The role of the carbonyl group in the intermolecular 1,3-cycloaddition of azido(2-heteroaryl)methanones with activated olefins

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Treatment of the azido(2-heteroaryl)methanones 1–5 with methyl (*E*)-3-pyrrolidinoprop-2-enoate at room temperature yielded the methyl 1,2,3-triazolecarboxylate **6** and (2-heteroaryl) (pyrrolidino)methanones **1a–5a** via an unusual 1,3-cycloaddition reaction. Analogous reactions of the azidomethanones **1** and **2** with the dipolarophiles methyl crotonate, methyl propiolate or methyl but-2-ynoate failed. In contrast, the strained 5-methylenebicyclo[2.2.1]hept-2-ene reacted smoothly with the carbonyl azides **1–5** to give triazoline adducts which subsequently formed the (2-heteroaryl)(6-methylene-3-azatricyclo[3.2.1.0^{2,4}]octan-3-yl)methanones **1b–5b** by loss of molecular nitrogen.

The 1,3-dipolar cycloaddition (1,3-DC) of organic azides to dipolarophile olefins constitutes a powerful synthetic route to 1,2,3-triazoline¹ and 1,2,3-triazole² substructures. Reactions of this type enable the synthesis of azole-cyclic systems containing a large range of functionalities, and give access to compounds of preparative importance.³ Such azole-cyclic systems have practical applications in fields such as agriculture and medicine.⁴ The reaction is markedly favoured with activated ethylenes and acetylenes (*i.e.*, strained olefins and those carrying functional groups like OR, NR₂, COOR)⁵ or when high-pressure techniques are employed.⁶

Our interest in this topic is focused on the molecular orientation in the 1,3-DC of aryl and heteroaryl azides with terminally substituted olefins.⁷ All such azides undergo 1,3-DC to terminally silylated (or carboxylated) alkynes *via* a concerted pathway and the additions are almost regiospecific.⁸ The 1,3-DC procedure was employed both as a method for trapping thermally unstable heteroaryl azides and as a synthetic method to obtain cyclic compounds. The chemistry of these reactions was found to depend on the nature of the N-1 azido substituent.^{5,7} In addition to the chemistry of 1,3-DC products against *Mycobacterium avium* and *M. tuberculosis*.⁹ The large number of cycloaddition reactions available allows the preparation of many candidate compounds that can be tested for biological activity.

Addition of azides to double or triple C–C bonds is well characterized from both a theoretical¹⁰ and synthetic¹⁻⁴ standpoint; however, the literature on 1,3-DC reactions in which heteroaroyl azides are the dipole component is limited to a few intramolecular reactions.¹¹ Moreover, these azidocycloadditions were found to be in competition with the Curtius rearrangement. To our knowledge, no report has described the intermolecular 1,3-DC of heteroaroyl azides with dipolarophiles as a route to azoles. Related examples would be the known 1,3-DC involving azidoformates and benzoyl azide.¹²

High reactivity and regioselectivity have been observed in the 1,3-DC of a number of aryl^{13a} and heteroaryl azides^{13b} and methyl 3-pyrrolidinoacrylate (**MePA**). In addition, there is experimental evidence that the triazoline adducts undergo fragmentation to form *N*-substituted 1,2,3-triazole 4-carb-

oxylates and pyrrolidine. In the present study we examine the chemistry of the 1,3-DC of a number of azido(2-heteroaryl)methanones by using MePA, 5-methylenebicyclo[2.2.1]hept-2-ene (MBH), methyl crotonate [methyl (*E*)-2-methylbut-2-enoate], (MeC) methyl propiolate (methyl propynoate) (MeP) and methyl but-2-ynoate (MeB) as dipolarophiles. The 2-heteroaryls selected are furan- (1), thiophene- (2), 5-methylthiophene- (3), selenophene- (4), and thieno[3,2-*b*]thiophene-(5)-2-carbonyl azides. This work was undertaken to elucidate the applicability of 1,3-DC to the synthesis of triazoles starting from deactivated azides whose HOMO and LUMO energies are presumably depressed. With this aim, ¹H-NMR spectroscopy was used to analyse the main products during the course of the reactions.

