A Novel Acyclic Addition of Ketenes to Oxazoles/Oxazolines

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The addition of *n*-butyryl chloride (**1**) to 5-phenyloxazole (**6**) or 4,5-dihydro-5-methyl-4-[(4′-methylphenyl)-sulfonyl]oxazole (**8**) in the presence of triethylamine lead to 1-(5′-phenyloxazol-2′-yl)-1-buten-1-yl butanoate (**7**) and 1-(5′-methyl-4′-[4″-methylphenylsulfonyl]4′,5′-dihydrooxazol-2′-yl)-1-buten-1-yl butanoate (**9**), respectively.

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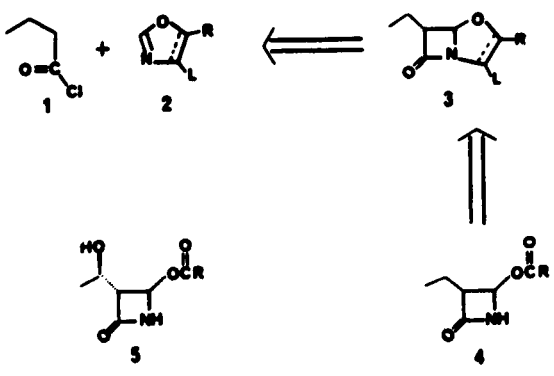
The reaction of imines with certain acid chlorides in the presence of tertiary amines to obtain azetidinones has been reported in the literature [1-3]. On the other hand, under similar conditions, acetyl chloride does not yield an azetidinone but a product which was believed to be 1,3-oxazetidine [4,5] and was subsequently shown to be dihydrooxazinone [6]. Some early reports indicate that the addition of acid chlorides to imidates in the presence of a tertiary amine does not lead to azetidinone [7], but subsequent workers claim that the azetidinones can be synthesized from imidates under the above conditions [8]. Recently, the synthesis of oxocephams has been reported by the reaction of 1,3-oxazines (a cyclic imidate) with mixed acid anhydride [9] or acid chloride [10] in the presence of triethylamine. The latter report also points out that the ratio of acid chloride/triethylamine to cyclic imines determines the type of product obtained. In all the above cases, the addition of ketene across the C = N bond of a variety of substrates resulted in cyclic products. Our work towards the synthesis of azetidinones has led us to a novel acyclic addition product.

Our aim was to develop a synthesis of azetidinones as outlined in Scheme I. Though our target compound was the 3-(*R*)-hydroxyethylazetidinone **5**, due to the ready availability of *n*-butyryl chloride **1** we decided to use it as a model substrate towards the synthesis of the azetidinone **4**. Thus when **1** was reacted with either the oxazole **6** or

Scheme I



the dihydrooxazole **8** in the presence of triethylamine (TEA), the resultant, isolated, major product from each reaction showed an ir absorption between 1750 and 1765 cm^{-1}. Such absorption is acceptable for β-lactams such as **3**. On the other hand, ^1H nmr signals of these products were more complex than the one expected for the compounds of type **3**. The mass spectral and elemental analysis of these products clearly indicated that these products had resulted from the addition of two equivalents of ketene generated from **1** to one equivalent of oxazole **6** or dihydrooxazole **8**. Based on a detailed nmr study, the following structures for the oxazole **7**, and for the dihydrooxazole **9** were established. The two-dimensional ^1H nmr spectra and nmr data for the oxazoles **6** and **7** are listed in

Scheme II

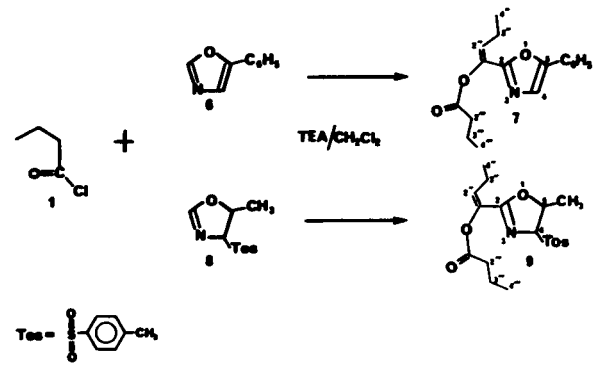


Figure 1 and Table I, whereas the same for dihydrooxazoles **8** and **9** is listed in Figure 2 and Table II. As expected, the ^1H and ^{13}C nmr shifts for the butene moiety (No. 1″-4″) of **7** and **9** are downfield when compared to the shifts for the butyl moiety (No. 1‴-4‴) of **7** and **9**. Their connectivities are shown in Figure 1 and Figure 2 respectively. The nmr shifts for the rest of the nuclei of **7** and **9** are also in agreement with the structures.

