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Photoreaction of some 5-alkylidene-2,5-dihydroisoxazoles: facile construction of novel unclassical β-lactam containing heterocycles

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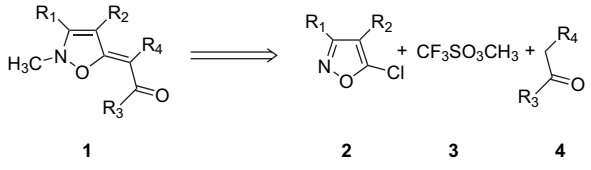
Abstract—The photochemical behaviour of some 5-alkylidene-2,5-dihydroisoxazoles was investigated. This reaction produced *cis*-4,5-dihydrofuroazetidinones in high yields.

1. Introduction

The synthesis of novel β-lactam cores continues to attract the attention of the scientific community as these molecules possess a wide range of biological activities.[1] Following initial reports on the antibacterial and anti-β-lactamase activities of β-lactams,[2,3] several accounts appeared in which β-lactams of unusual structure were found useful in tackling the human cytomegalovirus.[4]

Recently, β-lactams were also found to be useful as anti-tumour compounds.[5] Aza-sugars[6] or spirocyclopentenones[7] were prepared from the β-lactam core demonstrating the potential of this class of compounds to act as synthetic precursors. As a part of our endeavours in developing synthetically useful photochemical processes, we became interested in 5-alkylidene-2,5-isoxazoles **1** (Fig. 1).[8]



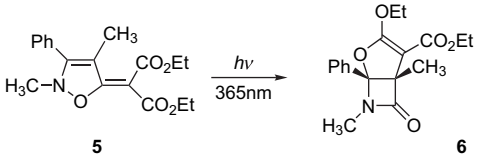
R_1-R_2 = Alkyl or Aryl; R_3 = Me, -OEt; R_4 = CN,COMe,COOEt

Figure 1. A family of photoreactive isoxazoles.

This family of compounds could be rapidly assembled from an opportunely substituted 5-chloroisoxazole **2**, an alkylating agent **3** and an enolisable compound **4** (Fig. 1). Hence the preparation of **1** is modular and offers the advantage of a rapid introduction of diversity.[9]

5-Alkylidene-2,5-isoxazoles **1** hold great potentials for the development of diversity orientated syntheses as they contain a number of photochemically switchable groups that could be used to dictate the reaction outcome. For instance, the N–O bond in the isoxazole moiety could be reacted by irradiation with ultraviolet light.[10] The resulting diradical species usually rearranges to a reactive acyl-azirin intermediate that eventually evolves to a stable oxazole.[10] Compounds **1** contain two conjugated carbonyl functionalities, which could be exploited to initiate radical cascades of the Norrish I type.[11] The latter mode of reaction expands the number of molecular types that are available from **1**.

We have reported that irradiation of 5-alkylidene-2,5-dihydroisoxazole **5** resulted in the formation of the 4,5-dihydrofuroazetidinone **6** (Scheme 1), which is a novel heterocyclic nucleus that contains a β-lactam core.[8]



Scheme 1. Photolysis of 5-alkylidene-2,5-dihydroisoxazole **5**.

Keywords: β-Lactam; Isoxazole photochemistry.
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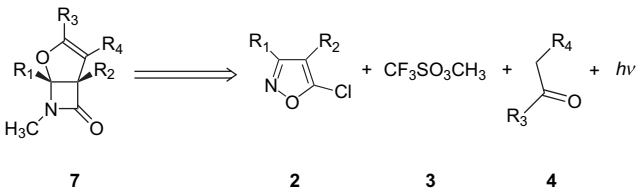


Figure 2. A new modular approach to the preparation of 4,5-dihydrofuroazetidinones **7**.

We reasoned that if an alkylidene isoxazole **5** could be converted efficiently to 4,5-dihydrofuroazetidinones **6**, then a novel approach to the synthesis of **7** could be envisaged that starts from an opportunely substituted 5-chloroisoxazole **2**, an alkylating agent **3**, an enolisable compound **4** and light (Fig. 2). To confirm this hypothesis, we started a programme of research aimed at identifying the scope for the photochemical rearrangement of compounds **1**. Herein we report the results of this study, which was focused on the nature of the alkylidene moiety.

