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4,5- AND 2,5-ADDITIONS TO OXAZOLES[1]

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Abstract: An investigation of the reaction of variously substituted oxazoles 1a-j with Br_2 in methanol revealed the formation of non-aromatic addition products. In general the presence of an aromatic substituent at the 4-position of oxazoles or the presence of a 4-methyl group if the 2-substituent is also aliphatic favors formation of 2,5-dimethoxy-3-oxazolines 3, while an aromatic substituent at the 2-position favors formation of ring-opened amides 2 or 7 or of 4,5-dimethoxy-2-oxazolines 5. Valuable information about intermediates in these reactions can be obtained by following the bromination of 1 in CD_3OD by ^1H- and ^{13}C-NMR.

INTRODUCTION

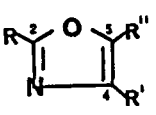
The oxazole ring system despite its aromaticity can undergo 4,5- and 2,5-addition reactions[2]. Many cases of Diels-Alder reactions have been reported involving oxazoles as the diene component[2a,3] or of 2,5-additions of singlet oxygen to oxazoles[4], however, in most of the cases the primary 3-oxazoline adduct could not be detected. Concerning 2-oxazolines, there are only sporadic examples of their formation as a result of 4,5-additions to oxazoles[5]. In connection with studies on 3-oxazolines[6] we were interested in examining the possibility of 2,5-additions to oxazoles and are reporting here on successful additions to oxazoles yielding 2- or 3-oxazolines.

RESULTS

As reported earlier[2a], we found that oxazoles 1 form aromatic substitution products under most bromination conditions. For instance, 1h reacted with Br_2, in AcOH-AcONa at room temperature, followed by water workup to give 4-bromo-2,5-diphenyloxazole and a small amount of N-benzoyl-2-amino-2-hydroxy-1-phenylethanone. However, when the reaction was carried out in methanol in the presence of solid K_2CO_3, at low temperature, non-aromatic methanol-trapping products were obtained in good yield. In general, three types of products were formed: a. ring opened amides of type 2 and 7; b. 3-oxazolines as two stereoisomers 3 and 4 (products of 2,5-addition) and c. 2-oxazolines 5 as one stereoisomer (product of 4,5-addition). The type of product formed depends on the substituents and their position (see Table).

For instance, 2-phenyloxazole 1i reacted at 0°C to produce the ring opened trimethoxy amide 2i in quantitative yield. On the other hand, at -78°C,

2,4,5-trimethyloxazole 1a led to isolation of cis and trans 2,5-dimethoxy-3-oxazolines 3a-4a in 60% conversion without evidence of formation of ring opened products. The influence of temperature is indicated by formation of a higher proportion of ring opened product 2 vs 2-oxazoline 5 as the reaction temperature was raised or as the reaction proceeded for a longer period (e.g. when 1h reacted with Br_2/MeOH at -15 to -5°C, for 5 h, 5h and 2h formed in a 1:2.2 ratio; however, when the reaction proceeded at -15°C for 3 days, only 2h was isolated). Formation of benzil as a side product was observed in some cases (see 1b-d) with more side product being formed as the reaction temperature was raised. Benzil has been reported to result from 4,5-diaryloxazoles under oxidizing conditions[7].



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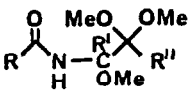

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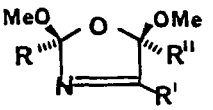

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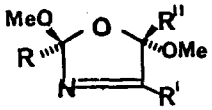


4

a) R=R'=R"=Me

b) R=Me, R'=R"=Ph

c) R=H, R'=R"=Ph

d) R=R"=H, R'=Ph

e) R=R'=R"=Ph

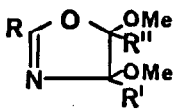
f) R=Ph, R'=H, R"=Me

g) R=R"=Ph, R'=Me

h) R=R"=Ph, R'=H

i) R=Ph, R'=R"=H

j) R=4-NO_2-C_6H_4, R'=R"=H



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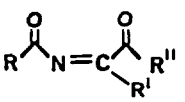

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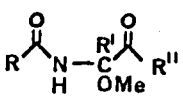


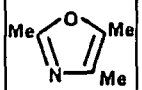
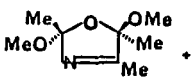
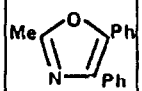
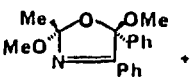
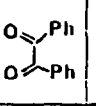
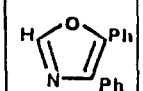
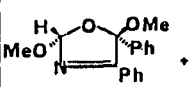
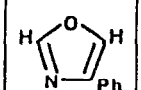
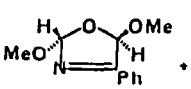
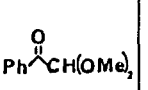
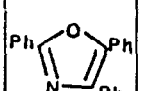
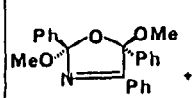
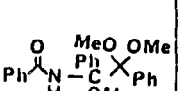
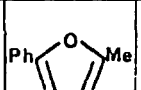
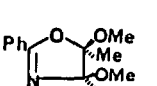
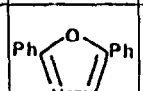
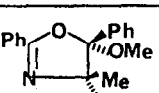
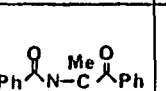
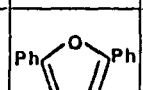
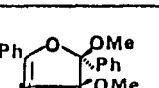
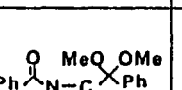
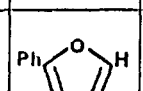
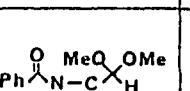
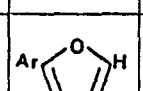
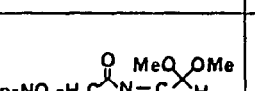
7

In order to determine possible interconversions between 2, 3 and 5, we examined the products from 2,5-diphenyloxazole 1h and found that 2h remained unchanged under reaction conditions (Br_2-MeOH-K_2CO_3 at -15°C), while 4,5-dihydrooxazole 5h was converted slowly at -15°C to -10°C to an 80:20 mixture of amido ketal 2h and amido ketone 7h. On the other hand, the 3-oxazoline 3b was stable to Br_2 in MeOH at 0°C.