Results and discussion

The reactions of the carbonyl azides 1-5 with MePA (exact equimolar ratio; each 2×10^{-3} mol) in CDCl₃ (1.0 cm⁻³) proceeded smoothly at room temperature, giving a solid precipitate within 20-25 days. The first ten days of reaction were monitored by removing small aliquots from the reaction mixture and analysing them by ¹H-NMR spectroscopy. The time evolution of the ¹H-NMR spectra showed a monotonic decrease in the peak intensities associated with the reactants 1-5 and MePA, and the concomitant appearance of ¹H-NMR proton signals that are firmly assignable to a mixture of the triazole 6 and the (2-heteroaryl)(pyrrolidino)methanones 1a-5a. The spectra showed no evidence of other compounds. After NMR analysis showed the disappearance of the starting carbonyl azide, the suspensions were treated with a mixture of hexane-chloroform $(5 \text{ cm}^3; 4: 1, v/v)$ and then stirred for 10 h. The resulting suspensions were filtered and the solid products characterized. In all cases the product was found to be the triazole 6 (90%)¹⁴ Manipulation of the mother liquor yielded the (2-heteroaryl)(pyrrolidino)methanones 1a-5a with comparable purities (85-88% yield). Structural assignments of 1a-5a and the triazole 6 were made on the basis of IR, ¹H-, ¹³C-NMR, and exact mass spectra. The ¹H-NMR spectrum of compound **6** showed two singlets in a 1 : 3 ratio at δ 8.34 and 3.88 assignable to the CH and OCH₃ moieties and the NH

1420 J. Chem. Soc., Perkin Trans. 1, 2002, 1420–1425

signal is absent. Identical NMR, MS and physical data were observed for a sample of **6** synthesized using the literature procedure.¹⁴ The mass spectrum of **6** displayed a peak at m/z 127 corresponding in mass and isotopic abundance to the molecular ion. However, no primary nitrogen loss (M – 28), typical for the 1*H*-isomer, was observed. In contrast, the peak at m/z 42 was twofold higher than the peak at m/z 41, typical for 2*H*-triazoles.¹⁵

Our findings indicate that the 1,3-DC of heteroaroyl azides 1–5 with **MePA** occurs smoothly to produce a single adduct Ia (Scheme 1). This elusive adduct [*i.e.*, methyl 5-pyrrolidino-1-(2-heteroarylcarbonyl)-4,5-dihydro-1*H*-1,2,3-triazole-4-carboxylate] undergoes displacement of the pyrrolidine from the triazoline ring as previously observed in the cases of aryl and heteroaryl azides.¹³ The basic pyrrolidine attacks the carbonyl carbon, *via* nucleophilic addition at the trigonal

X = O

X = S

X = S

X = Se



carbon, presumably to afford methyl 1-[hydroxy(pyrrolidino)(2heteroaryl)methyl]-1H-1,2,3-triazole-4-carboxylate (**Ib**), which in turn releases the triazole **6** and the pyrrolidinomethanones **1a**–**5a** in high yields. The observation of **6** as a product in all of these reactions suggests, but does not require, the existence of the tetrahedral intermediate **Ib** shown in Scheme 1.

The ¹H- and ¹³C-NMR spectra of compounds **1a–5a** before manipulation indicated restricted rotation around the partialdouble carbonyl-pyrrolidine bond. A brief description of this behaviour can be ascertained by the ¹H-NMR spectra in $CDCl_3$, which display the four α -geminal protons as two pseudotriplets centred at δ 3.5–3.8 (pyrrolidine α and α' , two protons each) separated by 32.6, 18.3, 24.0, 15.8 and 22.7 Hz, respectively. A similar but less extensive effect is observed for the β-protons. The possibility of measuring by NMR spectroscopy the torsional barrier of the C-N bond in heteroaryl carboxamides and their dependence upon the medium as been reported.¹⁶ Compounds 1a-5a after work-up and samples of 1a and 2a, synthesized by displacement of the corresponding heteroarene: carbonyl chloride with pyrrolidine,¹⁷ show identical ¹H-NMR spectra. In these instances the α-proton signals were essentially broad singlets centered at the same frequencies. These signals become separated upon addition of trace amounts of pyrrolidine. The evidence suggests that the presence of pyrrolidine modifies the C-N torsional barriers through base-catalysed prototropic exchange.