We postulate that overall, these products are formed by the mechanism parallel to the one suggested for thiazoles by Dondoni *et at* [11] (Scheme III). This involves the following steps. Ketene **11**, resulting from the reaction of butyryl chloride **1** with triethylamine (TEA) reacts with

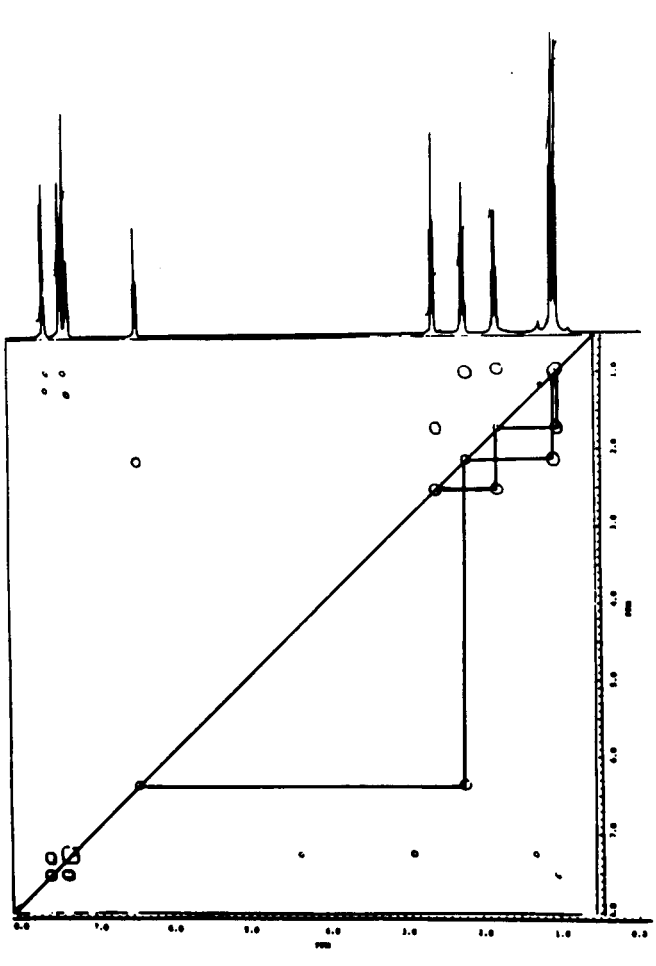


Figure 1. Two-dimensional (400 MHz) homonuclear shift-correlated (COSY) spectrum of **7**.

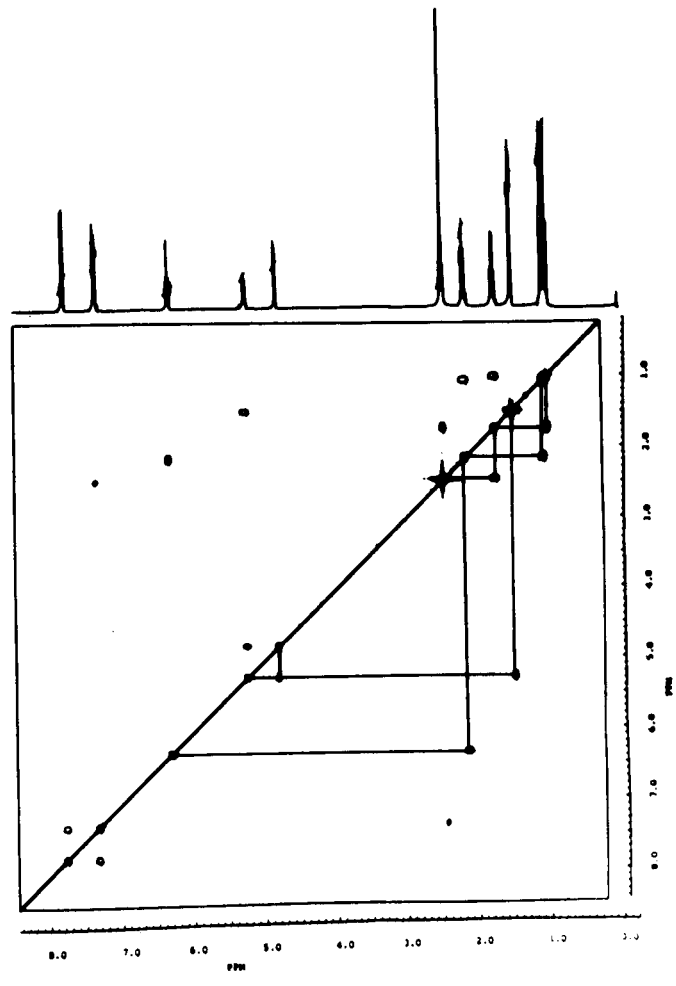


Figure 2. Two-dimensional (400 MHz) homonuclear shift-correlated (COSY) spectrum of **9**.