The structure proof for the products is based on ^1H and ^{13}C-NMR and mass spectra as well as chemical conversions. Both 2- and 3-oxazolines can be

TABLE

Product Distribution from Bromination of Oxazoles 1a-1j in MeOH

ENTRY	OXAZOLE	°C TEMP.	hr. TIME	OXAZOLINE	OTHER PRODUCTS	YIELD % oxzoline	others
a		-78	5			60	
b		-78 → -5	1½			76	13
c		-5 → 20	12			40	38
d		-78	1			42	7
e		-78	½			~100	
f		-78	2			43	
g		0	1			69	10
h		-15 → -5	5			23	55
i		0	4			98	
j		0	2			96	

hydrolyzed with 5% HCl in dioxane or methanol; for instance 5g gave 6g, while 3a-4a were converted to 6a and its alcohol adduct 7a.

A differentiation between 2- and 3-oxazolines comes from their NMR spectra. For instance, the presence of a hydrogen at C-4 (4.5 ppm in 5h) or of a Me group (1.4 ppm in 5g) permits assignment of the 2-ene-structure, since one may expect the 3-ene-isomer to show typical imino CH or Me absorption at lower field. Similarly, the presence of a hydrogen or methyl at C-2 allowed the 3-oxazoline assignment to products 3d and 3a respectively. Furthermore, a pattern emerged which allowed the 3-oxazoline assignment when the ortho hydrogens of the PhC=N occurred at 7.93-7.99 ppm and the C=N ^{13}C absorption at 171-173 ppm, while for 2-oxazolines these absorptions were found at 8.11-8.14 ppm and 163-165 ppm respectively. In the ring opened amides 2 the ortho protons of Ph-CO-NH absorbed at 7.82-7.92 ppm and the amide carbonyl carbon at 167 ppm. In most of the cases it was difficult to assign the cis or trans configuration to 3-oxazolines 3 and 4. This determination was possible for 3d and 4d on the basis of W-coupling between H-2 and H-5 (3.5 Hz and 0 Hz for the cis and trans isomers respectively). The cis assignment (4-MeO trans to Ph at 3.71 ppm) for isomer 5h was possible after preparing the trans isomer 5h' as shown below[8] (4-MeO cis to Ph at 3.26 ppm).

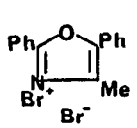
It is interesting to note that while 5h was ring opened to 2h and 7h in the presence of Br_2-MeOH, ring closure of 2h to 5h' can be effected only by BF_3.etherate in an inert solvent. Substituting PhSeBr for Br_2 in the reaction with oxazole 1h led to isolation of ring opened amides 7h in 65% yield.

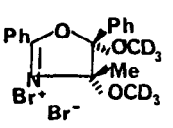
DISCUSSION AND EXPLORATION OF PATHWAYS BY NMR

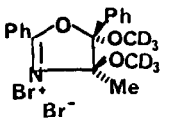
The data from the Table indicate a preference for formation of ring opened products when a 2-aryl rather than a 2-Me or 2-H substituent is present, see 1g-j. On the other hand, formation of 3-oxazolines is favored over their 2-isomers when a 4-phenyl substituent is present, see 1b-e, or if there is a 4-methyl present as long as the 2-substituent is methyl and not phenyl, compare 1a and 1g.

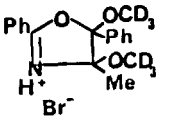
In order to explain these results it became necessary to examine the bromination of oxazoles in more detail and, because intermediates were unstable and difficult to isolate, NMR became our method of choice. First we treated oxazole 1g with 1 equivalent of Br_2 in benzene and isolated an insoluble Br_2-oxazole complex 8g, as described by Gompper and Ruhle[5]. The NMR spectrum of 8g in $CDCl_3$ was consistent with its structure and showed a methyl absorption which due to the presence of an iminium salt was shifted downfield (2.68 ppm) compared to the parent 1g (2.55 ppm). Dissolution of 8g in CD_3OD and examination by NMR showed the presence of 9g; ultimately products 5g and 7g

were isolated, indicating that 8 may be an intermediate to 9.


8g

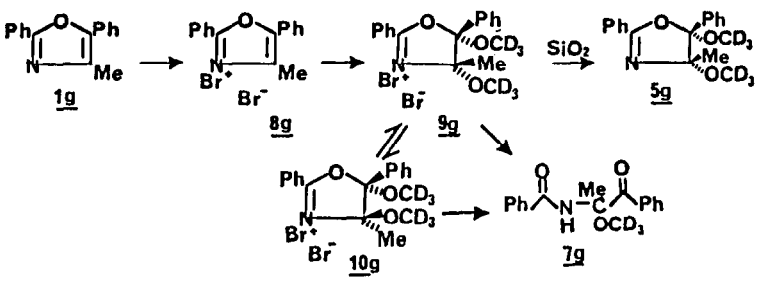

9g


10g


11g

We then monitored the reaction of 1g with Br_2 in CD_3OD in the presence of solid K_2CO_3 at -14°C by NMR at 300 MHZ and observed an immediate spectral change (Me shifted to 1.97 ppm) consistent with formation of 9g. Due to the positive charge on nitrogen the methyl absorption was downfield compared to 5g (Me at 1.83 ppm). Within 5 min in the presence of 2 equivalents of Br_2, all the oxazole 1g had been consumed and 9g was formed as the only product. After 18 min, 9g together with small amounts of 10g and 7g were present. After 2 hr at 0°C, the concentration of 9g was reduced by half and the amounts of 7g and 10g had increased. Below -15°C, 9g was stable in solution for several hours.