The main purpose of the present work was to further characterize the reactivity of azido(2-heteroaryl)methanones with dipolarophile olefins. However, our attempts to obtain isolable triazolines (or triazoles) by 1,3-DC reaction of the azides **1** and **2** in neat methyl crotonate, methyl propiolate or methyl but-2-ynoate failed. Even after two months, the ¹H-NMR spectrum of the reaction mixture remained unchanged. In contrast, 1,3-DC of the azides **1–5** with the strained 5-methylenebicyclo[2.2.1]hept-2-ene (**MBH**) (exact equimolar ratio; each 2×10^{-3} mol) in CDCl₃ (1.0 cm³) proceeded smoothly, affording (2-heteroaryl)(6-methylene-3-azatricyclo[3.2.1.0^{2,4}]octan-3-yl)methanones **1b–5b** as the major product (Scheme 2).



At room temperature the reactions were virtually complete within 17–25 days. Release of molecular nitrogen was observed in this period.

As a representative example, the ¹H-NMR spectrum measured after nine days of reaction of the azide **1** showed the formation of a novel 2-substituted heteroaryl AMX system of **1b** in the ratio 1 : 2.5. This indicates that the product **1b**, characterized by the three heteroaryl-proton signals (three doublets of doublets) at δ 7.55, 7.13 and 6.51, is produced at the expense of the starting compound **1**, whose resonances are at δ 7.66, 7.27 and 6.56.¹⁸ The relative shielding observed suggests a reduction in the electron-withdrawing effect of the carbonyl carbon. Of the compounds tested, the slowest reaction was observed for the 5-methylthiophene **3**, for which the ratio **3** : **3b** was 1 : 0.8 after nine days. The corresponding ratios for the other compounds studied were **2** : **2b** (1 : 1.5), **4** : **4b** (1 : 2) and **5** : **5b** (1 : 2).

It is clear from Fig. 1 (traces b and c, c being that of the

Fig. 1 ¹H NMR spectra in CDCl₃ at 200 MHz in the region δ 2.6–6.4 Traces: **a**) neat 5-methylenebicycyclo[2.2.1]hept-2-ene; **b**) reaction sample registered after nine days; **c**) final product **1b**.

final product **1b**) that significant reaction occurs to produce mainly a single compound characterized by a novel H-2' and H-3' AB-system at δ 2.96 and δ 2.87. (Primed loads are used to denote the bicycloheptene numbering system) This system is formed at the expense of the broad multiplet at δ 6.1 corresponding to the ethylenic protons H-2' and H-3' of the bicyclic olefin (trace **a**). It is noteworthy that the single peaks corresponding to H-8' are almost unchanged during the reaction, whereas the signals of other protons undergo various shifts. H-7' (particularly the B-part of an AB-type quartet with J 10.3 Hz), H-4' and H-1' are remarkably shielded, whereas H-6' (particularly the B-part of an AB-type quartet with J 15.8 Hz) appears to be deshielded. In the light of the present 'H-NMR data and those reported for related systems,¹⁹ an *exo* ring-fused carbonyl aziridine structure is assigned to **1b**.

Comparison of the GC-MS mass spectrum of the final mixture before chromatographic separation with the mass

Table 1 Calculated HOMOs and LUMOs energies of azides 1-5 and some dipolarophiles at HF/6-31G* level of theory^{*a*}

Compound	$E_{\rm HOMO}$	E_{LUMO}	
1	-9.17	2.27	
2	-9.35	1.95	
3	-9.03	2.03	
4 ^b	-9.12	1.77	
5	-8.62	1.63	
MePA ^c	-8.18	4.09	
\mathbf{MBH}^{d}	-8.99	4.63	
MeC ^e	-10.22	3.38	
MeP ^f	-11.42	3.30	
MeB ^g	-10.80	3.59	

^{<i>a</i>} In eV (1 eV = 23 kcal = 96.5 kJ). ^{<i>b</i>} Pseudopotential associated with				
6-31G* basis set is used for heavy selenium atom. ^c Methyl (E)-				
3-pyrrolidinoprop-2-enoate. ^d 5-Methylenebicyclo[2.2.1]hept-2-ene.				
^e Methyl crotonate. ^f Methyl propiolate. ^g Methyl but-2-ynoate.				

spectrum of the separated product confirmed the main product to be the aziridine **1b** (77%, m/z 215). Analysis of the chromatogram also indicated the presence of small amounts of four isomers giving signals at m/z 215 (global 23%). These isomers presumably arise from thermal rearrangement in the injector and are not detected on the NMR time-scale.²⁰ Similar behaviour was observed for the azides **2–5**. The structures of the resulting compounds **1b–5b** were assigned on the basis of elemental analyses, IR, NMR and MS spectral data.

