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Photochemical synthesis of a 4,5-dihydrofuroazetidinone, a novel β-lactam system

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Abstract—2,4-Dimethyl-3-phenylisoxazole anhydrobases were easily prepared from the corresponding 5-chloroisoxazolium trifluoromethanesulfonate and carbon anions of 1,3-dioxo compounds in the presence of triethylamine. Photorearrangement of 2-(2,4-dimethyl-3-phenyl-2*H*-isoxazol-5-ylidene)malonic acid diethyl ester gave a 4,5-dihydrofuroazetidinone in good yield.

β-Lactam antibiotics are widely employed in the treatment of bacterial infections. Unfortunately, resistance is usually developed by the target bacteria, mainly through the expression of β-lactamases which eliminate or strongly reduce the effectiveness of the therapeutic agent.[1]

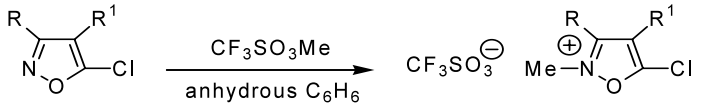
As a consequence, there is continuous attention directed towards the synthesis of new β-lactam derivatives with high molecular diversity in order to avoid the enzymatic inhibition of the drug.[2]

Following our interest in the synthetic applications of isoxazoles[3a,b] and taking into account that, some years ago, we obtained an iminoazetidine (β-lactam analogue) by photorearrangement of a 4-isoxazolylmethylamine,[4] we consider here the potential of isoxazole photochemistry as a means of access to new condensed β-lactam systems.

5-Chloro-2-methylisoxazolium triflates **1a–c** were obtained in good yields as hygroscopic solids by reaction of the corresponding chloroisoxazoles with methyl trifluoromethanesulfonate in anhydrous benzene (Scheme 1).[5]

Treatment of compound **1b** with the sodium salt of 1,3-dioxo compounds **2a–c**, followed by the addition of triethylamine (1 equiv.)[6] gave the corresponding isoxazolium anhydrobases **3a–c** (Scheme 2). Only very few examples of this highly reactive class of compounds have been reported.[7]

The compounds **3a–c**[8] are yellow–orange solids or oils which are quite stable in the dark at low temperature (<0°C); the configuration of the exocyclic double bond of compound **3c** (isolated as a single stereoisomer) remains at present unassigned. Irradiation of **3a** in acetonitrile[9] gave compound **4** (60%), which was iden-



	R	R1
1a	Me	Ph
1b	Ph	Me
1c	Me	COOEt

Scheme 1.

Keywords: isoxazole; anhydrobases; photochemistry; azetidinone; β-lactam.
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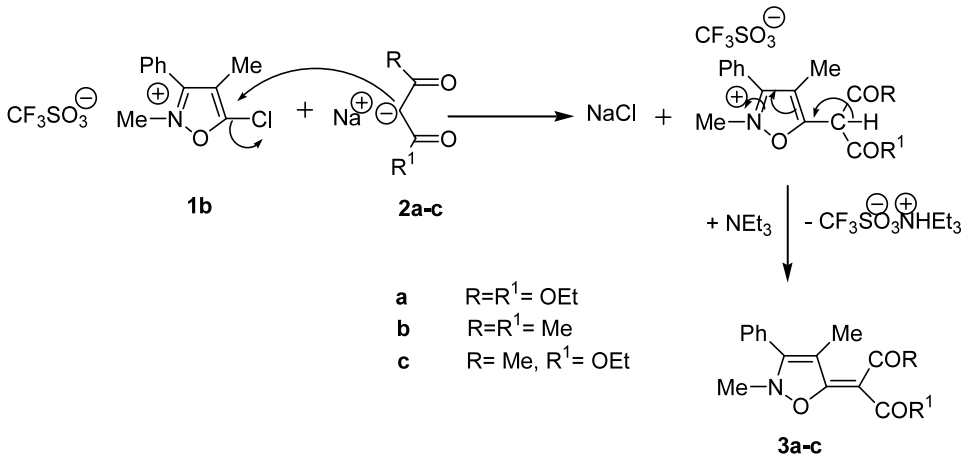


Scheme 2.