The structure of 9g is based on ^1H and ^{13}C-NMR spectra. The presence of two OCD_3 groups was indicated by septets at 53.46 and 51.27 ppm and the sp^3, nature of carbons 4 and 5 was evident from their absorption at 98.14 and 120.92 ppm respectively. The iminium ether carbon (C-2) absorbed at 173.24 ppm. The electron withdrawing iminium center in 9g causes large downfield shifts of the ortho protons (8.37 vs 8.10 ppm for 5g, as well as separation of o-, m- and p-protons of the phenyl group attached to the C=N+ moiety. Similar effects were observed for the para carbon of the C-2 phenyl group (139.2 vs 133.9 ppm for 5g) and for the methyl absorption (1.97 vs 1.83 ppm for 5g). Furthermore, the NMR experiment indicated an isomerization of the complex 9g to what we assume to be the trans isomer 10g and which shows a Me absorption at 1.92 ppm[9].

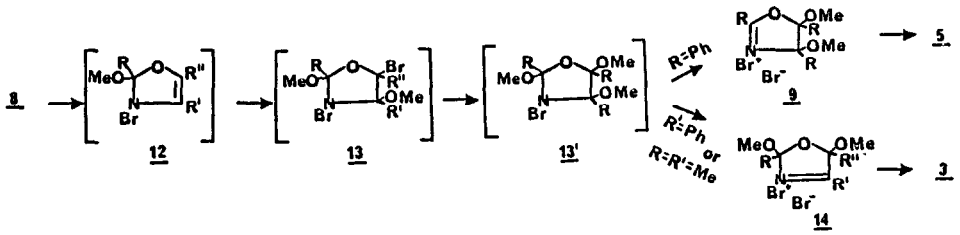


When this solution was chromatographed 5g and 7g were isolated. To ensure that 9g was not the hydrobromide salt of 5g, the latter was treated with HBr in ether to produce 11g which showed similar but not identical NMR spectra to 9g (e.g. Me of 11g at 1.90 ppm, ortho protons of C-2 phenyl at 8.29 ppm).

When the reaction of 1f in Br_2-MeOH at -43°C was followed by NMR a product analogous to 9g (typical NMR: C-4 at 96.76, C-5 at 121.17, C-2 at 173.28 ppm, H-4 at 6.34 ppm) and its conversion product 2f were observed.

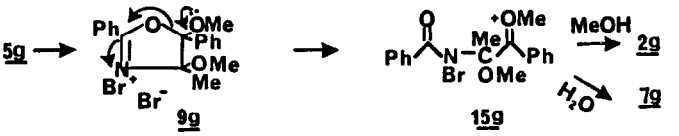
During the monitoring of the reaction of 1b by NMR, intermediate 14 was detected. This intermediate led to 3-oxazolines 3 and 4, and its spectral features resemble those of 9g (e.g. Me protons at 2.03 ppm, Me carbon at 16.64 ppm, 4-Ph ortho protons at 8.04 ppm).

On the basis of these studies, we propose a rational pathway to explain the divergent products observed in the bromination of oxazoles. The first product of interaction of 1 with Br_2 is probably the complex 8, which reacts rapidly with Br_2 in methanol to produce 9, from which the open chain products 2 and 7 are derived. Debromination of 9 occurs during chromatography on silica gel to give the dimethoxy-2-oxazoline 5. The details of the mechanism probably involve addition of MeOH to the iminium salt 8 which is expected to be facile. The resulting enamine 12 should be more reactive towards Br_2 in methanol than the original oxazole, and may produce 13. Substitution of Br by MeO, anchimerically assisted by oxygen, will lead to 13'. The latter can be converted either to 9 or 14 by elimination of MeO^-.



The relative stability of species 14 and 9, which are the precursors of 3-4 and 5 respectively, depends on the role that the 2- and 4-substituents play in stabilizing the C=N. A 4-phenyl substituent favors the 3-oxazoline structure 14, hence 3-4, while a 2-phenyl substituent favors the 2-oxazoline structure 9 and therefore leads to 5 or to ring opened products (see Table).

Ring opening of 5 (or actually of 9) (which occurs under the reaction conditions) can take place via 15 to produce 2 or 7.



Consistent with this picture is also the reaction of 1h with PhSeBr in MeOH, with the PhSe moiety, like Br, being able to play the dual role of an electrophile or of a leaving group.

EXPERIMENTAL

The NMR spectra were recorded on a Bruker AM300 instrument: ^{1}H at 300 MHz and ^{13}C at 75.5 MHz in $CDCl_3$, except where indicated, using TMS as an internal standard. The ^{13}C NMR assignments are based on chemical shifts and off-resonance decoupling. The numbering in the spectral assignments for all compounds is based on the oxazole ring 1 from which they are derived. Mass spectra were recorded in a Finnigan 4021 instrument and reported as M (relative abundance). Elemental analyses were performed at the Hebrew University Jerusalem. Oxazoles 1a, 1b, 1h were obtained from Aldrich Chemical Co., all others were prepared as indicated. All oxazoles were purified before use by distillation or chromatography. Methanol was distilled over magnesium. Chromatography was performed on silica gel and mixtures of EtOAc:hexane were used as the eluent.