Table I

NMR Data for the Oxazoles **6** and **7** [a]

	^{1}H NMR Data [b]		^{13}C NMR Data	
No.	**6**	**7**	**6**	**7**
2	7.85	– – –	150.4	156.6
4	7.30	7.32	121.5	123.1
5	– – –	– – –	151.5	151.2
1′ Phenyl	– – –	– – –	127.7	127.7
2′-6′ Phenyl	7.40 to 7.70	7.30 to 7.60	128.9 (x 2), 128.7, 124.4 (x 2)	128.8 (x 2), 128.3, 124.2 (x 2)
1″	– – –	– – –	– – –	153.3
2″, 3″, 4″	– – –	6.42, 2.24, 1.12	– – –	126.3, 19.3, 13.1 [c]
1‴	– – –	– – –	– – –	171.2
2‴, 3‴, 4‴	– – –	2.62, 1.83, 1.07	– – –	35.7, 18.5, 13.7

[a] All values are in ppm compared to TMS = 0 ppm. [b] Proton resonances had required multiplets. [c] The methyl chemical shifts are interchangeable.

Table II

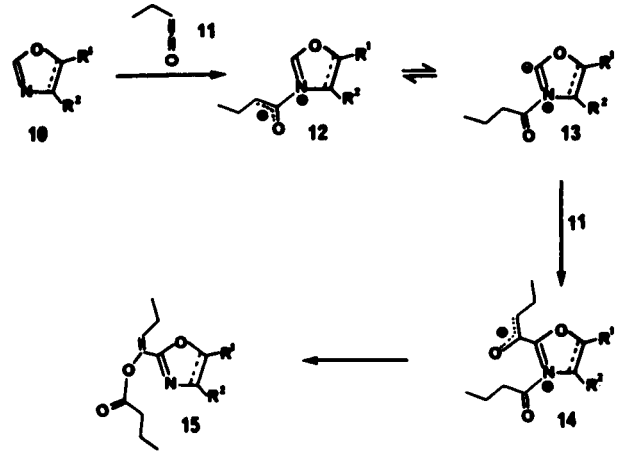
NMR Data for the Dihydrooxazoles **8** and **9** [a]

No.	^{1}H NMR Data [b]		^{13}C NMR Data	
	8	**9**	**8**	**9**
2	6.95	– – –	159.9	164.3
4	4.75	4.80	75.9	77.5
5	5.22	5.22	91.6	92.8
5-CH_3	1.45	1.46	22.2	22.2
1′ Tosyl	– – –	– – –	146.0	145.7
2′-6′ Tosyl	7.30-7.80	7.32-7.76	130.0 (x 2), 130.3 (x 2), 133.7	130.1 (x 2), 130.2 (x 2), 133.7
4′-CH_3 Tosyl	2.45	2.45	21.5	21.5
1″	– – –	– – –	– – –	135.5
2″, 3″, 4″	– – –	6.30, 2.15, 1.02	– – –	133.4, 20.2, 13.2 [c]
1‴	– – –	– – –	– – –	171.5
2‴, 3‴, 4‴	– – –	2.45, 1.74, 0.98	– – –	36.2, 18.9, 14.2

[a] All values are in ppm compared to TMS = 0 ppm. [b] Proton resonances had required multiplets. [c] These methyl chemical shifts are interchangeable.

oxazole/dihydrooxazole **10** to form a zwitterion **12** which is in equilibration with the ylide **13** possibly *via* an intramolecular five membered cyclic intermediate. In the case of oxazolium species, it is well established that C(2) hydrogen is rapidly exchangeable [12,13]. The attack of the second molecule of the ketene on the zwitterion **12** leads to other minor products whereas the attack of ketene **11** on ylide **13** leads to the formation of another zwitterion **14** which is eventually converted to enol acetate **15** *via* either the intramolecular or the intermolecular reaction. Again, as pointed out for the thiazoles, the intramolecular attack is probably more likely in the case of oxazoles/dihydrooxazoles as well [14]. The oxazole and dihydrooxazole enol acetates **7** and **9** are stable enough to survive silica gel column chromatography, though streaking during the column chromatography and tlc was clearly evident (especially in the case of **7**) which may imply that some hydrolysis/decomposition of the products **7** and **9** took place resulting in lower isolated yields.

Scheme III



This C-C bond formation reaction for the C_2 position of oxazole and dihydrooxazoles is new, and with further optimisation it may find its application in the synthesis of otherwise difficult to obtain 2-substituted oxazoles/dihydrooxazoles.