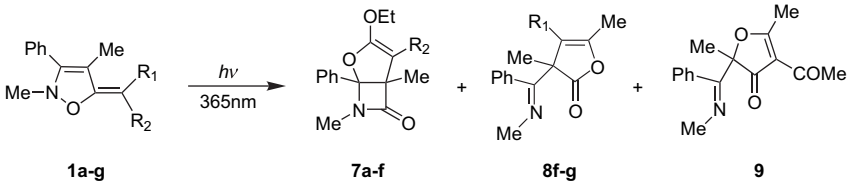
2. Results and discussion

Compounds **1a–g** (Scheme 2) were prepared following a procedure established in our laboratories,[8] and were subsequently photoreacted using a 365 nm light until complete conversion of the starting materials was observed (Scheme 2 and Table 1). In most cases, β-lactam products **7a–f** were obtained in high yields (Table 1).

While compounds **1a–e** afforded β-lactams **7a–e** as the exclusive products and in high yields (Table 1, entries 1–5), compound **1f** furnished **7f** only in a limited amount (Table 1, entry 6). In this reaction, lactone **8f** appeared as the principal product and was isolated in 68% yield. Compound **1g** furnished upon irradiation a mixture of lactone **8g** and furanone **9** (Table 1, entry 7). Surprisingly, in this reaction no β-lactam was formed. The structures of compounds **7b–f** were assigned by comparison of the ^{1}H and ^{13}C NMR data with those of **7a** whose structure was determined by X-ray crystallographic analysis.[8] We also determined the structure of compound **7c** as 1,2a-dimethyl-6a-phenyl-2a,4,5,6a-tetrahydro-1*H*-6-oxa-1-aza-cyclobuta[*a*]pentalene-2,3-dione and of compound **7e** as 1,2a,4,6-tetramethyl-7a-phenyl-1,2a,6,7a-tetrahydro-7-oxa-1,4,6-triaza-cyclobuta[*a*]indene-2,3,5-trione by X-ray crystallography (Fig. 3).[12]

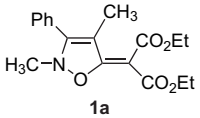
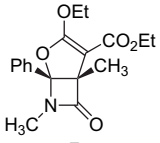
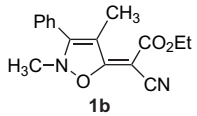
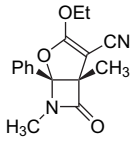
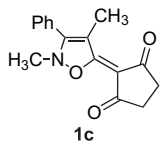
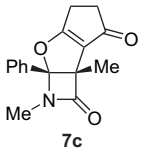
The structures of lactones **8f**,**g** and furanone **9** were assigned using mono- and two-dimensional NMR spectra and also by comparison of their ^{1}H and ^{13}C NMR chemical shifts with those of known compounds.[13–15] While lactones **8f**,**g** were isolated using column chromatography, furanone **9** did not survive exposure to silica gel and rapidly decomposed. For this reason, **9** was characterised without isolating it from **8g**.

The data collected (Table 1) pointed out that more than one reaction pathway is available for the photoreaction of compounds **1**. We believe that compounds **7**, **8** and **9** arise



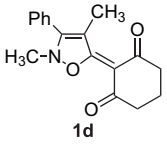
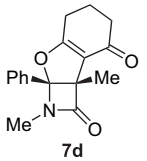
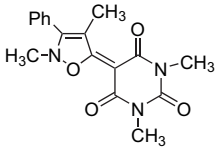
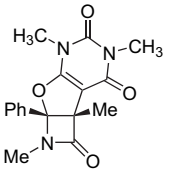
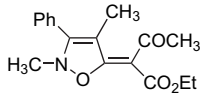
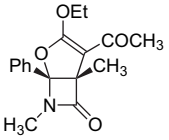
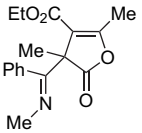
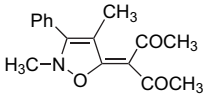
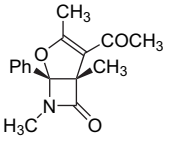
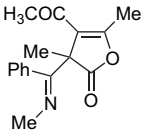
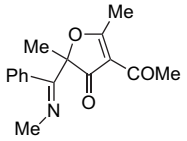
Scheme 2. Photoreaction of isoxazoles **1a–g**.

