Synthesis of Biheteroaromatic Compounds via the Isoxazoline Route

Sami S. Ghabrial,* I. Thomsen and K. B. G. Torssell

Department of Organic Chemistry, Chemical Institute, University of Aarhus, DK-8000 Århus C, Denmark

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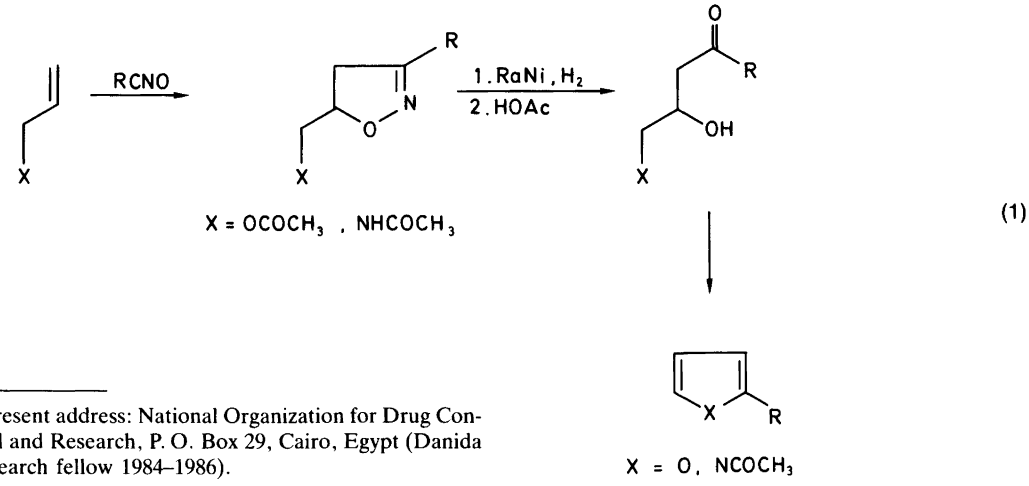
A number of heteroaromatically substituted furans, thiophenes, pyrroles, pyridines and benzenes have been prepared via the 2-isoxazoline route. *N*-Acetylnornicotyrine is prepared from *N*-allylacetamide and 3-pyridinecarboxaldoxime.

It was shown earlier that reductive ring cleavage of 5-α-oxyalkylsubstituted 2-isoxazolines followed by acid-catalyzed cyclization led to furans.[1] Analogously, the 5-α-aminoalkyl-substituted 2-isoxazolines gave pyrroles [2] [eqn. (1)]. In the present work this method is applied to the preparation of biheteroaromatic compounds, some of which are more cumbersome to prepare by other methods.

The furan, thiophene, pyridine and pyrrole aldoximes are chlorinated selectively to the corresponding hydroxamic acid chlorides in high yields by *N*-chlorosuccinimide (NCS).[3] No nuclear chlorination is observed at 0–25 °C when one equivalent of NCS is used. Treatment of thiophene-2-aldoxime with two equivalents of NCS in chloroform under reflux gives 5-chlorothiophene-2-hydroxamoyl chloride, and under the same conditions, thiophene-3-aldoxime gives 2-chlorothiophene-3-hydroxamoyl chloride [eqns. (2) and (3)]. The pyrrole-2-aldoxime is extremely sensitive to NCS and gives immediately a dark-coloured precipitate at 0 °C in chloroform and acetonitrile. By performing the NCS chlorination at −70 °C in the presence of triethylamine and the olefin in a mixture of chloroform and acetonitrile as solvent, a good yield of the anticipated cycloaddition product, **11**, is obtained. By carrying



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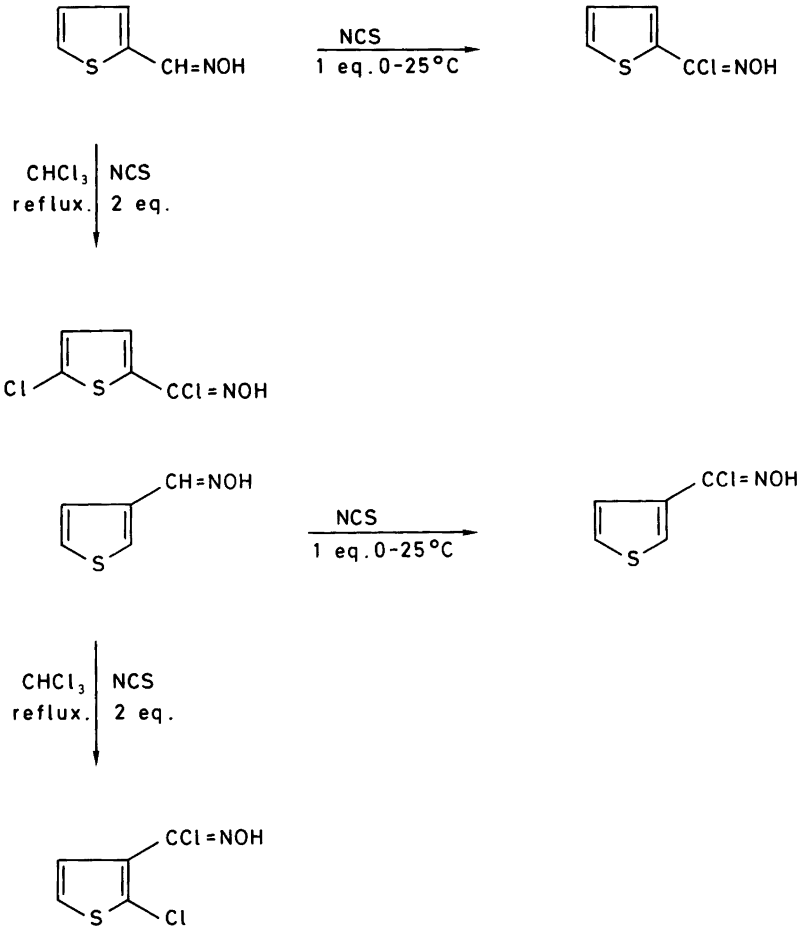
*Present address: National Organization for Drug Control and Research, P. O. Box 29, Cairo, Egypt (Danida research fellow 1984–1986).