As expected, the 1,3-DC occurs almost exclusively at the strained double bond C-2=C-3 of the bicycloheptene, leading to formation of a labile triazoline adduct **IIa** which is then converted to single aziridines by thermal release of molecular nitrogen.^{12b} (Scheme 2) The present study using deactivated azides provides evidence for the applicability of 1,3-DC to the synthesis of cyclic azoles with **MePA** or **MBH** as the dipolarophile but not **MeC**, **MeP** or **MeB**. According to Frontier Molecular Orbital (FMO) theory, the 1,3-DC reactivity between an electron-poor azide and an electron-rich dipolarophile involves interaction between the LUMO on the 1,3-dipole and the HOMO on the dipolarophile.²¹

To provide a quick method that might confirm this, we performed time-inexpensive theoretical calculations focusing on the HOMO and LUMO energies of the reactants. Calculations are carried out by using the set of programs in Spartan '02 Windows.²² The RHF/6-31G* level of theory was used to obtain structures and energies of the ground-state reactants 1-5, and MePA, MBH, MeC, MeP and MeB. A pseudopotential associated with the 6-31G* basis set is used to replace the all-electron basis set for heavy selenium atom of compound 4. The calculated HOMO and LUMO energies presented in Table 1 agree reasonably with those obtained by spectroscopic techniques.²¹ It is clear from the data that the HOMO and LUMO energy trends of the azides 1-5 are almost the same; the small energy differences observed among the different azides would be accounted for by the nature of the heteroaryl moiety. Examining the sequence of the FMO energies we can argue that the 1,3-DC reactions with the smallest energy gap are those dominated by the interaction of the LUMOs of the azides 1-5 and the HOMOs of the dipolarophiles MePA and MBH. None of the other combinations are likely to provide more favoured 1,3-DC interaction because of their larger energy gaps.

Conclusions

The 1,3-DC reactions between five azido(2-heteroaryl)methanones and various activated dipolarophiles were studied. The reactivity towards different alkenes and alkynes of these carbonylazides varied considerably with respect to that of the aryl and heteroaryl azides. It is noteworthy that only the dipolarophiles particularly activated or strained, like methyl (E)-3pyrrolidinoprop-2-enoate and 5-methylenebicyclo[2.2.1]hept-2ene, were found to be suitable for the synthesis of cyclic azoles. In these instances, the 1,3-adducts initially formed were thermally labile or unstable, causing them to undergo further reaction either by displacement of pyrrolidine or by loss of molecular nitrogen. The carbonyl moiety of the azido-(2-heteroaryl)methanones imposes practical limitations on the choice of dipolarophile; however, the 1,3-DC of **1–5** with 5methylenebicyclo[2.2.1]hept-2-ene constitutes one of the most important approaches for the synthesis of carbonyl aziridines. Simple FMO calculations performed by self-consistent field (SCF) method could be, at first hand, useful for predicting the more favoured interactions of the carbonyl azides with different dipolarophiles.

Experimental

Materials

2-Furoyl chloride, thiophene-2-carbonyl chloride, thionyl dichloride, buthyl-lithium, ethyl chloroformate and sodium azide were purchased from Aldrich Chimica Italiana and used as received. Thieno[3,2-b]thiophene-2-carboxylic acid was prepared from the corresponding 2-lithio-derivative and carbon dioxide according to the literature procedure.²³ Methyl (*E*)-3-(pyrrolidinoprop-2-enoate was prepared following the procedure described by Huisgen.²⁴ The heteroaroyl azides 1–5 were prepared from the appropriate carboxylic acids *via* mixed carboxylic-carbonic anhydride or carbonyl chloride and sodium azide following the procedure described.^{18,25} Chromatographic filtration was carried out on 'Florisil' BDH, 60–100 mesh.