Table 1. Products obtained photoreacting isoxazoles **1a–g**

Entry	Alkylidene	β-Lactam	Yield[a] (%)	Alternative products
1	 **1a**	 **7a**	71	—
2	 **1b**	 **7b**	74	—
3	 **1c**	 **7c**	78	—

(*continued*)

Table 1. (*continued*)

Entry	Alkylidene	β-Lactam	Yield[a] (%)	Alternative products
4	 **1d**	 **7d**	78	—
5	 **1e**	 **7e**	74	—
6	 **1f**	 **7f**	14	 **8f**
7	 **1g**	 **7g**	0	 **8g**  **9**

[a] Isolated yields of chromatographically pure material.

from a common intermediate, which we identified as cyclopropanone **12** (Scheme 3). The photochemical behaviour of a 5-alkylidene isoxazole similar to **5** has been reported and a cyclopropanone was proposed as the main product of this reaction.[10] Therefore, it is possible that upon irradiation with an opportune wavelength, the N–O bond present in **5** opened to form a diradical species **10**. Intermediate **10** then rearranged to give the cyclopropanone intermediate **12**.

Cyclopropanones have been extensively studied.[16] They are intermediates in important reactions such as the Favorskii rearrangement[17] or precursors of oxyallyl cations, a widely used class of reactive synthons.[18] As a result of the severe angle strain, cyclopropanones possess large amount of energy waiting to be released by ring opening. Experimentally this fact manifests itself as a low activation energy that justifies the high reactivity of cyclopropanones even at low temperatures.

We speculated that upon photolysis compounds **1a–g** rearranged to cyclopropanones **13** that at this point could undergo two diverse kinds of rearrangements a and b (Scheme 4).[19] Rearrangement a (Scheme 4) involved photolysis of the imine moiety that triggered the rearrangement of the cyclopropanone moiety to a β-lactam diradical species **15**. Intermediate **15** could either cyclise to yield the expected azetidinone **7** or further rearrange to furnish lactone **8**. Rearrangement b (Scheme 4) involved the homolytic ring opening of cyclopropanones **13** to give a diradical species **17**, which finally cyclised to give **9**.

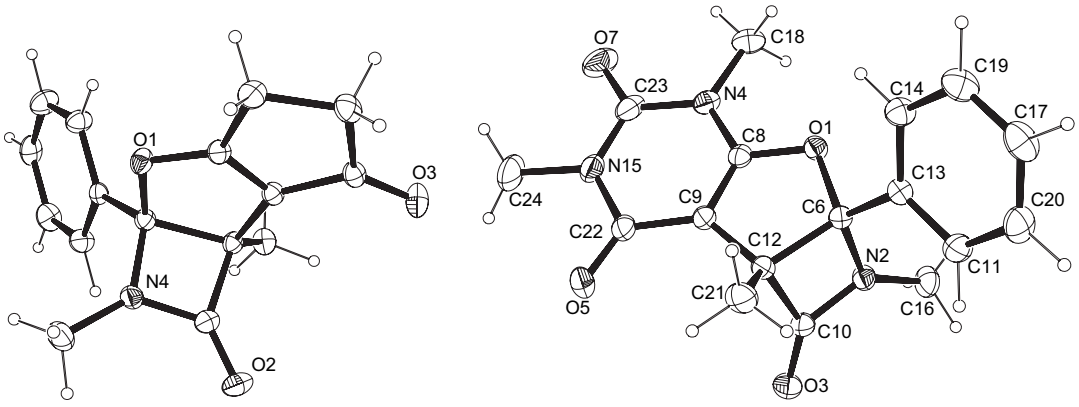
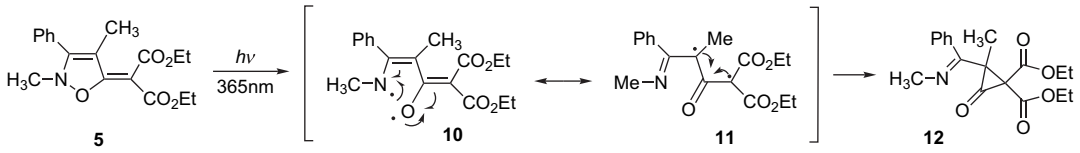
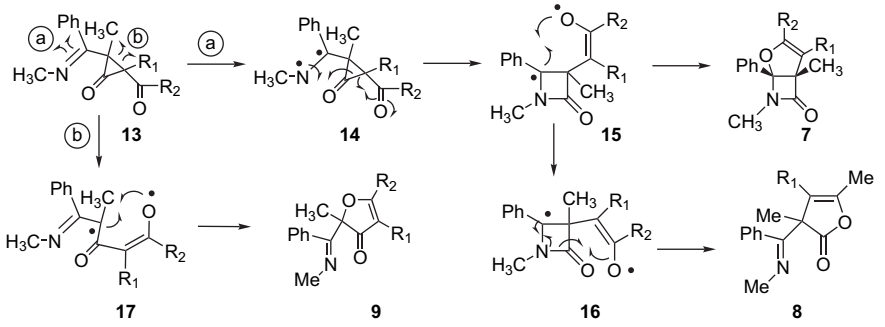