(2)

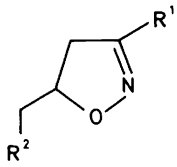
(3)

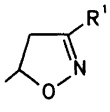
out the chlorination and cycloaddition in ether at 0 °C it is posssible to obtain compound **12** in a yield of 28 %. Chlorination by free chlorine cannot be employed because it gives nuclear chlorination, but nitrosyl chloride has been used in some cases for chlorination of aldoximes with other reactive functions.[4,5] The nitrile oxides are generated by addition of triethylamine.[6] Minor amounts of furoxans are formed as by-products.

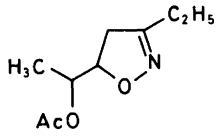
An attempt was made to prepare the 5-mercaptomethyl derivative **18** by thiolation of the bromide **19**. However, the disulfide **17** was the only compound isolated.

The classical procedure for formylation of acetic ester and subsequent oximation of the sodium salt[7] to give the oxime of formylacetic ester (**23**) is capricious and gives a low yield. The route from formyl Meldrum's acid[12,13] (**22**) is superior, and **23** can be prepared directly from the crude formylacetic ester [eqn. (4)]. The oxime is converted into the hydroxamoyl chloride (**24**) using NCS in the presence of pyridine as catalyst, and the corresponding nitrile oxide is formed by addition of triethylamine as shown for the synthesis of compound **20**. In the absence of pyridine the methylene group is chlorinated.

The isoxazolines are hydrogenated catalytically over Raney-Ni to the β-hydroxy ketones. Addition of boric acid to the medium suppresses over-reduction.[8] Reduction of **9**, which requires rather large quantities of catalyst, gives a mixture of the expected acetate **25g** and **26**. When the pyrrylisoxazoline **11** is reduced without acid added, the main product is the pyrrole derivative **28**. In the



1:	R^1 = 2-furyl	R^2 = OAc
2:	R^1 = 2-furyl	R^2 = NHAc
3:	R^1 = 2-thienyl	R^2 = OAc
4:	R^1 = 2-thienyl	R^2 = NHAc
5:	R^1 = 3-thienyl	R^2 = OAc
6:	R^1 = 3-thienyl	R^2 = NHAc
7:	R^1 = 3-[2-chlorothienyl]	R^2 = NHAc
8:	R^1 = 2-[5-chlorothienyl]	R^2 = NHAc
9:	R^1 = 3-pyridyl	R^2 = OAc
10:	R^1 = 3-pyridyl	R^2 = NHAc
11:	R^1 = 2-pyrryl	R^2 = OAc
12:	R^1 = 2-pyrryl	R^2 = NHAc
13:	R^1 = phenyl	R^2 = OAc
14:	R^1 = phenyl	R^2 = NHAc
15:	R^1 = ethyl	R^2 = OAc
16:	R^1 = *t*-butyl	R^2 = OAc
17:	R^1 = butyl	R^2 = -S-S- 
18:	R^1 = butyl	R^2 = SH
19:	R^1 = butyl	R^2 = Br
20:	R^1 = CH_2COO-*t*-butyl	R^2 = OAc

21: 

presence of acetic acid the anticipated product **25i** is formed.

The cyclization of the acetates **25** to furans [eqn. (1)] is carried out in chloroform under reflux, with *p*-toluenesulfonic acid as catalyst. The yields are often quantitative and the reaction can easily be followed by NMR by running it on a micro scale directly in the NMR tube at 50 °C. 3-Thienyl-2-furan (**29d**) is obtained directly by reduction of **5** in acidic solution with Ti^{3+} [9] in a yield of 67 %. The amides are best cyclized to the *N*-acetylated pyrroles in acetic acid at 100 °C with a small amount of acetyl chloride as catalyst. The pyrroles **25i,j** are very acid-labile and do not give the desired 2-(2-furyl)-pyrrole and 2(2-pyrryl)-*N*-acetylpyrrole (**30b**), respectively, when heated in acetic acid at 100 °C.

Some **30b** is obtained (< 10 %) together with ca. 20 % of 2,2-dipyrryl (**31**) when **25j** is heated with zinc trifluoromethanesulfonate in dimethylformamide at 150 °C for 15 min. The cyclization of **25b** to **30a** also proceeds in poor yield (ca. 20 %). A second product was isolated, the structure of which was determined to be **32** by MNR and mass spectroscopy. The parent peak is not observed, but the fragment of highest molecular weight, 309, corresponds to loss of acetamide and the peak at *m/z* 93 indicates the presence of the furoyl fragment. The ^{13}C NMR and ^1H NMR spectra clearly show the presence of two *N*-acetyl groups, as well as the substitution patterns of the two furan nuclei and the 2-substituted pyrrole ring and the structure of the 3-membered carbon chain.