2,4,5-Triphenyloxazole (1e): To a solution of N-benzoyl-2-amino-2-methoxyphenylethanone 7h (0.1g, 0.37 mmol) in freshly distilled benzene (3 ml) in a dry system under Ar, BF_3.ether (0.07 ml, 1.5 eq) was added. The solution was heated under reflux for 1 h. An equimolar amount of chlorosulfonyl isocyanate (0.032 ml) was added and the reflux continued for 0.5 h. The solution was poured on ice-water, basified (10% $NaHCO_3$) to pH 10 and extracted with $CHCl_3$ (3x5 ml). The crude product was chromatographed on silica-gel (EtOAc:hexane 1:3.5) to give 1e as a white solid, mp 115°C (lit.[16] 116°C) (0.075 g, 73%). 1e: ^{1}H NMR: 8.17 (2-Ph-o, 2H), 7.74 (4-Ph-o, 2H), 7.69 (5-Ph-o, 2H), 7.45-7.35 (other Ar-H). ^{13}C NMR: 160.10 (C-2), 145.52 (C-5), 136.75 (4-Ph-i), 132.54 (2-Ph-i), 130.31 (2-Ph-p), 128.97 (C-4), 128.72 (4-Ph-m), 128.62 (2-Ph-m), 128.58 (5-Ph-m), 128.52 (4-Ph-p), 128.37 (5-Ph-i), 128.19 (5-Ph-p), 128.12 (4-Ph-o), 126.53 (2-Ph-o), 126.44 (5-Ph-o). MS (CI) m/e: 298 (M+1, 100%).

2-Phenyl-5-methyloxazole (1f): A solution of benzamide (3.92 g, 0.032

mmol) and freshly distilled chloroacetone (2.58 ml, 0.032 mmol) in toluene (30 ml) was heated under reflux for 20 h. After evaporation of the toluene, the residue was dissolved in chloroform and washed with 10% $NaHCO_3$ to pH 9. The solvent was evaporated and the residue was chromatographed (EtOAc:hexane 1:1). The product 1f was obtained as a light brown oil (1.94 g, 38%). 1f: ^1H NMR: 8.01 (2-Ph-o, 2H), 7.45-7.39 (other Ar-H + 4-H), 2.24 (Me, 3H, d, J=1.2 Hz). MS (CI) m/e: 160 (M+1, 100%).

N-Benzoyl-1,2,2-trimethoxy-2-phenylethyl amine (2h) and 4,5-Dimethoxy-2,5-diphenyl-2-oxazoline (5h): A mixture of 2,5-diphenyloxazole 1h (1.1 g, 5 mmol) and K_2CO_3 (0.68 g, 5 mmol) in MeOH (25 ml) was stirred at -78°C. A solution of Br_2 (0.25 ml, 5 mmol) in MeOH (7 ml) was added dropwise within 1 h. After the addition, the temperature was raised to -15°C and the reaction was left for 3 days at -15°C. The solvent was evaporated and the residue was washed with $CHCl_3$. The salt was removed by filtration and the oily residue obtained after evaporation was chromatographed (EtOAc:hexane, 1:3.5) to yield 2h (1.5 g, 95.5%). The product was obtained as a white solid, mp 73°C. 2h: ,^1H NMR: 7.66 (2-Ph-o, 2H), 7.51 (2-Ph-p, 1H), 7.60 (5-Ph-o, 2H), 7.5-7.4 (other Ar-H), 6.07 (NH, 1H, d, J=8.5 Hz), 5.69 (CH, 1H, d, J=8.5 Hz), 3.43 (OMe, 3H, s), 3.34, 3.35 (OMe, 6H, s). ^{13}C NMR: 167.04 (C=O), 136.19 (5-Ph-i), 133.62 (2-Ph-i), 131.83 (2-Ph-p), 128.72 (5-Ph-p), 128.57 (2-Ph-m), 128.22 (5-Ph-m), 128.03 (5-Ph-o), 126.86 (2-Ph-o), 102.11 ($C(OMe)_2$), 81.60 (CHOMe), 56.60 (OMe), 50.09, 49.63 (OMe). MS (CI) m/e: 284 (M-MeOH, 20%), 151 ($PhCOMe_2$, 100%). Anal. calcd. for $C_{18}H_{21}NO_4$: C 68.55, H 6.7. Found: C 68.87, H 6.69.

When the reaction was carried out at -15 to -5°C for 5 h, 5h and 2h were isolated in a 1:2.2 ratio. 5h: ^1H NMR: 8.11 (2-Ph-o, 2H), 7.55 (2-Ph-m, 2H), 7.57 (5-Ph-o, 2H), 7.5-7.4 (other Ar-H), 5.23 (CH, 1H, s), 3.71 and 3.40 (OMe, 6H, s). ^{13}C NMR: 163.3 (C-2), 138.8 (5-Ph-i), 132.1 (2-Ph-p), 128.9 (5-Ph-p), 128.7 (5-Ph-o), 128.5 (5-Ph-m), 128.4 (2-Ph-m), 127.2 (2-Ph-i), 108.7 (C-5), 104.0 (C-4), 58.2, 52.4 (OMe). MS (CI) m/e: 284 (M+1, 26%), 252 (M-MeOH, 28%). Anal. calcd. for $C_{17}H_{17}NO_3$: C 72.06; H 6.05. Found: C 71.87; H 5.89.