Figure 3. ORTEP drawing of compounds **7c**,**e** with 20% probability thermal ellipsoids.



Scheme 3. Photochemical rearrangement of alkylidene isoxazole **5**.



Scheme 4. Proposed reaction pathway for the rearrangement of cyclopropanones **13**.

In conclusion we have studied the photochemical rearrangement of some 5-alkylidene-2,5-isoxazoles to afford β-lactams. With the correct choice of alkylidene moiety this reaction could be used to assemble families of β-lactam compounds rapidly and efficiently.

3. Experimental

3.1. General experimental

Melting points were measured with a Kofler apparatus and are uncorrected. The ^{1}H and ^{13}C NMR spectra were recorded with a Bruker AC200 instrument operating at 200.13 MHz for ^{1}H and at 50.33 MHz for ^{13}C. The *J*-long range heterocorrelations were recorded with a Bruker DRX600 instrument with *J* in the range 0–10 Hz. ESI-MS spectra were recorded with an LCQ-DECA Thermo Finnigan instrument. TLC was performed on precoated 4×6.7 silica gel 60 F254 plates silica gel on aluminium with detection by UV light. Column chromatography was carried out on silica gel (0.040–0.063). Irradiation was carried out in a Rayonet apparatus operating at 365 nm.

3.2. General procedure for the preparation of compounds 1a–g

To a stirred solution of the desired enolisable compound (3 mmol) in anhydrous benzene (15 mL) were sequentially added NaH 60% in oil (3 mmol) and dry Et_3N (3 mmol). To this suspension was then slowly added 5-chloro-2,4-dimethyl-3-phenylisoxazol-2-ium trifluoromethanesulfonate (3 mmol) and the resulting yellow solution stirred for 1 h. After this time the reaction mixture was concentrated in vacuo and the residue treated with water (20 mL) and extracted with CH_2Cl_2 (2×15 mL). The organic layer was dried over Na_2SO_4, the solvent evaporated and the resulting oil purified by column chromatography (eluent CH_2Cl_2/CH_3OH 95:5) to give compounds **1a–g**. The spectral data of compounds **1a**,**f**,**g** were reported in a previous communication.[8]

3.2.1. Cyano-(2,4-dimethyl-3-phenyl-2*H*-isoxazol-5-ylidene)-acetic acid ethyl ester 1b. Yellow solid (512 mg, 60% yield), R_f=0.6, mp 133–135 °C (ethanol); ν_{max} (film)/cm^{-1}: 2241s, 1735s; δ_H (200 MHz, $CDCl_3$) 7.61–7.30 (5H, m, Ph), 4.22 (2H, q, *J*=7, OCH_2CH_3), 3.48 (3H, s, N–CH_3), 2.21 (3H, s, CH_3), 1.31 (3H, t, *J*=7, OCH_2CH_3); δ_C (50 MHz, $CDCl_3$) 174.0, 165.1, 159.0, 131.5, 129.6, 128.9, 125.5, 119.0, 105.5, 65.0, 60.1, 39.5, 14.5, 9.4; *m*/*z*: 285 (100%, MH^+). Anal. Calcd for $C_{16}H_{16}N_2O_3$: C, 67.59; H, 5.67; N, 9.85. Found: C, 67.85; H, 5.64; N, 9.82.