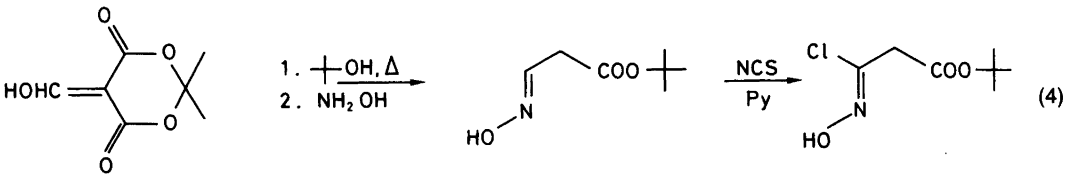
By using α-substituted allyl acetates as the starting material it is possible to obtain 2,5-disubstituted furans, as demonstrated by the synthesis of the furan **33** via the isoxazoline **21**.

N-Acetylnornicotyrine (**30c**) is prepared from *N*-allylacetamide and 3-pyridinecarboxaldoxime.

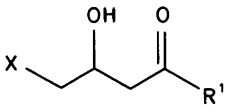
Experimental

The NMR-spectra were recorded with a Varian 60 MHz instrument.

α-2-Furfuraldoxime.[10] Freshly distilled furfural (9.6 g, 0.1 mol) in methanol (20 ml) is added slowly with stirring to a cold mixture of hydroxyl-

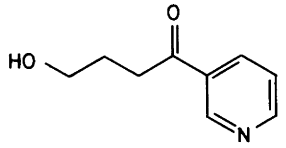


22 **23** **24**



25

a: R^1 = 2-furyl X = OAc
b: R^1 = 2-furyl X = NHAc
c: R^1 = *t*-butyl X = OAc
d: R^1 = 2-thienyl X = NHAc
e: R^1 = 3-thienyl X = OAc
f: R^1 = 3-thienyl X = NHAc
g: R^1 = 3-pyridyl X = OAc
h: R^1 = 3-pyridyl X = NHAc
i: R^1 = 2-pyrryl X = OAc
j: R^1 = 2-pyrryl X = NHAc
k: R^1 = phenyl X = OAc
l: R^1 = phenyl X = NHAc



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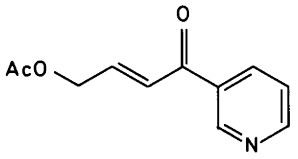

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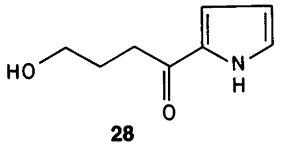

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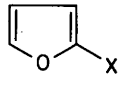
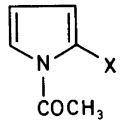


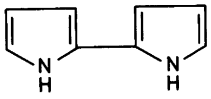
29

a: X = 2-furyl
b: X = 3-pyridyl
c: X = *t*-butyl
d: X = 3-thienyl
e: X = phenyl

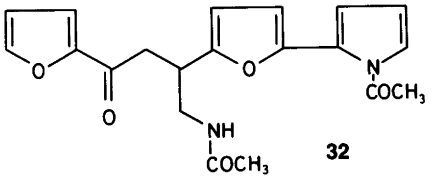


30

a: X = 2-furyl
b: X = 2-pyrryl
c: X = 3-pyridyl
d: X = 2-thienyl
e: X = 3-thienyl
f: X = phenyl



31



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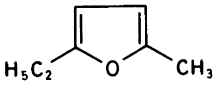
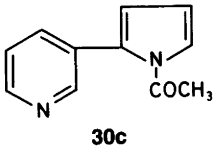


33



30c

amine hydrochloride (7.6 g, 0.11 mol) and sodium hydrogen carbonate (9.3 g, 0.11 mol) in water (50 ml). The mixture is kept for one hour at ca. −10 °C, and saturated aqueous ammonium chloride is added until the solution becomes turbid. Furfuraldoxime (9.5 g, crude) precipitates slowly in the cold. It is filtered, dried, dissolved in a small amount of benzene (not above 40 °C) and, if necessary, the solution is filtered. Addition of light petroleum precipitates pure α-furfuraldoxime (7.8 g, 69 %); m.p. 75–76 °C.

3-(2-Furyl)-5-acetoxymethylisoxazoline (**1**). *General procedure:* To α-furfuraldoxime (1.1 g, 10 mmol) in chloroform, *N*-chlorosuccinimide (1.33 g, 10 mmol), and 3 drops of pyridine are added with stirring at room temperature. After ca. 10 min the chlorination is completed, and a precipitate appears. Chlorination of a mixture of α- and β-furfuraldoximes occurs with evolution of heat, which reduces the yield. In this case it is necessary to perform the chlorination at 0 °C. Allyl acetate (1.2 g, 12 mmol) is added, and then triethylamine (1.1 g, 11 mmol) dropwise over 30 min. The solution is heated under reflux for two hours, whereby the precipitate goes into solution. Washing with water, drying over sodium sulfate and evaporation give 1.6 g of crude **1**, which after purification by prep. TLC (silica; $CHCl_3$, 5 % CH_3OH) yields pure **1** as an oil (1.3 g, 62 %). ^{1}H NMR ($CDCl_3$): δ 2.03 (3H,s), 3.10 (lH,dd, *J* 17 and 8 Hz, ABX spectrum), 3.34 (1H,dd, *J* 17 and 10 Hz), 4.14 (2H,d, *J* 5 Hz), 4.8 (1H,m), 6.40 (1H,dd, *J* 2 and 3.5 Hz), 6.65 (1H,d, *J* 3.5 Hz), 7.42 (1H,d, *J* 2 Hz).