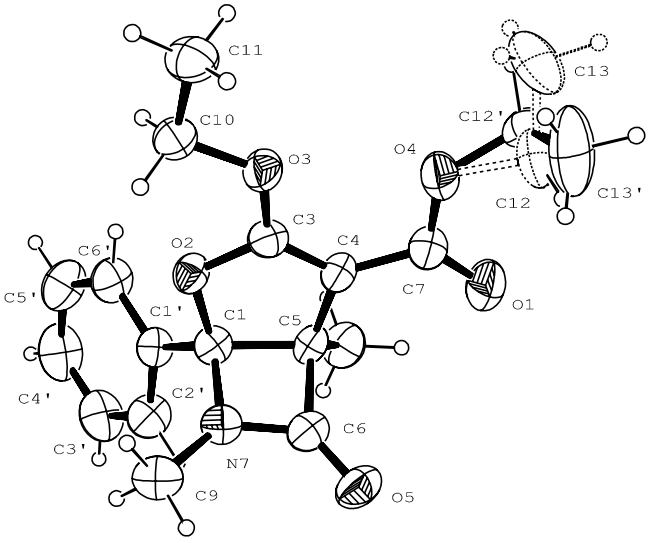
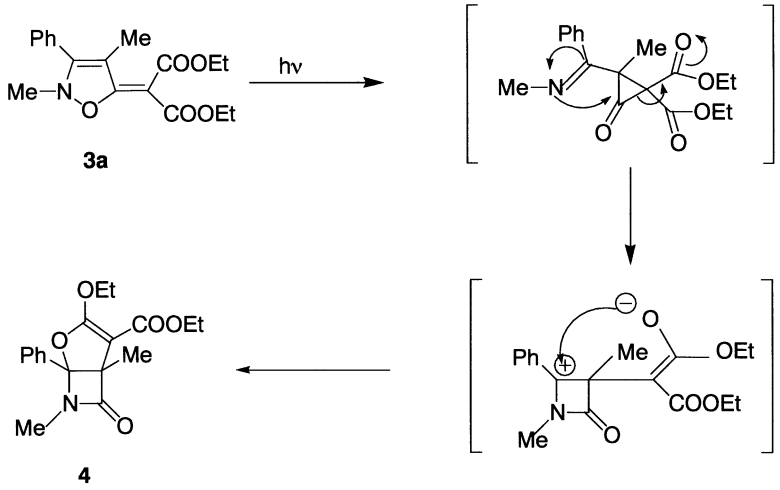


Figure 1. ORTEP drawing of compound **4**, with 50% probability thermal ellipsoids. The ethyl group, C12–C13 appears disordered between two configurations.

tified as 1-phenyl-2-oxa-3-ethoxy-4-carbethoxy-5,7-dimethyl-6-oxo-7-azabicyclo[3.2.0]hept-3-ene by X-ray crystallography (Fig. 1).[10]

Taking into account the unique example of the photochemistry of an isoxazolium anhydrobase previously reported,[7] the mechanistic interpretation of this result involves (Scheme 3) photochemical N–O bond cleavage, followed by the formation of a cyclopropanone intermediate.

Nucleophilic attack on the ketone by the imine nitrogen gives the β-lactam ring and is followed by the attack of the ester oxygen on the electrophilic C-4 to give the condensed dihydrofuran system. The easy preparation of isoxazolium anhydrobases from **1** using a large variety of active methylene compounds in principle renders this mechanism a valuable route to substituted bicyclic β-lactams.



Scheme 3.