N-Benzoyl-1,2,2-trimethoxyethyl amine (2i): To a solution of 2-phenyloxazole[10] 1i (0.4 g, 2.75 mmol) in MeOH (5 ml) at 0°C was added Br_2 (0.14 ml, 2.75 mmol). The reaction was completed after 4 h. $CHCl_3$ was added and the mixture was washed with aqueous $Na_2S_2O_3$ solution. The aqueous solution was extracted with $CHCl_3$ (2x10 ml), dried over $MgSO_4$ and chromatographed (EtOAc:hexane 1:1). The product was obtained as a white solid (0,65 g,

99%) mp 114°C. 2i: ^{1}H NMR: 7.82 (Ph-o, 2H), 7.53 (Ph-p, 1H), 7.45 (Ph-m, 2H), 6.86 (NH, 1H, d, J=9.5 Hz), 5.42 (CH, 1H, dd, J=9.5 Hz, 2.0 Hz), 4.44 (CH, 1H, d, J=2.0 Hz), 3.53 (OMe, 3H, s). 3.46, 3.47 (OMe, 6H, s). ^{13}C NMR: 167.85 (C=O), 133.75 (Ph-i), 131.88 (Ph-p), 128.56 (Ph-m), 127.11 (Ph-o), 104.04 (CH(OMe)$_2$), 80.39 (CHOMe), 56.31, 56.28, 55.52, (OMe). MS (EI) m/e: 239 (M, 18%), 207 (M-MeOH, 100%). Anal. calcd. for $C_{12}H_{17}NO_4$: C 60.24; H 7.16; N 5.85. Found: C 59.96; H 7.22, N 5.84.

N-(p-Nitrobenzoyl)-1,2,2-trimethoxyethyl amine (2j): Compound 2j was obtained from 1j[11] (0.21 g, 1.1 mmol) as described for 2i. The reaction time was 1.5 h. The product 2j was obtained as a yellowish solid (0.298 g, 96%), mp 86°C. 2j: ^{1}H NMR: 8.28 (2-Ph-o, 2H), 7.97 (2-Ph-m, 2H), 6.96 (NH, 1H, d, J=10 Hz), 5.38 (CH, 1H, dd, J=10 Hz, 5.4 Hz), 4.45 (CH, 1H, d, J=5.4 Hz), 3.54 (OMe, 3H, s), 3.48, 3.47 (OMe, 6H, s). MS (CI) m/e: 285 (M+1, 5%), 253 (M-OMe, 100%). Anal. calcd. for $C_{12}H_{16}N_2O_6$: C 50.70; H 5.67. Found: C 51.01; H 5.52.

2,5-Dimethoxy-4,5-diphenyl-3-oxazoline (3c-4c): A solution of Br_2 (0.07 ml, 1.35 mmol) in MeOH (2 ml) was added to a solution of 4,5-diphenyloxazole[12] 1c (0.3 g, 1.35 mmol) in MeOH (6 ml) at -5°C, followed by the addition of Et_3N (0.38 ml, 2.7 mmol). The temperature was raised to 20°C and the reaction was left overnight. The crude mixture was chromatographed (EtOAc:hexane, 1:12). Benzil (0.11 g, 38%) was obtained initially, followed by 3c-4c (ratio 1:1.2) obtained as a colorless oil (0.15 g, 40% yield). 3c: ^{1}H NMR: 7.95 (4-Ph-o, 2H), 7.46 (5-Ph-o, 2H), 7.4-7.2 (other Ar-H), 6.51 (2-H, 1H, s), 3.68, 3.41 (OMe, 6H, s). ^{13}C NMR: 171.09 (C-4), 139.10 (5-Ph-i), 131.97 (4-Ph-p), 129.11 (4-Ph-i), 128.97 (4-Ph-o), 128.79 (4-Ph-p), 128.44 (5-Ph-p), 128.20 (5-Ph-m), 126.54 (5-Ph-o), 118.16 (C-2), 112.43 (C-5), 55.53, 51.27 (OMe). MS (CI) m/e: 284 (M+1, 3%), 252 (M-MeOH, 100%). 4c: ^{1}H NMR: 7.95 (4-Ph-o, 2H), 7.62 (5-Ph, o, 2H), 7.4-7.2 (other Ar-H), 6.66 (2-H, 1H, s), 3.64, 3.33 (OMe, 6H, s). ^{13}C NMR: 171.09 (C-4), 138.91 (5-Ph-i), 131.97 (4-Ph-p), 129.07 (4-Ph-i), 129.04 (4-Ph-o), 128.67 (5-Ph-p), 128.44 (4-Ph-m+5-Ph-m), 125.78 (5-Ph-o), 119.26 (C-2), 112.79 (C-5), 55.14, 50.66 (OMe). HRMS[15]: 252.0858 ($C_{17}H_{17}NO_3$ - OMe) calcd. for $C_{16}H_{14}NO_2$ 252.1024.