*3-(2-Furyl)-5-*N*-acetylaminomethylisoxazoline* (**2**) is prepared from *N*-allylacetamide by following the method for **1**. The yield is 70 %; m.p. 129–130 °C. ^{1}H NMR ($CDCl_3$): δ 1.97 (3H,s), 3.08 (1H,dd, *J* 17 and 8 Hz), 3.32 (1H,dd, *J* 17 and 10 Hz), 3.5 (2H,m), 4.7 (1H,m), 6.37 (1H,dd, *J* 2 and 4 Hz), 6.2 (1H, NH, br), 6.60 (1H,dd, *J* 4 Hz), 7.40 (1H,d, *J* 2 Hz).

*3-(2-Thienyl)-5-*N*-acetoxymethylisoxazoline* (**3**) *and 3-(2-thienyl)-5-*N*-acetylaminomethylisoxazoline* (**4**) are prepared according to the general procedure, from finely divided 2-thiophenecarboxaldoxime (m.p. 128–130 °C, lit.[4] 136 °C), NCS, and allyl acetate or allyl acetamide, respectively. The aldoxime is, from the start of the reaction, not completely dissolved in the amount of chloroform used (ca. 1 g of oxime in 20 ml of $CHCl_3$), but this does not affect the yield. A precipitate is formed during the chlorination and goes into solution during the final heating. The reaction can be carried out in acetonitrile with the same yield. **3**: m.p. 99–100 °C (from ether), yield 52 %, prep. TLC (SiO_2; $CHCl_3$, 5 % CH_3OH). ^{1}NMR ($CDCl_3$): δ 2.04 (3H,s), 3.09 (1H,dd, *J* 17 and 8 Hz), 3.37 (1H,dd, *J* 17 and 10 Hz), 4.15 (2H,d, *J* 5 Hz), 4.8 (1H,m), 6.7–7.3 (3H,m).

4: m.p. 125–127 °C (from ether), yield 48 %, prep. TLC (SiO_2; $CHCl_3$, 5 % CH_3OH). ^{1}H NMR ($CDCl_3$): δ 1.98 (3H,s), 3.07 (1H,dd, *J* 17 and 8 Hz), 3.47 (1H,dd, *J* 17 and 10 Hz) 3.5 (2H,m), 4.8 (1H,m), 6.0 (1H, NH,br), 6.8–7.4 (3H,m).

3-(3-Thienyl)-5-acetoxymethylisoxazoline (**5**) *and 3-(3-thienyl)-5-*N*-acetylaminomethylisoxazoline* (**6**) are prepared by the method described for compound **1**, from 3-thiophenecarboxaldoxime (m.p. 128–129 °C, lit. [11] 111–112 °C), NCS, and allyl acetate or *N*-allylacetamide, respectively. The chlorination is performed at 0 °C and is completed in 1–1.5 h.

5: m.p. 92 °C (from ether), yield 50 %. ^{1}H NMR ($CDCl_3$): δ 2.05 (3H,s), 3.08 (1H,dd, *J* 16.5 and 7.5 Hz), 3.38 (1H,dd, *J* 16.5 and 9.5 Hz), 4,16 (2H,d, *J* Hz), 4.8 (1H,m), 7.1–7.6 (3H,m).

6: m.p. 186–188 °C (from ether), yield 53 %. ^{1}H NMR ($CDCl_3$): δ 1.95 (3H,s), 3.01 (1H,dd, *J* 16.5 and 8 Hz), 3.15–3.65 (3H,m), 4.7 (1H,m), 7.1–7.5 (3H,m).

*3-(2-Chloro-3-thienyl)-5-*N*-acetylaminomethylisoxazoline* (**7**). When 3-thiophene carboxaldoxime is heated under reflux in chloroform with two equiv. of NCS for 1 h, the nucleus is also chlorinated in the 2-position. The oximino chloride obtained is converted into **7** by cycloaddition to *N*-allylacetamide, following the method described for **1**.

7: m.p. 174 °C, yield 68 %. ^{1}H NMR ($CDCl_3$): δ 1.97 (3H,s), 2.9–3.8 (4H,m), 4.75 (1H,m), 6.2 (1H,br.s), 7.00 (1H,d, *J* 6 Hz), 7.13 (1H,d, *J* 6 Hz). MS: 259 and 261 (M+1) 186, 188, 73.

*3-(5-Chloro-2-thienyl)-5-*N*-acetylaminomethylisoxazoline* (**8**) is obtained by chlorination of

2-thiophenecarboxaldoxime with two equiv. of NCS in chloroform, first at 25 °C for 1 h and then at reflux temperature for 1 h followed by cycloaddition to *N*-allylacetamide as described for *1*.

8: m.p. 179–180 °C, yield 37 %. ^{1}H NMR ($CDCl_3$): δ 1.97 (3H,s), 2.8–3.7 (4H,m), 4.8 (1H,m), 6.8 (2H,m).

3-(3-Pyridyl)-5-acetoxymethylisoxazoline (**9**). NCS (1.33 g, 10 mmol) is added with stirring to a mixture of 3-pyridinecarboxaldoxime (1.22 g, 10 mmol) and allyl acetate (1.2 g, 12 mmol) in chloroform (25 ml). The mixture is heated under reflux for 10 min. The temperature is lowered to 25 °C and triethylamine (1.1 g, 11 mmol) is added dropwise over a period of 30 min. The mixture is then heated under reflux again for 15 min, washed with water (2 × 15 ml) and dried over magnesium sulfate. Evaporation of the solvent and purification of the product by prep. TLC (SiO_2; $CHCl_3$, 5 % CH_3OH) give 59 % of **9**; m.p. 74–75 °C (from ether). ^{1}H NMR ($CDCl_3$): δ 2.04 (3H,s) 3.11 (1H,dd, *J* 16.5 and 8 Hz), 3.41 (1H,dd, *J* 16.5 and 10 Hz), 4.20 (2H,d, *J* 4.8 Hz), 4.9 (1H,m), 7.25 (1H,m), 7.95 (1H,dt, *J* 8 and 2 Hz), 8.55 (1H,dd, *J* 5 and 2 Hz), 8.7 (1H,d, *J* 2 Hz).

