Synthesis of *N*-Substituted Pyrroles From Azlactones via 1,3-Oxazolium 5-Oxides

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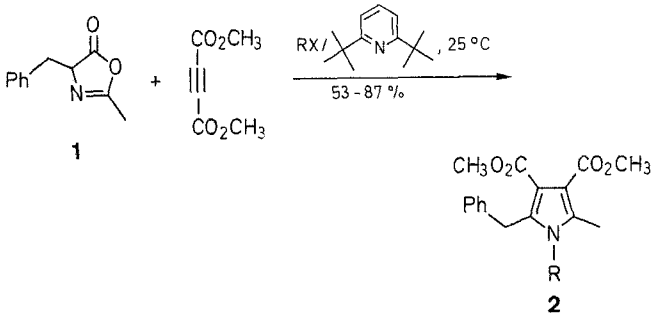
In situ *N*-alkylation of azlactones (1,3-oxazol-5(4*H*)-ones) with reactive alkylating agents has been successfully accomplished. The resulting mesoionic 1,3-oxazolium 5-oxides (munchnones) are further transformed into *N*-alkylated pyrroles via a 1,3-dipolar cycloaddition reaction with a dipolarophile (dimethyl acetylenedicarboxylate) in the presence of 2,6-di-*tert*-butylpyridine.

Mesoionic 1,3-oxazolium 5-oxides (munchnones) are reactive, versatile 1,3-dipoles that have been used in the preparation of a number of heterocyclic systems, primarily those containing a pyrrole moiety.[1] Normally, such dipoles are generated *in situ* by the cyclodehydration of *N*-substituted *N*-acyl α-amino acids.[2] This method furnishes *N*-substituted pyrroles, however, the preparation of the requisite *N*-substituted-α-amino acid starting material is often a difficult task. Although the tautomeric equilibrium of 2-oxazolin-5-ones (azlactones) with mesoionic oxazoles has been reported,[3] the use of azlactones in 1,3-dipolar cycloadditions has only provided a synthetic route to pyrroles with no substituent on the ring nitrogen.

We now describe a simple method to effect *in situ* *N*-alkylation of readily available azlactones which are transformed into *N*-substituted pyrroles. This method provides an alternate strategy for obtaining reactive 1,3-dipolar munchnone derivatives while avoiding the lengthy preparation of *N*-substituted α-amino acid starting materials. In keeping with our earlier experiences,[4-7] the munchnones were generated in the presence of a suitable dipolarophile in order to trap the reactive species as it formed. For the purposes of this study, dimethyl acetylenedicarboxylate was used throughout as the dipolarophile.

Using the azlactone **1** derived from phenylalanine,[8] we examined a variety of alkylating agents to determine the level of reactivity required to alkylate the ring nitrogen and form the desired mesoionic system. Highly reactive alkylating agents, such as methyl trifluoromethanesulfonate or triethyloxonium tetrafluoroborate, were required in order to obtain the desired pyrroles in good yields. Interestingly, there was no evidence that alkylation had occurred at the C-4 position of the azlactone under these conditions.[9] The use of less reactive alkylating agents such as methyl iodide, dimethyl sulfate, or benzyl bromide furnished the expected pyrroles in very low (< 5%) yields.

The inclusion of 2,6-di-*tert*-butylpyridine was critical. In the synthesis of pyrrole **2a**, failure to include a base in the reaction mixture reduced the yield of pyrrole product to 15%. Replacement with other bases, such as the hindered tertiary amine, *N,N*-diisopropylethylamine, or a proton scavenger such as barium carbonate, also failed to provide the desired pyrrole product in reasonable yields.



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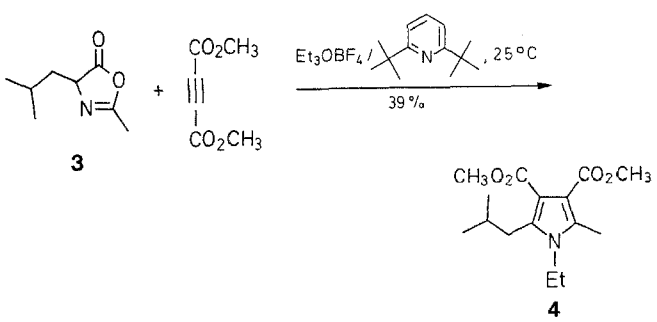
2	RX	R	Isolated Yield (%)
a	Et_3OBF_4	Et	80
b	$CH_3OSO_2CF_3$	CH_3	87
c	$BrCH_2CH_2CH_2OSO_2CF_3$	$BrCH_2CH_2CH_2$	53