3.2.2. 2-(2,4-Dimethyl-3-phenyl-2*H*-isoxazol-5-ylidene)-cyclopentane-1,3-dione 1c. Yellow solid (525 mg, 65% yield), R_f=0.5, mp 227–230 °C (ethanol); ν_{max} (film)/cm^{-1}: 1718s; δ_H (200 MHz, $CDCl_3$) 7.65–7.36 (5H, m, Ph), 3.95 (3H, s, N–CH_3), 2.53 (4H, m, CH_2CH_2), 2.12 (3H, s, CH_3); δ_C (50 MHz, $CDCl_3$) 200.0, 170.5, 157.9, 132.1, 129.7, 128.7, 123.4, 110.8, 100.9, 38.1, 34.0, 9.1; *m*/*z*: 270 (100%, MH^+). Anal. Calcd for $C_{16}H_{15}NO_3$: C, 71.36; H, 5.61; N, 5.20. Found: C, 71.02; H, 5.63; N, 5.17.

3.2.3. 2-(2,4-Dimethyl-3-phenyl-2*H*-isoxazol-5-ylidene)-cyclohexane-1,3-dione 1d. Yellow solid (340 mg, 40% yield), R_f=0.5, mp 190–193 °C (ethanol); ν_{max} (film)/cm^{-1}: 1721s; δ_H (200 MHz, $CDCl_3$) 7.30–7.52 (5H, m, Ph), 3.91 (3H, s, N–CH_3), 2.21 (4H, t, CH_2 and CH_2), 1.61–1.82 (5H, m, CH_2 and CH_3); δ_C (50 MHz, $CDCl_3$) 193.3, 175.4, 157.6, 132.1, 129.7, 128.9, 123.8, 113.5, 101.1, 38.0, 37.7, 20.6, 9.8; *m*/*z*: 284 (100%, MH^+). Anal. Calcd for $C_{17}H_{17}NO_3$: C, 72.07; H, 6.05; N, 4.94. Found: C, 72.02; H, 6.07; N, 4.90.

3.2.4. 5-(2,4-Dimethyl-3-phenyl-2*H*-isoxazol-5-ylidene)-1,3-dimethyl-pyrimidine-2,4,6-trione 1e. Yellow solid (688 mg, 70% yield), R_f=0.3, mp 198–201 °C (CH_2Cl_2); ν_{max} (film)/cm^{-1}: 1723s; δ_H (200 MHz, $CDCl_3$) 7.23–7.64 (5H, m, Ph), 3.98 (3H, s, N–CH_3), 3.30 (6H, s, N–CH_3), 2.00 (3H, s, Me); δ_C (50 MHz, $CDCl_3$) 173.9, 161.8, 157.9, 152.8, 132.3, 129.8, 128.8, 123.5, 112.9, 81.1, 38.0, 27.6, 10.0; *m*/*z*: 328 (100%, MH^+). Anal. Calcd for

$C_{17}H_{17}N_3O_4$: C, 62.38; H, 5.23; N, 12.84. Found: C, 62.13; H, 5.24; N, 12.78.

3.3. General procedure for the irradiation of 1a–g

A solution of **1a–g** (1 mmol) in anhydrous CH_3CN (40 mL) in the presence of activated molecular sieves (4 Å, 100–150 mg) was irradiated for 15 h in a Pyrex tube at 365 nm. After this time the molecular sieves were decanted, washed with further CH_3CN (10 mL) and the solvent removed in vacuo. The oil obtained was purified by column chromatography (eluent CH_2Cl_2/CH_3OH 95:5) to give pure compounds **7a–f**. The spectral data of compound **7a** were reported in a previous communication.[8]