*3-(3-Pyridyl)-5-*N*-acetylaminomethylisoxazoline* (**10**) is prepared analogously to **9** by using *N*-allylacetamide as olefin. **10**: 134–135 °C (from ether), yield 50 %. ^{1}H NMR ($CDCl_3$): δ 1.97 (3H,s), 3.13 (1H,dd, *J* 17.5 and 8 Hz), 3.47 (1H,dd, *J* 17.5 and 10 Hz), 3.5 (2H,m), 4.85 (1H,m), 6.4 (1H,br.), 7.3 (1H,m), 7.90 (1H,dt, *J* 8 and 2 Hz), 8.6 (1H,dd, *J* 5 and 2 Hz), 8.8 (1H,d, *J* 2 Hz).

3-(2-Pyrryl)-5-acetoxymethylisoxazoline (**11**). To 2-pyrrolecarboxaldoxime (0.55 g, 5 mmol), allyl acetate (0.55 g, 5.5 mmol) and triethylamine (0.55 g, 5.5 mmol in chloroform (15 ml) is added NCS (0.70 g, 5.2 mmol) in acetonitrile (8 ml) dropwise over 10 mm at −70 °C. The temperature is slowly raised, and the mixture is heated under reflux for 15 min. Addition of ice-water (50 ml), filtration through a thin layer of Celite, separation of phases, drying over sodium sulfate, and evaporation of the solvent gives crude **11** (0.77 g), which by prep. TLC (SiO_2; $CHCl_3$, 4 % CH_3OH) gives pure **11** as an oil (0.64 g, 62 %). ^{1}H NMR ($CDCl_3$): δ 2.02 (3H,s), 3.03 (1H,dd, *J* 17 and 8 Hz), 3.31 (1H,dd, *J* 17 and 9.5 Hz), 4.12 (1H,d, *J* 5.5 Hz), 4.73 (1H,m), 5.95–6.4 (2H,m), 6.8 (1H,m), 10.2 (1H,br.s). MS: 207(M), 135,73. A second minor fraction with a slightly smaller R_F-value consisted of 3,5-(di-2-pyrryl)-1,2,4-oxadiazole. MS: 200(M^+).

*3-(2-Pyrryl)-5-*N*-acetylaminomethylisoxazoline* (**12**) is prepared by adding NCS to a stirred suspension of 2-pyrrolecarboxaldoxime and *N*-allylacetamide in ether at 0 °C, followed by dropwise addition of triethylamine in ether. The cooling bath is removed and the stirring is continued at room temperature for 1 h. saturated aqueous sodium chloride is added at 0 °C, and the precipitate consisting of impure **12** is filtered off and washed first with a small portion of icewater and then with cold acetone. It is recrystallized from water; m.p. 192–196 °C. The yield is 28 %. ^{1}H NMR (DMSO,d_6): δ 1.82 (3H,s), 2.7–3.6 (2H,m), 4.5 (1H,m), 6.07 (1H,br.s), 6.30 (1H,br.s), 6.83 (1H,br.s) 8.0 (1H,t, NHAc), 11.5 (1H,br.s., NH).

3-Phenyl-5-acetoxymethylisoxazoline (**13**) *and 3-phenyl-5-*N*-acetylaminomethylisoxazoline* (**14**) are prepared according to the general procedure of Larsen and Torssell.[3]

13: m.p. 66 °C, yield 69 %. ^{1}H NMR ($CDCl_3$): δ 2.05 (3H,s), 3.12 (1H,dd, *J* 16.5 and 8 Hz), 3.40 (1H,dd, *J* 16.5 and 10 Hz), 4.19 (2H,d, *J* 5 Hz), 4.87 (1H,m), 7.15–7.7 (5H,m).

14: m.p. 167 °C, yield 67 %. ^{1}H NMR ($CDCl_3$): δ 1.97 (3H,d), 3.05 (1H,dd, *J* 17 and 8 Hz), 3.34 (1H,dd, *J* 17 and 10 Hz), 3.5 (2H,m), 4.8 (1H,m), 6.2 (1H,br.s), 7.1–7.7 (5H,m).

3-Ethyl-5-acetoxymethylisoxazoline (**15**) is synthesized from propanaldoxime and allyl acetate[3] in a yield of 84 %; b.p. 140 °C/2 mm Hg. ^{1}H NMR ($CDCl_3$): δ 1.17 (3H,t, *J* 7.5 Hz), 2.05 (3H,s), 2.37 (2H,q, *J* 7.5 Hz), 2.74 (H,dd, *J* and 8 Hz), 3.03 (1H,dd, *J* 17 and 10 Hz), 4.10 (2H,dd, *J* 4.6 Hz), 4.7 (1H,m).

*3-*t*-Butyl-5-acetoxymethylisoxazoline* (**16**) is synthesized from privalaldoxime and allyl acetate[3] in a yield of 95 %; b.p. 132 °C/1.5 mmHg. ^{1}H NMR ($CDCl_3$): δ 1.19 (9H,s), 2.03 (3H,s), 2.74 (1H,dd, *J* 17 and 8 Hz), 2.97 (1H,dd, *J* 17 and 10

Hz), 4.06 (2H,d, *J* 4.5 Hz), 4.7 (1H,m). The chlorination of pivalaldoxime is carried out in chloroform under reflux for 1 h.