It is likely that the added base is necessary for its role as a proton scavenger as well as to promote enolization. It also appears that the pK of the base is important and explains the difference in yields observed in switching from 2,6-di-*tert*-butylpyridine to *N,N*-diisopropylethylamine. The former is the weaker base which promotes enolization to the reactive species for cycloaddition. The later compound, which is a stronger base, is likely to favor the corresponding enolate anion subsequently inhibiting the reaction from proceeding.

Using this methodology, it is feasible to readily prepare *N*-substituted pyrroles where the substituent on the ring nitrogen contains a reactive group such as a halogen atom. For example, by using the triflate of 3-bromo-1-propanol as the alkylating agent, it was possible to synthesize pyrrole **2c** in 53% yield.



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Finally, to demonstrate that this reaction was not restricted to any particular azlactone, we carried out this reaction with the azlactone **3** derived from leucine using the optimum reaction conditions developed with azlactone **1**. In this case, the desired pyrrole **4** was obtained in only 39% yield due to the instability of this particular azlactone.

In conclusion, the *in situ* alkylation reaction of azlactones with reactive alkylating agents, when done in the presence of dipolarophiles such as dimethyl acetylenedicarboxylate, offers a new method for the synthesis of *N*-substituted pyrroles.

Melting points were obtained on a Thomas Hoover Capillary melting point apparatus and are uncorrected. ^{1}H-NMR spectra were recorded with a Varian EM-390 NMR spectrometer using TMS as the internal standard. Purity was determined by microanalysis and by TLC using 0.25 mm thick plates coated with silica gel-G as the stationary phase. IR spectra were recorded with a Nicolet XS-20 FT-IR spectrophotometer. All compounds possessed microanalytical and spectral data consistant with the structures proposed.

Dimethyl 1-Ethyl-2-methyl-5-(benzyl)-1*H*-pyrrole-3,4-dicarboxylate (2a):

A mixture of 2-methyl-4-(benzyl)oxazol-5(4*H*)-one (**1**;[8] 1.0 g, 6.4 mmol) and dimethyl acetylenedicarboxylate (3.6 g, 25 mmol) is cooled to 0 °C, and 2,6-di-*tert*-butylpyridine (2.6 mL, 9.6 mmol) is added. The cooling bath is removed and a solution of Et_3OBF_4 (1.36 g, 6.4 mmol) in CH_2Cl_2 (5 mL) is added slowly over 2 h via syringe pump. The reaction is stirred for an additional 30 min and then poured into a mixture of ether (25 mL) and EtOAc (25 mL), filtered, and evaporated. The resulting oil is chromatographed (silica gel, 30%, EtOAc in hexane) to afford **2a** as an oil; yield: 1.44 g (80%).

$C_{15}H_{23}NO_4$	calc.	C 64.04	H 8.24	N 4.98
(281.4)	found	64.38	8.45	4.99

IR (film): ν = 2956, 2872, 1705, 1538, 1445 cm^{-1}.

^{1}H-NMR ($CDCl_3$): δ = 0.91 (d, 6H, J = 6.8 Hz); 1.23 (t, 3H, J = 8.4 Hz); 1.80 (br m, 1 H); 2.35 (s, 3 H); 2.64 (d, 2 H, J = 7.3 Hz); 3.74 (s, 3 H); 3.76 (s, 3 H); 3.80 (q, 2 H, J = 8.4 Hz).

Dimethyl 1,2-Dimethyl-5-(benzyl)-1*H*-pyrrole-3,4-dicarboxylate (2b):

The same procedure described for **2a** is followed using methyl trifluoromethanesulfonate (1.06 g, 6.4 mmol) replacing $EtOBF_4$ as the alkylating agent. The product is chromatographed (silica gel 35% EtOAc in hexane) affording pure **2b**; yield: 1.66 g (87%); mp 68–72 °C.

$C_{17}H_{19}NO_4$	calc.	C 67.76	H 6.36	N 4.65
(301.4)	found	67.73	6.07	4.64

IR (KBr): ν = 2983, 2947, 1702, 1603, 1541 cm^{-1}.