3.3.1. 3-Ethoxy-5,7-dimethyl-6-oxo-1-phenyl-2-oxa-7-aza-bicyclo[3.2.0]hept-3-ene-4-carbonitrile 7b. Orange oil (210 mg, 74% yield), R_f=0.6; ν_{max} (film)/cm^{-1}: 1648s, 1638s; δ_H (200 MHz, $CDCl_3$) 7.51–7.38 (5H, m, Ph), 4.47 (2H, q, J=7, OCH_2CH_3), 2.79 (3H, s, N–CH_3), 1.37 (3H, t, J=7, OCH_2CH_3), 0.93 (3H, s, CH_3); δ_C (50 MHz, $CDCl_3$) 171.4, 170.5, 131.9, 130.7, 128.4, 116.5, 102.6, 87.9, 70.5, 69.9, 25.5, 15.7, 13.7; *m/z*: 307 (100%, MNa^+). Anal. Calcd for $C_{16}H_{16}N_2O_3$: C, 67.59; H, 5.67; N, 9.85. Found: C, 67.84; H, 5.64; N, 9.81.

3.3.2. 1,2a-Dimethyl-6a-phenyl-2a,4,5,6a-tetrahydro-1*H*-6-oxa-1-aza-cyclobuta[*a*]pentalene-2,3-dione 7c. Pale yellow solid (210 mg, 78% yield), R_f=0.4, mp 180–182 °C (CH_2Cl_2); ν_{max} (film)/cm^{-1}: 1710s, 1645s, 1634s; δ_H (200 MHz, $CDCl_3$) 7.40–7.22 (5H, m, Ph), 2.76 (3H, s, N–CH_3), 2.69–2.64 (4H, m, CH_2CH_2), 0.98 (3H, s, CH_3); δ_C (50 MHz, $CDCl_3$) 195.4, 193.6, 168.6, 157.9, 130.3, 128.7, 126.0, 121.8, 112.8, 95.0, 69.2, 39.1, 24.1, 22.8, 11.0; *m/z*: 270 (100%, MH^+). Anal. Calcd for $C_{16}H_{15}NO_3$: C, 71.36; H, 5.61; N, 5.20. Found: C, 71.03; H, 5.60; N, 5.23.

3.3.3. 1,2a-Dimethyl-7a-phenyl-1,2a,4,5,6,7a-hexahydro-7-oxa-1-aza-cyclobuta[*a*]indene-2,3-dione 7d. Yellow solid (220 mg, 78% yield), R_f=0.4, mp 190–194 °C; ν_{max} (film)/cm^{-1}: 1710s, 1643s, 1634s; δ_H (200 MHz, $CDCl_3$) 7.22–7.38 (m, 5H, Ph), 2.72 (3H, s, N–CH_3), 2.50–2.62 (2H, m, CH_2), 2.35 (2H, m, CH_2), 2.05 (2H, m, CH_2), 1.04 (3H, s, CH_3); δ_C (50 MHz, $CDCl_3$) 194.3, 176.7, 170.1, 131.2, 126.5, 128.9, 129.6, 115.6, 103.2, 70.4, 37.1, 24.4, 24.2, 21.3, 11.9; *m/z*: 284 (100%, MH^+). Anal. Calcd for $C_{17}H_{17}NO_3$: C, 72.07; H, 6.05; N, 4.94. Found: C, 72.01; H, 6.04; N, 4.98.

3.3.4. 1,2a,4,6-Tetramethyl-7a-phenyl-1,2a,6,7a-tetrahydro-7-oxa-1,4,6-triaza-cyclobuta[*a*]indene-2,3,5-trione 7e. Yellow solid (242 mg, 74% yield), R_f=0.2, mp 203–206 °C; ν_{max} (film)/cm^{-1}: 1701s, 1647s, 1631s; δ_H (200 MHz, $CDCl_3$) 7.23–7.64 (m, 5H, Ph), 3.42 (3H, s, N–CH_3), 3.24 (3H, s, N–CH_3), 2.84 (3H, s, N–CH_3), 1.20 (3H, s, CH_3); δ_C (50 MHz, $CDCl_3$) 170.7, 163.1, 161.2, 152.8, 132.2, 131.7, 130.7, 128.5, 106.6, 89.9, 71.7, 30.6, 28.7, 25.5, 13.1; *m/z*: 328 (100%, MH^+). Anal. Calcd for $C_{17}H_{17}N_3O_4$: C, 62.38; H, 5.23; N, 12.84. Found: C, 62.50; H, 5.21; N, 12.89.