2,5-Dimethoxy-4-phenyl-3-oxazoline (3d-4d): A solution of Br_2 (0.085 ml, 1.65 mmol) in MeOH (2 ml) was added to a solution of 4-phenyl-oxazole[13] 1d (0.24 g, 1.65 mmol) and K_2CO_3 (0.23 g, 1.65 mmol) in MeOH (3 ml) at -78°C. After 1 h the cold solution was evaporated under high vacuum (0.5-1mm Hg), and the mixture was chromatographed (EtOAc:hexane 1:8). Phenylglyoxal dim-

ethyl acetal (0.02 g, 7%) was obtained initially, followed by 3d-4d (0.143g, 42%, 12:1 ratio) obtained as a colorless oil. 3d: ^{1}H NMR: 7.99 (4-Ph-o, 2H), 7.5-7.4 (other Ar-H), 6.70 (2-H, 1H, d, J=3.5 Hz), 6.18 (5-H, 1H, d, J=3.5 Hz), 3.49, 3.48 (OMe, 6H, s). ^{13}C NMR: 169.97 (C-4), 132.43 (4-Ph-p), 129.45 (4-Ph-i), 128.92 (4-Ph-o), 128.75 (4-Ph-m), 120.37 (C-2), 105.24 (C-5), 54.19, 52.03 (OMe). MS (CI) m/e: 208 (M+1, 35%), 176 (M-OMe, 100%). 4d: ^{1}H NMR: 7.99 (4-Ph-o, 2H), 7.5-7.4 (other Ar-H), 6.49 (2-H, 1H, s), 5.98 (2-H, 1H, s), 3.43, 3.42 (OMe, 6H, s). ^{13}C NMR: 169.77 (C-4), 132.35 (4-Ph-p), 129.33 (4-Ph-i), 128.75 (4-Ph-m+p), 119.19 (C-2), 104.81 (C-5), 54.53, 52.90 (OMe). HRMS^{15}: 176.0762 ($C_{11}H_{13}NO_3$ - OMe) calcd. for $C_{10}H_{10}NO_2$ 176.0712.

2,5-Dimethoxy-2,4,5-trimethyl-3-oxazoline (3a-4a): A solution of Br_2 (0.51 ml, 0.01 mol) in MeOH (2 ml) was added to a solution of 1a (1.16 ml, 0.01 mol) and K_2CO_3 (1.39 g, 0.01 mol) at -78°C in the dark. After 5 h, the solvent was evaporated and the residue was dissolved in $CHCl_3$ and filtered. The solvent was evaporated and the yellowish residue was distilled to give 3a-4a as a colorless oil, bp 53-54°C/8 mm Hg (1.04 g, 60%, ratio 5:1). 3a: ^{1}H NMR: 2.08 (4-Me, 3H, s), 1.65 (2-Me, 3H, s), 1.54 (5-Me, 3H, s), 3.22, 3.18 (OMe, 6H, s). ^{13}C NMR: 173.55 (C-4), 123.35 (C-2), 110.52 (C-5), 50.22, 49.64 (OMe), 24.77 (2-Me), 21.04 (5-Me), 13.92 (4-Me). MS (CI) m/e: 174 (M+1, 32%), 142 (M-OMe, 97%), 112 (M-2OMe+1, 46%). 4a: ^{1}H NMR: 2.07 (4-Me, 3H, s), 1.58 (2-Me, 3H, s), 1.46 (5-Me, 3H, s), 3.31, 3.27 (OMe, 6H, s). ^{13}C NMR: 173.30 (C-4), 122.46 (C-2), 109.95 (C-5), 50.36, 50.13 (OMe), 24.92 (2-Me), 21.30 (5-Me), 13.76 (4-Me). HRMS^{15}: 142.0180 ($C_8H_{15}NO_3$ - OMe) calcd. for $C_7H_{12}NO_2$ 142.0868.

Ring opening of (3a-4a): To a solution of 3a-4a (0.096 g, 0.55 mmol) in MeOH (2 ml) was added 5% HCl (5 drops) and the solution was stirred at room temperature for 0.5 h. The solvent was evaporated to give a mixture of 6a and 7a in quantitative yield. 7a: ^{1}H NMR: 3.41 (OMe, 3H, s), 2.02 (Me, 3H, s), 1.98 (Me, 3H, s), 1.62 (Me, 3H, s). MS (CI) m/e: 160 (M+1, 98%), 60 ($Me(CO)NH_2$+1, 42%). 6a: ^{1}H NMR: 2.31 (Me, 6H, s), 2.27 (Me, 3H, s). MS (CI) m/e: 128 (M+1, 100%), 86 ($CH_3(CO)(CO)CH_3$, 37%).

2,5-Dimethoxy-4,5-diphenyl-2-methyl-3-oxazoline (3b-4b): The mixture of isomers 3b-4b was obtained from 1b (0.45 g, 1.9 mmol) as described for 3d-4d, at -78 to -5°C and reaction time was 2.5 h. The eluent was EtOAc:hexane 1:4. Benzil was isolated in 13% yield, and the 3b-4b mixture was obtained as a colorless oil (0.43 g, 76%, ratio 7.3:1). 3b: ^{1}H NMR: 7.96 (4-Ph-o, 2H), 7.60 (5-Ph-o, 2H), 7.42 (4-Ph-p, 1H), 7.35-7.3 (other

Ar-H), 3.37, 3.36 (OMe, 6H, s), 1.93 (2-Me, 3H, s). ^{13}C NMR: 169.32 (C-4), 138.62 (5-Ph-i), 131.62 (4-Ph-p), 129.60 (5-Ph-p), 128.97 (4-Ph-o), 128.66 (4-Ph-i), 128.38 (4-Ph-m), 128.11 (5-Ph-m), 126.69 (5-Ph-o), 123.17 (C-2), 112.97 (C-5), 51.12, 50.96, (OMe), 23.29 (Me). MS (CI) m/e: 266 (M-OMe, 100%), 236 (M-2OMe + 1, 3%). 4b: ^{1}H NMR: 7.93 (4-Ph-o, 2H), 7.48 (5-Ph-o, 2H), 7.3 (other Ar-H), 3.48, 3.42 (OMe, 6H, s), 1.86 (Me, 3H, s). ^{13}C NMR: 169.61 (C-4), 138.27 (5-Ph-i), 131.43 (4-Ph-p), 129.74 (4-Ph-i), 128.73 (4-Ph-o), 126.55 (5-Ph-o), 123.06 (C-2), 112.29 (C-5), 51.33, 50.60 (OMe), 24.08 (Me). Anal. calcd. for $C_{18}H_{19}NO_3$: C 72.70; H 6.44. Found: C 72.70; H 6.26.

