d<sub>6</sub>)  $\delta$ : 2.46 (dt, *J* = 6.0 and 2.0 cps, 2H), 3.76 (t, *J* = 6.0 cps, 2H), 3.85 (s, 3H), 4.56 (broadened s, 2H), 8–10 (broad and flat signal, 1H). The *tert*-butylester corresponding to **43** has been described (1). Compounds **42** (22) and **43**: mixture mp 122–124°C (dec.).

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