Disulfide of 3-butyl-5-mercaptomethylisoxazoline (**17**) is prepared from diallyl disulfide (0.37 g, 2.5 mmol), NCS (1.01, 7.5 mmol), butanaldoxime (0.76 g, 7.5 mmol) and triethylamine (0.80 g, 7.6 mmol) in chloroform according to the literature procedure.[3] The yield of **17** is 0.58 g, 68 %; m.p. 95 °C. MS: 345 (M+1), 344, 205, 174, 173 (M/2 +1), 172, 140, 126. ^{1}H NMR ($CDCl_3$): δ 0.91 (6H,t, *J* 6.5 Hz), 1.1–1.9 (8H,m), 2.3 (4H,t *J* 6.5), 2.5–3.2 (8H,m), 4.7 (2H,m). **17** was also obtained when **19** was heated under reflux with thiourea in 96 % ethanol for 55 h and the product hydrolyzed with ethylamine (50 % aq. solution) for 4 h.

3-Butyl-5-bromomethylisoxazoline (**19**) is obtained crude in a yield of 81 % from allyl bromide and pentanaldoxime;[3] b.p. 80–84 °C/0.2 mmHg (slight decompn.). ^{1}H NMR ($CDCl_3$): δ 0.93 (3H,br.t), 1.1–1.9 (4H,m), 2.33 (2H,br.t), 2.5–3.6 (4H,m), 4.7 (1H,m).

*3-Carbo-*t*-butoxymethyl-5-acetoxymethylisoxazoline* (**20**). The oxime of *t*-butyl formylacetate (**23**) is chlorinated in the presence of a few drops of pyridine at room temp. according to the usual method,[3] and reacted with allyl acetate and triethylamine to give **20** as an oil in a yield of 30 %, purified by prep. TLC (SiO_2; $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 1.43 (9H,s), 2.87 (1H,dd, *J* 16 and 7 Hz), 3.16 (1H,dd, *J* 16 and 9 Hz), 3.34 (2H,s), 4.11 (2H,d, *J* 5 Hz), 4.8 (1H,m).

3-Ethyl-5-α-acetoxyethylisoxazoline (**21**) is obtained as a distereoisomeric mixture in a yield of 66 % from 3-acetocy-1-butene and propanaldoxime. It is purified by chromatography (SiO_2; CH_2Cl_2, 10 % EtOAc). ^{1}H NMR ($CDCl_3$): δ 1.15 (3H,t, *J* 7.5 Hz), 1.22 (3H,d, *J* 7 Hz), 2.01 (3H,s), 2.35 (2H,q, *J* 7.5 Hz), 2.8 (2H,m), 4.5 (1H,m), 4.9 (1H,m).

The oxime of t*-butyl formylacetate* (**23**). Formyl Meldrum's acid[12] (1.72 g, 10 mmol) and *t*-butyl alcohol (0.83 g, 11 mmol) are heated under reflux for 3 h in benzene (5 ml). The solvent is evaporated *in vacuo* at 25 °C and the crude *t*-butyl formylacetate[13] is oximated with an aqueous solution of hydroxylamine [0.74 g of hydroxylamine hydrochloride and 0.92 g of sodium hydrogen carbonate in water (20 ml)] at 25 °C for 20 h. Extraction with methylene chloride gives 1.0 g (69 %) of crude oily oxime, which is used without further purification. The *syn-anti* hydrogens of the oxime function appear as triplets at 6.9 and 7.4 ppm.

General procedure for reduction of the isoxazolines. The isoxazoline (10 mmol) is hydrogenated in aquaous methanol (20 ml; ca. 15 % H_2O) over Raney-Ni in the presence of boric acid (ca. 30 mmol) at room temp. and atmospheric pressure. The reduction is completed in ca. 2–4 h. The solution is filtered through a thin layer of Celite, evaporated to a small volume (ca. 3 ml) and extracted with chloroform. Drying over sodium sulfate and evaporation of the chloroform gives **25** in good yields (50–80 %). The product is purified by prep. TLC. A few amides, e.g. **10**, are less soluble in aqueous methanol. In this case methanol or ethanol is used as solvent for the reduction. The pyridine derivatives require a reduction time of ca. 10–20 h.

25a: oil; ^{1}H NMR ($CDCl_3$): 2.04 (3H,s), 3.01 (2H,d, *J* 6 Hz), 3.3 (1H,br.s), 4.10 (2H,d, *J* 4 Hz), 4.3 (1H,m), 6.46 (1H,dd, *J* 4 and 2 Hz), 7.18 (1H,d, *J* (Hz), 7.54 (1H,s).

25b: m.p. 102–103 °C; ^{1}H NMR ($CDCl_3$): δ 1.97 (3H,s), 2.97 (2H,d, *J* 6 Hz), 3.3 (2H,m), 4.2 (1H,m, + O*H*), 6.38 (1H,dd, *J* 4 and 2 Hz), 7.0 (1H,br.s), 7.07 (1H,d, *J* 4 Hz), 7.47 (1H,br.s).

25c: oil; ^{1}H NMR ($CDCl_3$): δ 1.23 (9H,s), 2.06 (3H,s), 2.69 (2H,d, *J* 6 Hz), 3.5 (1H,br.s), 3.95–4.45 (3H,m).

25d: mp. 106–108 °C (from $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 1.99 (3H,s), 3.05 (2H,d, *J* 6 Hz), 3.35 (2H,m), 4.28 (1H,m), 6.4 (1H,br.s), 6.9–7.2 (1H,m), 7.5–7.8 (2H,m).