N-Benzoyl-2-amino-2-methoxy-1,2-diphenylethanone (7e) and 2,5-Dimethoxy-2,4,5-triphenyl-3-oxazoline (3e-4e): A mixture of 7e and 3e-4e was obtained from 1g (0.035 g, 0.12 mmol) as described for 3d-4d. The reaction was completed after 0.5 h and no starting material was detected by ^{1}H NMR or TLC. All attempts at chromatographic separation failed. The ratio of 7e:3e:4e was 5:1:0.6. 7e: ^{1}H NMR: 8.04 (5-Ph-o, 2H), 7.95 (2-Ph-o, 2H), 7.69 (4-Ph-o, 2H), 7.6-7.4 (other Ar-H), 3.93 (OMe, 3H, s). MS (CI) m/e: 314 (M-OMe, 19%), 224 (M-PhCNH$_2$, 21%). 3e: ^{1}H NMR: 7.99 (4-Ph-o, 2H), 7.89 (2-Ph-o, 2H), 7.73 (5-Ph-o, 2H), 7.6-7.4 (other Ar-H), 3.24, 3.11 (OMe, 6H, s). MS (CI) m/e: 328 (M-OMe, 38%), 282 (M-Ph, 13%). 4e: ^{1}H NMR: 7.95 (4-Ph-o), 7.5 (5-Ph-o), 7.6-7.4 (other Ar-H), 3.56, 3.32 (OMe, 6H, s).

4,5-Dimethoxy-5-methyl-2-phenyl-2-oxazoline (5f): To a solution of 1f (0.29 g, 18 mmol) in MeOH (4 ml) at -78°C, was added Br$_2$ (0.092 ml, 18 mmol) and the mixture was stirred for 2.5 h. The solvent was evaporated and the residue was dissolved in $CHCl_3$ and poured into aqueous $Na_2S_2O_3$. After extraction with $CHCl_3$ (2x10 ml), drying and evaporation of the solvent, the mixture was chromatographed (EtOAc:hexane 1:5) to give 5f as a yellow oil (0,16 g, 43%). 5f: ^{1}H NMR: 8.01 (2-Ph-o, 2H), 7.51 (2-Ph-p, 1H), 7.42 (2-Ph-m, 2H), 5.31 (CH, 1H, s), 3.60, 3.32 (OMe, 6H, s), 1.52 (Me, 3H, s). ^{13}C NMR: : 166.73 (C-2), 133.67 (2-Ph-p), 129.71 (2-Ph-o), 129 58 (2-Ph-m), 128.07 (2-Ph-i), 109.89 (C-5), 107.51 (C-4), 57.86, 50.15 (OMe), 19.12 (5-Me). MS (CI) m/e: 222 (M+1, 43%), 190 (M-OMe, 100%). HRMS^{15}: 190.0873 ($C_{12}H_{15}NO_3$ - OMe) calcd. for $C_{11}H_{12}NO_2$, 190.0868.

N-Benzoyl-2-amino-2-methoxy-1-phenylpropanone (7g) and 4,5-Dimethoxy-2,5-diphenyl-4-methyl-2-oxazoline (5g): A solution of 1g[11] (0.2 g, 0.85 mmol), Br$_2$ (0.044 ml, 0.85 mmol) and K_2CO_3 (0.117 g, 0.85 mmol) in MeOH (3 ml) was stirred at 0°C, in the dark for 1 h. The solvent was evaporated and the residue was dissolved in $CHCl_3$. The obtained solution was fil-

tered, 1:5.5) to give 5g as a colorless oil (0.175 g, 69%). Compound 7g was obtained (0.024 g, 10%) was obtained as a white solid, mp 111-112°C. When the reaction time was 4.5 h the ratio 7g:5g was 1:1.3. 5g: ^{1}H NMR: 8.14 (2-Ph-o, 2H), 7.6-7.4 (other Ar-H), 3.22, 3.00 (OMe, 6H, s), 1.76 (Me, 3H, s). ^{13}C NMR: 163.9 (C-2), 134.7 (5-Ph-i), 132.1 (2-Ph-p), 128.6 (5-Ph-p), 128.4 (2-Ph-m), 112.3 (C-5), 102.8 (C-4), 51.2, 50.3 (OMe), 18.5 (Me). MS (CI) m/e: 298 (M+1, 100%), 266 (M-MeOH, 67%), 236 (M-2MeO, 15%). HRMS^{15}: 235.0984 ($C_{16}H_{19}NO_3$ - 2OMe) calcd. for $C_{16}H_{13}NO$ 235.0996. 7g: ^{1}H NMR: 8.38 (5-Ph-o, 2H), 8.12 (NH, 1H, br s), 7.91 (2-Ph-o, 2H), 7.64 (5-Ph-p, 1H), 7.6-7.5 (other Ar-H), 3.26 (OMe, 3H, s), 2.12 (Me, 3H, s). MS (CI) m/e: 284 (M+1, 3%), 252 (M-MeOH, 100%).

Ring opening of (5g): To a solution of 5g (0.041 g, 0.14 mmol) in dioxane (2 ml), 5% HCl (2 drops) was added. The solution was stirred at room temperature for 40 min. A small amount of water was added, the solution was neutralized, extracted with $CHCl_3$, dried and evaporated. The residue was chromatographed (EtOAc:hexane 1:2.5) to give 6g (7 mg, 20%). 6g: ^{1}H NMR: 8.31 (3-Ph-o, 2H), 7.83 (1-Ph-o, 2H), 7.6-7.4 (other Ar-H), 2.18 (Me, 3H, s). MS (CI) m/e: 252 (M, 17%), 122 ((CO)NH_2, 100%).