Acknowledgements

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References

1. Kotra, L. P.; Mobashery, S. *Bull. Inst. Pasteur* **1998**, *96*, 139–150.
2. Del Buttero, P.; Baldoli, C.; Molteni, G.; Pilati, T. *Tetrahedron: Asymmetry* **2000**, *11*, 1927–1941.
3. (a) Donati, D.; Fusi, S.; Ponticelli, F. *Tetrahedron Lett.* **2002**, *43*, 9527–9530 and references cited therein; (b) Donati, D.; Fusi, S.; Ponticelli, F. *Synthesis* **2003**, in press.
4. Donati, D.; Fusi, S.; Ponticelli, F. *Gazz. Chim. Ital.* **1991**, *121*, 329–334.
5. To a solution of compounds **1a**–**c** (10 mmol) in anhydrous benzene (20 ml) was added methyl trifluoromethanesulfonate (10 mmol). The reaction mixture was refluxed for a few minutes, and the solvent was removed to give a colourless oil which crystallised on treatment with anhydrous diethyl ether (yield 70–75%).
6. To a stirred solution of compound **2a**–**c** (3 mmol), NaH 60% (3 mmol), dry Et_3N (3 mmol) in anhydrous benzene (15 ml) was slowly added compound **1b**. The yellow solution was evaporated in vacuo and the residue was quenched with water and extracted with CH_2Cl_2. The organic solvent was evaporated in vacuo and the residue was chromatographed eluting first with CH_2Cl_2/CH_3OH 95/5 and then with CH_2Cl_2/CH_3OH 90/10 to give compound **3a**–**c** (yield 45% for **3a** and **3c** and 35% for **3b**).
7. Becker, D. A.; Anderson, F. E.; McKibben, B. P.; Merola, J. S.; Glass, E. *Synlett* **1993**, 866–868 and references cited therein.
8. All new compounds gave satisfactory analytical data (within 0.3%). ^1H and ^{13}C NMR spectra were recorded with a Bruker AC 200 spectrometer at 200.13 and 50.33 MHz, respectively. ^{13}C assignments were established based on chemical shift considerations and DEPT experiments. APCI MS specta were recorded with a LCQ-DECA Thermo Finningan instrument and EI MS spectra were obtained with a VG 70 250S instrument. The reported yields are relative to the isolated product.
5-Chloro-2,3-dimethyl-4-phenylisoxazol-2-ium trifluoromethanesulfonate ***1a***: mp 83–86°C; ^1H NMR ($CDCl_3$) δ: 2.87 (s, 3H, 3-CH_3), 4.31 (s, 3H, NCH_3), 7.38–7.52 (m, 5H, Ph). ^{13}C NMR ($CDCl_3$) δ: 12.02 (CH_3), 39.42 (NCH_3), 121.44 (C_4), 123.09, 129.19, 130.36 (Ph), 154.27 (C_3), 161.47 (C_5). MS (APCI), m/z: 210/208 (M^+).
5-Chloro-2,4-dimethyl-3-phenylisoxazol-2-ium trifluoromethanesulfonate ***1b***: mp 70–72°C; ^1H NMR ($CDCl_3$) δ: 2.14 (s, 3H, 4-CH_3), 4.26 (s, 3H, NCH_3), 7.51–7.74 (m, 5H, Ph). ^{13}C NMR ($CDCl_3$) δ: 7.58 (CH_3), 40.21 (NCH_3), 117.14 (C_4), 121.50, 129.44, 129.92, 133.47 (Ph), 156.52 (C_3), 161.52 (C_5). MS (APCI), m/z: 210/208 (M^+).