25f: mp. 108–110 °C (from $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 1.97 (3H,s), 2.99 (2H,d, *J* 6 Hz), 3.3 (2H,m), 4.24 (1H,m), 6.7 (1H,br.s), 7.20 (1H,dd, *J* 5 and 3 Hz), 7.39 (1H,dd, *J* 5 and 1 Hz), 8.01 (1H,dd, *J* 3 and 1 Hz).

The reductions of **9** and **10** proceed slowly (ca. 10–20 h) and require larger amounts of Raney-Ni. Two liquid products, **25g** and **26**, are ob-

tained from **9** in approximately equal yields (~ 30 % each) together with a small amount of starting material; prep. TLC (SiO_2; $CHCl_3$, 5% CH_3OH). No attempt was made to optimize the yield of **25g** by using other catalysts. **25h**, m.p. 102 °C, is obtained in a yield of 47 %. The aqueous phase is extracted with ethyl acetate and chloroform. ^1H NMR ($CDCl_3$): **25g**: δ 2.02 (3H,s), 3.20 (2H,m), 4.14 (2H, d, *J* 5 Hz), 4.47 (1H,m), 7.32 (1H,dd, *J* 8 and 4 Hz), 8.16 (1H,dt, *J* 8 and 2 Hz), 8.68 (1H,d, *J* 4 Hz), 9.03 (1H,s); **26**: δ 2.0 (2H,m), 3.09 (2H,t, *J* 7 Hz), 3.70 (2H,t, *J* 7 Hz), 4.5 (1H,br.s), 7.32 (1H,dd, *J* 8 and 4 Hz), 8.17 (1H,dt, *J* 8 and2 Hz), 8.64 (1H,d, *J* 4 Hz), 9.10 (1H,s); **25h**: δ 1.90 (3H,s), 3.05 (2H,d, *J* 6 Hz), 3.33 (2H,m), 3.8 (1H,br.), 4.20 (1H,m), 6.69 (1H,br.), 7.30 (1H,dd, *J* 8 and 4 Hz), 8.11 (1H,dt, *J* 8 and 2 Hz), 8.66 (1H,d, *J* 4 Hz), 9.03 (1H,s).

25i and **25j** are obtained in yields of ca. 60–70 % (prep. TLC: SiO_2; $CHCl_3$, 10 % CH_3OH), by catalytic reduction of **11** and **12** in the presence of two equivalents of acetic acid. ^1H NMR ($CDCl_3$): **25i**, oil: δ 2.02 (3H,s), 2.98 (2H,d, *J* 6 Hz), 3.4 (1H,br.s), 4.09 (2H,d, *J* 4 Hz), 4.3 (1H,m), 6.17 (1H,m), 6.85–7.05 (2H,m).

When the isoxazoline **11** is reduced without added acid, the main product is **28**. The yield is 50–60 %. ^1H NMR ($CDCl_3$): **28**: δ 1.9 (2.H,m), 2.85 (2H,t, *J* 7 Hz), 3.3 (1H,br.s), 3.63 (2H,t, *J* 7 Hz), 6.11 (1H,m), 6.13 (2H,m). MS 153 (M^+).

25k: oil; ^1H NMR ($CDCl_3$): δ 2.04 (3H,s), 3.15 (2H,d, *J* 6 Hz), 4.12 (2H,d, *J* 5 Hz), 4.40 (1H,m), 7.1–8.0 (5H,m).

25l: m.p. 136–139 °C; ^1H NMR ($CDCl_3$); δ 1.98 (3H,s), 3.10 (2H,d, *J* 5 Hz), 3.37 (2H,m), 4.20 (1H,m), 6.3 (1H,br.s), 7.1–7.9 (5H,m).

29a is formed in a yield of 64 % when **25a** (140 mg) is heated under reflux with *p*-TsOH (20 mg) for 3/4 h in chloroform (1 ml). The crude product is purified by prep. TLC (SiO_2; $CHCl_3$: CCl_4, 1: 2). ^1H NMR ($CDCl_3$): δ 6.31 (2H,dd, *J* 3 and 1 Hz), 7.41 (2H,d, *J* 3 Hz), 7.30 (2H,d, *J* 1 Hz).

29b and **27. 25g** (60 mg) is kept at 80–90 °C for 30 min in a mixture of acetic acid and trifluoroacetic acid (1 ml; 1: 1). Evaporation of the solvent and prep. TLC (SiO_2; $CHCl_3$, 2 % CH_3OH) gives **29b** (30 mg, 77 %) and **27** (10 mg, 15 %). ^1H NMR ($CDCl_3$): **29b**: δ 6.36 (1H,dd, *J* 4 and 2 Hz), 6.60 (1H,d, *J* 4 Hz), 7.21 (1H,m), 7.39 (1H,s), 7.83 (1H,dt, *J* 8 and 2 Hz), 8.35 (1H,br.d, *J* 4 Hz), 8.80 (1H,s); **27**: δ2.14 (3H,s), 4.79 (2H,d, *J* 2 Hz), 6.95 (2H,br.s), 7.30 (1H,m), 8.12 (1H,dt, *J* 8 and 2 Hz:, 8.69 (1H,br.d, *J* 5 Hz), 9.03 (1H,s), MS: 205 (M^+).

29c. Yield 82 %. ^1H NMR ($CDCl_3$): δ 1.21 (9H,s), 5.82 (1H,d, *J* 3 Hz), 6.24 (1H,dd, *J* 3 and 2 Hz), 7.27 (1H,d, *J* 2 Hz).

29d. 5 (0.45 g) dissolved in a mixture of methanol (4 ml) and 1,2-dimethoxyethane (10 ml) is reduced with aqueous Ti^{3+} solution (5 ml, 1 M) for one week.[9] Usual work-up and purification by prep. TLC gives **29d** (200 mg, 67 %). ^1H NMR ($CDCl_3$): δ 6.33 (2H,s), 7.1–7.45 (4H,m). **25e** was not observed in the crude reaction mixture.