Caution. Organic azides are potentially explosive! This category of compounds has been subjected to risk evaluation.²⁶ Explosions may occur when handling organic azides, although we experienced no problems in handling basic solutions of sodium azide or solid organic azides, which can be stored indefinitely at -18 °C.

Instrumentation

Melting points were determined on a Kofler hot-stage apparatus and are uncorrected. IR spectra were recorded in film on a Perkin-Elmer Spectrum 2000 FT–IR spectrometer. ¹H- and ¹³C-NMR spectra were recorded on a Varian Gemini 200 (200 and 50.3 MHz, respectively) or 300 (300 and 75.4 MHz, respectively) for solutions in CDCl₃ using TMS and CHCl₃ as internal standards. Chemical shifts are in δ -units and *J*-values are given in Hz. Mass spectra were recorded on VG7070E instruments using electron impact ionization (70 eV). GS–MS analyses were performed using a Hewlett-Packard G1800A instrument. Calculations were performed using the program Spartan '02 Windows,²² running on an AMD K7 processor at 1333 MHz.

Synthetic procedure for the azido(thieno[3,2-*b*]thiophen-2-yl)methanone 5

To solutions containing 0.05 mol of the thieno[3,2-*b*]thiophene-2-carboxylic acid (9.2 g) in 75 cm³ of anhydrous acetone at 0 °C was added 0.059 mol (5.95 g, 8.35 cm³) of triethylamine in acetone (23 cm³) and 0.066 mol (7.2 g) of ethyl chloroformate in acetone (23 cm³). The resulting mixtures were stirred at 0 °C for 45 min and then a solution containing 0.085 mol (5.5 g) of sodium azide in 19 cm³ of water was added dropwise over a period of 1 h, after which the solution was warmed to room temperature and stirred for another 30 min. The suspension was poured into cold brine and the resulting aqueous mixture was extracted twice with diethyl ether. The combined organic layers were washed with water and then dried over Na_2SO_4 . The solvent was eliminated under vacuum and the residue was chromatographed on 'Florisil' (100–200 U.S. mesh, BDH) column using petroleum ether (distillation range 30–60 °C) as the eluent.

The resulting azido(thieno[3,2-*b*]thiophen-2-yl)methanone **5** was characterized by ¹H-NMR, ¹³C-NMR, IR and high-resolution mass spectroscopy. Compound **5** (87%), mp 98–99 °C; v_{max}/cm^{-1} 2145 (N₃), 1680 (CO); $\delta_{\rm H}$ (200 MHz; CDCl₃) 8.04 (1H, d, *J* 0.8, H-3), 7.66 (1H, d, *J* 5.3, H-5) and 7.30 (1H, q, *J* 0.8 and 5.3, H-6); $\delta_{\rm C}$ (50.3 MHz; CDCl₃) 167.5, 146.1, 139.6, 136.2, 133.8 (d, *J* 187.0), 127.1 (d, *J* 176.2) and 120.3 (d, *J* 175.2); *m/z* 209 (M⁺, 100%), 181 (M - N₂, 40.8), 167 (49.6), 153 (95.5), 139 (20.4), 126 (39.1), 109 (53.8), 95 (27.9), 69 (59.5) and 45 (40.9); Found: M⁺, 208.9717. C₇H₃N₃OS₂ requires *M*, 208.9717.

Reactions of azido(2-heteroaryl)methanones 1–5 with methyl (*E*)-3-pyrrolidinoprop-2-enoate at 25 °C. General procedure

A solution $(2 \times 10^{-3} : 2 \times 10^{-3} \text{ mol}; \text{ exact equimolar ratio in } 1.0$ cm³ of CDCl₃) of a heteroaroyl azide (1, 0.274; 2, 0.306; 3, 0.334; 4, 0.400 5, 0.418 g) and MePA (0.310 g) was allowed to react in a screw-cap tube for the appropriate time (20-25 days). The time evolution of the reaction was monitored by analysing small aliquots from the solutions using ¹H NMR spectroscopy. In all cases the intensities of peaks associated with the starting azide 1-5 decreased and peaks appeared indicating the formation of a mixture of methyl 1H-1,2,3-triazole-4-carboxylate 6 and the (2-heteroaryl)(pyrrolidino)methanones 1a-5a (see text). After the disappearance of starting azide, the resulting suspensions were treated with 5.0 cm³ of dry *n*-hexanechloroform (4:1, v/v) mixture and stirred for an additional 10 h. The solid product was then filtered off under vacuum and the residue was washed with cold hexane. The solid was characterized as almost pure methyl 1,2,3-triazole-4-carboxylate 6.