5-Chloro-4-ethoxycarbonyl-2,3-dimethylisoxazol-2-ium trifluoromethanesulfonate ***1c***: mp 86–89°C; ^1H NMR ($CDCl_3$) δ: 1.30 (t, 3H, $J=7.2$ Hz, $COOCH_2\underline{CH_3}$), 2.64 (s, 3H, 3-CH_3), 4.32 (s, 3H, NCH_3), 4.43 (q, 2H, $J=7.2$ Hz, $COO\underline{CH_2}CH_3$). ^{13}C NMR ($CDCl_3$) δ: 12.87 (CH_3), 13.58 ($COOCH_2\underline{CH_3}$), 39.43 (NCH_3), 62.76 ($COO\underline{CH_2}CH_3$), 112.87 (C_4), 156.67 (C_3), 160.91 (C_5), 162.99 (CO). MS (APCI), m/z: 206/204 (M^+).
2-(2,4-Dimethyl-3-phenyl-2H-isoxazol-5-ylidene)malonic acid diethyl ester ***3a***: mp 82–84°C; ^1H NMR ($CDCl_3$) δ: 1.30 (t, 6H, $J=7.1$ Hz, $COOCH_2\underline{CH_3}$), 1.85 (s, 3H, 4-CH_3), 3.40 (s, 3H, NCH_3), 4.29 (q, 4H, $J=7.1$ Hz, $COO\underline{CH_2}CH_3$), 7.20–7.50 (m, 5H, Ph). ^{13}C NMR ($CDCl_3$) δ: 9.99 (4-CH_3), 14.36 ($COOCH_2\underline{CH_3}$), 39.80 (NCH_3), 59.78 ($COO\underline{CH_2}CH_3$), 85.29 ($\underline{C}$=C_5), 107.43 (C_4), 126.52, 128.94, 129.29, 130.97 (Ph), 158.31 (C_3), 166.54 (CO), 174.05 (C_5). MS (EI), m/z: 331 (M^+), 286, 259, 212, 187, 144, 118, 103, 91, 77.
2-(2,4-Dimethyl-3-phenyl-2H-isoxazol-5-ylidene)pentane-2,4-dione ***3b***: orange oil; ^1H NMR ($CDCl_3$) δ: 1.80 (s, 3H, 4-CH_3), 2.28 (s, 6H, $COCH_3$), 3.79 (s, 3H, NCH_3), 7.42–7.60 (m, 5H, Ph). ^{13}C NMR ($CDCl_3$) δ: 9.91 (4-CH_3), 28.78 ($CO\underline{CH_3}$), 37.5 (NCH_3), 88.11 ($\underline{C}$=C_5), 113.42 (C_4), 127.60, 128.40, 128.72, 132.90 (Ph), 156.61 (C_3), 164.80 (C_5), 194.72 (CO). MS (EI), m/z: 271 (M^+), 256, 228, 214, 188, 160, 118, 105, 91, 77.
2-(2,4-Dimethyl-3-phenyl-2H-isoxazol-5-ylidene)-3-oxobutanoic acid ethyl ester ***3c***: orange oil; ^1H NMR ($CDCl_3$) δ: 1.21 (t, 3H, $J=6.8$ Hz, $COOCH_2\underline{CH_3}$), 1.75 (s, 3H, 4-CH_3), 2.35 (s, 3H, $COCH_3$), 3.77 (s, 3H, NCH_3), 4.14 (q, 2H, $J=6.8$ Hz, $COO\underline{CH_2}CH_3$), 7.32–7.55 (m, 5H, Ph). ^{13}C NMR ($CDCl_3$) δ: 9.96 (4-CH_3), 14.47 ($COOCH_2\underline{CH_3}$), 29.61 ($CO\underline{CH_3}$), 38.08 (NCH_3), 58.97 ($COO\underline{CH_2}CH_3$), 85.01 ($\underline{C}$=C_5), 111.10 (C_4), 124.62, 128.84, 129.45, 131.59 (Ph), 157.51 (C_3), 167.87 ($\underline{C}OOCH_2CH_3$), 169.80 (C_5), 192.43 ($\underline{C}OCH_3$); MS (APCI), m/z: 324 (M^++Na), 296, 281, 188, 118.