4,5-Dimethoxy-2,5-diphenyl-2-oxazoline (5h'): To a solution of 2h (0.1 g, 0.45 mmol) in dry $CHCl_3$ (3 ml), BF_3.ether (0.141 g, 0.225 mmol) was added. The mixture was stirred at room temperature for 2 h. The solvent was evaporated and the residue was chromatographed on alumina (EtOAc:hexane 1:3) to give 5h' (0.053 g, 42%) as a colorless oil. 5h': ^{1}H NMR: 8.13 (2-Ph-o, 2H), 7.6-7.4 (other Ar-H), 5.23 (4-H, 1H, s), 3.30, 3.26 (OMe, 6H, s). ^{13}C NMR: 165.36 (C-2), 133.97 (5-Ph-i), 132.17 (2-Ph-p), 128.75 (5-Ph-m + p), 128.46 (2-Ph-m), 128.01 (5-Ph-o), 127.51 (2-Ph-i), 127.45 (2-Ph-o), 112.16 (C-5), 103.80 (C-4), 56.56, 51.36 (OMe). MS (CI) m/e: 284 (M+1, 26%), 252 (M-OMe, 28%).

Conversion of (5h) to (2h) and (7h): To a solution of 5h (0.085 g, 0.3 mmol) and K_2CO_3 (0.041 g, 0.3 mmol) in MeOH (2 ml) at -15°C, was added Br_2 (4 drops). The mixture was left for 2 days at -10°C. The solvent was evaporated. The residue was dissolved in $CHCl_3$ and the salt was filtered. The filtrate was evaporated and the residue (0.095g) contained 2h and 7h in the ratio of 80:20 (overall yield 95%). 7h: ^{1}H NMR: 8.12 (5-Ph-o, 2H), 7.92 (2-Ph-o, 2H), 7.68-7.37 (other Ar-H + NH, 7H), 6.57 (CH, 1H, d, J=7.3 Hz), 3.59 (OMe, 3H, s). ^{13}C NMR: 192.3 (C=O), 167.6 (NC=O), 134.2 (5-Ph-p), 133.6 (2-Ph-i), 133.3 (5-Ph-i), 129.3 (5-Ph-o), 128.8 and 128.6 (5 and 2-Ph-m), 127.4 (2-Ph-o), 78.6 (CH), 55.7 (OMe). MS (CI) m/e: 270 (M+1,

100%), 238 (M-OMe, 92%). Anal. calcd. for $C_{16}H_{15}NO_3$: C 71.36, H 5.61, N 5.23. Found: C 71.07, H 5.73, N 5.08.

2,5-Diphenyl-4-methyloxazole Br_2 complex (8g): Compound 8g was prepared from 1g (0.034 g, 3.9 mmol)[5]. The precipitate was crystallized from acetic acid to yield orange crystals mp 138-139°C. 8g: ^{1}H NMR: 8.31 (2-Ph-o, 2H), 7.69 (5-Ph-o, 2H), 7.6-7.4 (other Ar-H), 2.68 (Me, 3H, s).

4,5-Dimethoxy-2,5-diphenyl-4-methyl-2-oxazoline hydrobromide (11g): To a solution of 5g (0.03 g, 0.1 mmol) in dry ether, was added dropwise an ethereal solution of HBr till 11g as a white precipitate formed. 11g: ^{1}H NMR: (CD_3OD) 8.29 (2-Ph-o, 2H), 7.91 (2-Ph-p, 1H), 7.74 (2-Ph-m, 2H), 7.6-7.4 (5-Ph), 3.38, 3.34 (OMe, 6H, s), 1.90 (Me, 3H, s).

Monitoring the reaction of (1g) by NMR: A mixture of 1g (0.03 g, 0.13 mmol) and an equimolar amount of K_2CO_3 in CD_3OD (0.5 ml) was shaken in an NMR tube and cooled to -14°C. Br_2 (1 equivalent) was added and the ^{1}H NMR indicated the presence of 9g and starting material 1g. A second equivalent of Br_2 was added and within 5 min only 9g was detectable. The reaction was monitored by ^{1}H and ^{13}C NMR over a period of 5 h. The ratio of 9g:10g:7g gradually changed in favor of 7g. After 18 min at -14°C the ratio was 28:1.4:1 and after 1 h at -14°C followed by 1 h at 0°C it was 4.6:0.9:1. 9g: ^{1}H NMR: (CD_3OD) 8.37 (2-Ph-o, 2H), 8.02 (2-Ph-p, 1H), 7.82 (2-Ph-m, 2H), 7.6 (5-Ph), 1.97 (Me, 3H, s). ^{13}C NMR: 173.24 (C-2), 139.20 (2-Ph-p), 131.89 (2-Ph-o), 131.45 (5-Ph-p), 131.18 (2-Ph-m), 130.94 (5-Ph-i), 129.80 (5-Ph-m), 128.29 (5-Ph-o), 121.09 (2-Ph-i), 120.92 (C-5), 98.14 (C-4), 53.46, 51.27 (OCD_3), 15.83 (Me). 10g: ^{1}H NMR: ($CDCl_3$) 8.32 (2-Ph-o, 2H), 7.93 (2-Ph-p, 1H), 7.76 (2-Ph-m, 2H), 7.6-7.5 (5-Ph), 3.39, 3.34 (OMe, 6H, s), 1.92 (Me, 3H, s).

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