3.3.5. 4-Acetyl-3-ethoxy-5,7-dimethyl-1-phenyl-2-oxa-7-aza-bicyclo[3.2.0]hept-3-en-6-one 7f. Orange oil (42 mg, 14% yield), R_f=0.6; ν_{max} (film)/cm^{-1}: 1712s, 1652s, 1639s; δ_H (200 MHz, CD_3CN) 7.48–7.30 (5H, m, Ph), 4.41 (2H, m, CH_2CH_3), 2.79 (3H, s, N–CH_3), 2.29 (3H, s, CH_3), 1.40 (3H, t, J=7, CH_2CH_3), 0.99 (3H, s, N–CH_3); δ_C (50 MHz, $CDCl_3$) 192.8, 171.8, 168.7, 133.0, 131.4, 130.6, 128.5, 95.3, 84.5, 69.8, 50.0, 30.0, 24.9, 15.9, 13.9; *m/z*: 302 (100%, MH^+). Anal. Calcd for $C_{17}H_{19}NO_4$: C, 67.76; H, 6.36; N, 4.65. Found: C, 67.68; H, 6.38; N, 4.63.

3.3.6. 2,4-Dimethyl-4-(methylimino-phenyl-methyl)-5-oxo-4,5-dihydro-furan-3-carboxylic acid ethyl ester 8f. Orange oil (183 mg, 61% yield), R_f=0.4; ν_{max} (film)/cm^{-1}: 1736s; δ_H (200 MHz, CD_3CN) 7.40–7.31 (5H, m, Ph), 4.16 (2H, q, J=7, CH_2CH_3), 2.93 (3H, s, N–CH_3), 2.12 (3H, s, CH_3), 1.55 (3H, s, CH_3), 1.21 (3H, t, J=7, CH_2CH_3); δ_C (50 MHz, $CDCl_3$) 176.5, 167.6, 163.1, 163.0, 132.0, 128.9, 128.7, 126.7, 114.4, 60.5, 58.0, 40.5, 19.9, 13.7, 13.1; *m/z*: 302 (100%, MH^+). Anal. Calcd for $C_{17}H_{19}NO_4$: C, 67.76; H, 6.36; N, 4.65. Found: C, 67.55; H, 6.38; N, 4.68.

3.3.7. 4-Acetyl-3,5-dimethyl-3-(methylimino-phenyl-methyl)-3*H*-furan-2-one 8g. Orange oil (103 mg, 38% yield), R_f=0.4; ν_{max} (film)/cm^{-1}: 1741s; δ_H (200 MHz, CD_3CN) 7.50–7.39 (5H, m, Ph), 3.00 (3H, s, N–CH_3), 2.30 (2×3H, s, =CCH_3 and $COCH_3$), 1.65 (3H, s, CH_3); δ_C (50 MHz, $CDCl_3$) 192.5, 176.6, 166.1, 160.7, 131.7, 131.2, 129.3, 126.0, 123.1, 57.0, 41.8, 30.9, 21.1, 15.3; *m/z*: 272 (100%, MH^+). Anal. Calcd for $C_{16}H_{17}NO_3$: C, 70.83; H, 6.32; N, 5.16. Found: C, 71.09; H, 6.29; N, 5.19.

3.3.8. 4-Acetyl-2,5-dimethyl-2-(methylimino-phenyl-methyl)-furan-3-one 9. R_f=0.3; δ_H (200 MHz, CD_3CN) 7.48 (3H, m, Ph), 6.97–6.92 (2H, m, Ph), 3.09 (3H, s, N–CH_3), 2.39 (3H, s, $COCH_3$), 2.37 (3H, s, CH_3), 1.70 (3H, s, CH_3); δ_C (50 MHz, CD_3CN) 199.1, 196.0, 192.5, 164.1, 135.5, 133.1, 132.9, 129.0, 115.6, 94.1, 41.6, 30.3, 18.3, 15.0.

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