3-Ethoxy-5,7-dimethyl-6-oxo-1-phenyl-2-oxa-7-azabicyclo[3.2.0]hept-3-ene-4-carboxylic acid ethyl ester ***4***: mp 113–115°C (cyclohexane–ether); ^1H NMR ($CDCl_3$) δ: 1.11 (s, 3H, 5-CH_3), 1.27 (t, 3H, $J=7.1$ Hz, $OCH_2\underline{CH_3}$ or $COOCH_2\underline{CH_3}$), 1.43 (t, 3H, $J=7.1$ Hz, $COOCH_2\underline{CH_3}$ or $OCH_2\underline{CH_3}$), 2.85 (s, 3H, NCH_3), 4.16 (q, 2H, $O\underline{CH_2}CH_3$ or $COO\underline{CH_2}CH_3$), 4.48 (q, 2H, $J=7.1$ Hz, $COO\underline{CH_2}CH_3$ or $O\underline{CH_2}CH_3$), 7.24–7.51 (m, 5H, Ph). ^{13}C NMR ($CDCl_3$) δ: 13.10 ($COOCH_2\underline{CH_3}$ or $OCH_2\underline{CH_3}$), 14.08 ($OCH_2\underline{CH_3}$ or $COOCH_2\underline{CH_3}$), 15.20 (5-CH_3), 24.01 (NCH_3), 59.23 ($COO\underline{CH_2}CH_3$ or $O\underline{CH_2}CH_3$), 66.83 ($O\underline{CH_2}CH_3$ or $COO\underline{CH_2}CH_3$), 69.65 (C_5), 83.01 (C_1 or C_4), 99.33 (C_4 or C_1), 126.11, 128.82, 129.82, 131.44 (Ph), 164.11 ($\underline{C}OOCH_2CH_3$ or C_3), 165.81 (C_3 or $\underline{C}OOCH_2CH_3$), 170.90 (C_6). MS (EI), m/z: 331 (M^+), 258, 230, 212, 118, 77.
9. A solution of **3a** (1.5 mmol) in CH_3CN (40 ml) was irradiated for 15 h in a pyrex tube with a Rayonet apparatus operating at 355 nm.. Chromatographic purification on a silica gel column eluting with diethyl ether gave compound **4** (yield 60%) as a white solid.
10. Crystal data and structure refinement of compound **4**: $C_{18}H_{21}NO_5$, MW = 331.36, monoclinic, $a=9.228(2)$, $b=9.625(2)$, $c=20.872(4)$ Å, $V=1826(5)$ Å^3, space group $P2_1/n$, $Z=4$, $F(000)=704$, $D_{calcd}=1.205$ g cm^{-3}, μ(Mo Kα) 0.088 mm^{-1}. The data were collected on a Siemens P4 four-circle diffractometer with graphite monochromated Mo Kα radiation ($\lambda=0.71069$ Å) in the range $-1\le h\le 12$, $-1\le k\le 13$, $-29\le l\le 29$. Three standard

reflections measured every 147 reflections showed no variations. 5320 total reflections ($R_{int}=0.06$) were collected at 22°C. Absorption correction was not applied. The structure was solved by direct methods implemented in SHELXS-97.[11] The refinement was carried out by full-matrix anisotropic least-squares on F^2 for all reflections for all non-H atoms by using SHELXL-97.[11] The hydrogen atoms were localized in the Fourier map and included in the structure–factor calculations. Final refinement of 241 parameters and 42 restraints gave $R_1=0.085$ and $wR_2=0.127$ for $I>2\sigma(I)$. Weighting scheme was $w=1/[\sigma^2(F_o)^2+0.0504P^2]$, where $P=(F_o^2+2F_c^2)/3$. Minimum and maximum height in the last map were –0.154 and 0.143 e $Å^{-3}$, respectively. Atomic scattering factors, including f' and f'' were taken from Ref. 11. Lists of the fractional coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre (UK) as supplementary material no. CCDC-220334. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [Fax: +44(1223)336033; e-mail:deposit@ccdc.ac.uk].

11. Sheldrick, G. M. SHELXL-97 and SHELXS-97, University of Göttingen, Germany, 1997.