^{1}H-NMR ($CDCl_3$): δ = 2.28 (s, 3 H); 3.18 (s, 3 H); 3.72 (s, 3 H); 3.77 (s, 3 H); 4.10 (s, 2 H); 7.12 (m, 5 h).

Dimethyl 1-(3-Bromopropyl)-2-methyl-5-(benzyl)-1*H*-pyrrole-3,4-dicarboxylate (2c):

A solution of 3-bromo-1-propanol (2.1 g, 15 mmol) in distilled CH_2Cl_2 (30 mL) is cooled to 0 °C. 2,6-Di-*tert*-butylpyridine (4.3 g, 22.5 mmol) is added dropwise over 10 min and the resulting mixture stirred for 5 min. A solution of freshly distilled trifluoromethanesulfonic anhydride (4.70 g, 16.67 mmol) in CH_2Cl_2 (10 mL) is added dropwise over 15 min. The mixture is stirred for 16 h at 0 °C, reduced to 25% of its original volume and diluted with ether (40 mL). The mixture is filtered and evaporated to dryness and CH_2Cl_2 is added to achieve a total volume of 10 mL. This solution is added over 2 h via syringe pump to a mixture of **1** (2.84 g, 15 mmol), dimethyl acetylenedicarboxylate (8.52 g, 60 mmol) and 2,6-di-*tert*-butylpyridine (5.16 g, 27 mmol). The resulting mixture is stirred for 96 h at ambient temperature and then poured into a mixture of ether (25 mL) and EtOAc (25 mL), filtered, evaporated, and chromatographed (silica gel, 30% EtOAc in hexane). The solid product is recrystallized from cyclohexane to afford pure **2c**; yield 3.2 g (53%); mp 109–110 °C.

$C_{19}H_{22}BrNO_4$	calc.	C 55.89	H 5.43	N 3.43
(408.3)	found	56.16	5.49	3.37

IR (KBr): ν = 2940, 1712, 1700, 1603, 1538 cm^{-1}.

^{1}H-NMR ($CDCl_3$): $\delta = 1.85$ (m, 2H); 2.38 (s, 3H); 3.25 (t, 2H, $J = 6{,}0$ Hz); 3.79 (s, 3H); 3.83 (t, 2H, $J = 7.8$ Hz); 3.85 (s, 3H); 4.22 (s, 2H); 7.24 (m, 5H).

2-Methyl-4-(2-methylpropyl)oxazol-5(4*H*)-one (3):
DL-Leucine (13.1 g, 0.1 mol) is placed in acetic anhydride (150 mL) and the mixture heated to reflux over 20 min and maintained at reflux for 1 h. The acetic anhydride is removed *in vacuo* and the resulting oil distilled to afford **3**; yield: 8.0 g (52%); bp 60°C/1.33 mbar.

$C_8H_{13}NO_2 \cdot 0.25\ H_2O$	calc.	C 60.17	H 8.52	N 8.77
(159.6)	found	60.15	8.40	8.59

IR (film): $\nu = 2874, 1827, 1685, 1549, 1518\ cm^{-1}$.

^{1}H-NMR ($CDCl_3$): $\delta = 1.00$ (d, 6H, $J = 6.2$ Hz); 2.10–1.30 (m, 3H); 2.18 (d, 3H, $J = 1.8$ Hz); 4.11 (m, 1H).

Dimethyl 1-Ethyl-2-methyl-5-(2-methylpropyl)-1*H*-pyrrole-3,4-dicarboxylate (4):
The same procedure as for **2a** is used for the reaction of **3** with dimethyl acetylenedicarboxylate. The product is chromatgraphed (silica gel, 30% EtOAc in hexane) to afford pure **4** as an oil; yield: 0.7 g (39%).

$C_{15}H_{23}NO_4$	calc.	C 64.04	H 8.24	N 4.98
(281.4)	found	64.38	8.45	4.99

IR (film): $\nu = 2956, 2872, 1705, 1538, 1445\ cm^{-1}$.

^{1}H-NMR ($CDCl_3$): $\delta = 0.92$ (d, 6H, $J = 5.9$ Hz); 1.22 (t, 3H, $J = 7.0$ Hz); 1.84 (m, 1H); 2.43 (s, 3H); 2.72 (d, 2H, $J = 8.4$ Hz); 3.75 (s, 3H); 3.78 (s, 3H); 3.82 (q, 2H, $J = 7.0$ Hz).

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