29e. 25k (0.21 g) and *p*-TsOH (20 mg) in chloroform (2 ml) are heated under reflux for 1/2 h. Washing with aqueous sodium hydrogen carbonate, drying over magnesium sulfate and purification by prep. TLC give **29e** as an oil (0.09 g, 66 %). ^1H NMR ($CDCl_3$): δ 6.36 (1H,dd, *J* 4 and 2 Hz), 6.53 (1H,d, *J* 4 Hz), 7.1–7.7 (6H,m).

30a and **32**. The cyclization of **25b** (0.1 g) is carried out in acetic acid (1 ml, plus one drop of acetyl chloride) at 105 °C for one h. Evaporation of the solvent, addition of methylene chloride (5 ml), washing with aqueous sodium hydrogen carbonate, drying, evaporation and separation on a preparative plate (SiO_2; $CHCl_3$, 5% CH_3OH) give **30a** (ca. 20 %) and **32** (ca. 25 %). ^1H NMR ($CDCl_3$): **30a**: δ 2.30 (3H,s), 6.2–6.6 (4H,m), 7.3–7.5 (2H,m); **32**: δ 1.94 (3H,s), 2.42 (3H,s), 3.13 (2H,d, *J* 5 Hz), 3.56 (2H,m), 6.0–6.5 (6H,m), 7.0–7.25 (2H,m), 7.43 (1H,s). MS: (M^+), 309 (M^+-59 = CH_3CONH_2), 268, 254, 239, 159, 93 (furyl-CO^+).

30c is prepared by cyclizing **25h** (50 mg) in acetic acid (0.5 ml + 20 mg of acetyl chloride under reflux for 1/2 h. Evaporation *in vacuo,* washing with aqueous sodium hydrogen carbonate and purification by prep. TLC (SiO_2; $CHCl_3$, 10 % CH_3OH) gives **30c** in practically quantitative yield. ^1H NMR ($CDCl_3$): δ 2.44 (3H,s), 6.22 (2H,d, *J* 3 Hz), 7.17 (2H,m), 7.60 (1H,dt, *J* 8 and

2 Hz), 8.47 (2H,m). **30c** was obtained in an overall yield of 44 % by reducing **10**, evaporating the filtered solution to dryness *in vacuo* and heating the crude product with acetic acid under reflux as described above.

30d and **30e** are obtained in practically quantitative yields by cyclization of **25d** and **25f**, respectively, in acetic acid containing a catalytic amount of acetyl chloride (HCl) for 1 h at 100 °C. ^{1}H NMR ($CDCl_3$): **30d**: δ 2.31 (3H,s), 6.2 (2H,m), 6.95 (2H,m), 7.2 (2H,m); **30e**: δ 2.31 (3H,s), 6.16 (2H,m), 7.0 (1H,m), 7.2 (3H,m).

30f. **25l** is cyclized to **30f** in 71 % yield according to the procedure described for **30c**; reflux time 1 h. ^{1}H NMR ($CDCl_3$): δ 2.27 (3H,s), 6.17 (2H,m), 7.19 (1H,m), 7.27 (5H,s). IR (film): 1725 cm^{-1} (s).

33. Catalytic reduction of **21** over Raney-Ni and subsequent cyclization of the crude β-hydroxyketone in refluxing methylene chloride catalyzed by a few droplets of PBr_3 give **33** in an overall yield of 51 %. ^{1}H NMR ($CDCl_3$): δ 1.17 (3H,t, *J* 7.5 Hz), 2.19 (3H,s), 2.52 (2H,q, *J* 7.5 Hz), 5.74 (2H,s).

References

1. Das, N. B. and Torssell, K. B. G. *Tetrahedron 39* (1983) 2247.
2. Mukerji, S. K., Sharma, K. K. and Torssell, K. B. G. *Tetrahedron 39* (1983) 2231.
3. Larsen, K. E. and Torssell, K. B. G. *Tetrahedron 40* (1984) 2985.
4. Iwakura, Y., Uno, K., Shiraishi, S. and Hongu, T. *Bull. Chem. Soc. Jpn. 41* (1968) 2954.
5. Rheinholdt, H., Dewald, M., Jansen, F. and Schmitz-Dupont, O. *Liebigs Ann. Chem. 451* (1927) 161.
6. Huisgen, R. and Mack, W. *Tetrahedron Lett.* (1961) 583.
7. Von Pechmann, H. *Ber. Dtsch. Chem. Ges. 25* (1892) 1040; Michael, A. *Ber. Dtsch. Chem. Ges. 38* (1905) 2096; Hausser, C. R. and Hudson, B. T. Jr., *Org. React. 1* (1942) 266.
8. Curran, D. P. *J. Am. Chem. Soc. 105* (1983) 5826.
9. Andersen, S. H., Das, N. B., Jørgensen, R. D., Kjeldsen, G., Knudsen, J. S., Sharma, S. C. and Torssell, K. B. G. *Acta Chem. Scand., Ser. B 36* (1982) 1.
10. Brady, O. L. and Goldstein, R. F. *J. Chem. Soc.* (1927) 1959.
11. Steinkopf, W. and Schmit, H. F. *Liebigs Ann. Chem. 533* (1938) 264.
12. Bihlmayer, G. A., Derflinger, G., Derkosch, J. and Polansky, O. E. *Monatsh. Chem. 98* (1967) 564.
13. Sato, M., Yoneda, N., Katagira, N., Watanabe, H. and Kaneko. C. *Synthesis* (1986) 672.

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