EXPERIMENTAL

The infrared spectra were recorded on a Perkin-Elmer 1320 spectrophotometer. Elemental microanalyses were conducted by Schering Analytical Research Services. Melting points were recorded on a meltemp apparatus and are uncorrected. The electron impact mass spectra were recorded on a Varian MAT CH-5 spectrometer at 70 eV. The two-dimensional ^{1}H-^{1}H shift correlated (COSY) data for **7** and **9**, in deuteriochloroform, were acquired at a sweep width of 3000 Hz (512 data points) in the F2 domain, 256 spectra (4 scan each) were accumulated with a delay (D_1) of 2 seconds using a Varian XL-400 spectrophotometer. Chemical shifts are in parts per million downfield from tetramethylsilane. The term flash chromatography refers to the method described by Still [16].

5-Phenyloxazole (**6**) and 4,5-dihydro-5-methyl-4-(4′-methylphenylsulfonyl)oxazole (**8**) were synthesized according to the literature procedures [15].

1-(5′-Phenyloxazol-2′-yl)-1-buten-1-yl Butenoate (**7**).

To a solution of 3.0 g (20.6 mmoles) of 5-phenyloxazole (**6**) in 40 ml of dichloromethane containing 8.6 ml (61.8 mmoles) of dry triethylamine (TEA) under N_2 nitrogen gas, 6.4 ml (61.8 mmoles) *n*-butyryl chloride (**1**) in 20 ml of dichloromethane was slowly added at room temperature. The resultant mixture containing some white solid was stirred for *ca.* 18 hours. This process of addition of TEA and **1** to the reaction mixture followed by 18 hours stirring was repeated (twice). Next, the solvent was removed under vacuum, and the resultant oily mass was taken in 100 ml dry diethyl ether. The white solid was filtered (occasionally anhydrous sodium sulfate was added to the ethereal suspension to facilitate filtration) and washed with dry ether. The combined ether filtrates were dried in vacuum to obtain an oil. Flash chromatography [16] of this oil on a silica gel column using hexane gradually changing to ethyl acetate/hexane (1:9, v/v) as eluting solvents afforded 2.01 g (34%) of analytically

pure **7** as a major product; (due to extensive streaking, fractions which were contaminated with other byproducts were not combined with the above pure compound); ir (neat): 2960, 2940, 2880, 1765 cm^{-1}; nmr (deuteriochloroform): Figure 1 and Table I; ms: 285.3 (M^+).

Anal. Calcd. for $C_{17}H_{19}NO_3$: C, 71.56; H, 6.71; N, 4.91. Found: C, 71.23; H, 6.71; N, 4.42.

1-(5'-Methyl-4'-[4''-methylphenylsulfonyl]-4',5'-dihydrooxazol-2'-yl)-1-buten-1-yl Butanoate (**9**).

To a solution of 2.0 g (8.35 mmoles) of 4,5-dihydro-5-methyl-4-(4'-methylphenylsulfonyl)oxazole (**8**) in 50 ml of dichloromethane containing 2.6 ml (25.05 mmoles) of *n*-butyryl chloride (**1**) under nitrogen, 3.5 ml (25.05 mmoles) triethylamine (TEA) in 6 ml dichloromethane was added dropwise at room temperature. The resultant mixture containing some white solid was stirred for *ca.* 18 hours at room temperature. Next, 2.6 ml of *n*-butyryl chloride and 3.5 ml of TEA was added as above and the reaction mixture was stirred for an additional 18 hours. Next, the reaction mixture was concentrated to an oil under vacuum and then diluted with 100 ml of dry diethyl ether. This ethereal suspension was filtered to remove a white solid (occasionally anhydrous sodium sulfate was added to this suspension to facilitate the filtration), and the white solid was washed with ether. The combined ether filtrates were concentrated to an oil under vacuum. Flash chromatography [16] of this oil on a silica gel column using hexane gradually changing to ethylacetate/hexane (1:9, v/v) as eluting solvents afforded 1.39 g (44%) of analytically pure **9** as a white solid, mp 81-83°, (this was the major product in the crude oil); ir (chloroform): 3010, 2980, 2870, 1750 cm^{-1}; nmr (deuteriochloroform): Figure 2 and Table II; ms: 224 (loss of *p*-toluenesulfonic acid).

Anal. Calcd. for $C_{19}N_{25}NO_5S$: C, 60.14; H, 6.64; N, 3.69; S, 8.45. Found: C, 59.79; H, 6.54; N, 3.69; S, 8.82.

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[14] In the case of oxazoline **8**, where butyryl chloride (**1**) was added before TEA, it is conceivable that some *N*-acylation of **8** took place (tlc indicated that **8** was present even after the addition of a three fold excess of **1**) initially with the acid chloride. But this activated oxazolenium species converted to either **12** or **13** when TEA was added. Similar arguments may be applicable in the case of oxazole **6**.

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