The mother liquor contained the corresponding (2-heteroaryl)(pyrrolidino)methanone **1a–5a**, as confirmed by ¹H-NMR spectroscopy. This solution was concentrated by elimination of the solvent under vacuum, and the oily residue was filtered under nitrogen pressure on a 'Florisil' column using dry hexane and then characterized by ¹H-NMR, ¹³C-NMR, IR and high-resolution mass spectroscopy.

(2-Furyl)(pyrrolidino)methanone 1a. (88%), Mp 70–73 °C; v_{max} /cm⁻¹ 2974, 2878, 1616 (CO), 1481, 1423 and 755; $\delta_{\rm H}$ (300 MHz; CDCl₃) 7.55 (1H, q, J 0.8 and 1.7, H-5), 7.16 (1H, q, J 0.8 and 3.5, H-3), 6.54 (1H, q, J 1.7 and 3.5, H-4), 3.72 (4H, bs, H- α), and 1.99 (4H, bs, H- β); $\delta_{\rm C}$ (75.4 MHz; CDCl₃) 161.6, 149.1, 144.4 (d, J 203.7), 116.3 (d, J 177.7), 111.5 (d, J 177.2), 48.1 (t, J 142.8), 47.4 (t, J 142.8), 26.6 (t, J 132.3) and 23.7 (t, J 132.7); m/z 165 (M⁺, 33.4 %), 137 (M – 28, 4.8), 110 (6.2), 95 (100), 70 (6.3) and 55 (4.7); Found: M⁺, 165.0790. C₉H₁₁NO₂ requires *M*, 165.0790.

(2-Thienyl)(pyrrolidino)methanone 2a. (87%), Mp 66–68 °C; v_{max}/cm^{-1} 2974, 2878, 1616 (CO), 1430 and 725; $\delta_{\rm H}$ (200 MHz; CDCl₃) 7.58 (1H, q, *J* 1.2 and 3.8, H-3), 7.50 (1H, q, *J* 1.2 and 5.05, H-5), 7.08 (1H, q, *J* 3.8 and 5.05, H-4), 3.53 (4H, bs, H- α) and 2.00 (4H, bs, H- β); $\delta_{\rm C}$ (50.3 MHz; CDCl₃) 160.3, 139.3, 129.0 (d, *J* 185.9), 128.5 (d, *J* 168.8), 126.5 (d, *J* 168.2), 47.8 (t, *J* 142.8), 46.4 (t, *J* 142.8), 25.6 (t, *J* 132.8) and 23.0 (t, *J* 132.8); *m*/*z* 181 (M⁺, 43.7%), 153 (M – 28, 7.7), 111 (100), 83 (6.7) and 39 (19.0); Found: M⁺, 181.0561. C₉H₁₁NOS requires *M*, 181.0561.

(5-Methyl-2-thienyl)(pyrrolidino)methanone 3a. (85%), Mp 59–61 °C; v_{max} /cm⁻¹ 3098, 2970, 2876, 1590 (CO), 1457, 812, and 739; $\delta_{\rm H}$ (300 MHz; CDCl₃) 7.37 (1H, d, *J* 3.7, H-3), 6.75 (1H, q, *J* 1.0 and 3.7, H-4), 3.74 (4H, bs, H- α), 2.50 (3H, d,

J 1.0, Me) and 1.95 (4H, bs, H- β); $\delta_{\rm C}$ (50.3 MHz; CDCl₃) 161.4, 145.4, 139.1, 130.7 (d, J 167.0), 125.8 (d, J 166.5), 49.1 (t, J 142.8), 47.7 (t, J 142.8), 26.7 (t, J 132.8), 24.1 (t, J 132.8) and 15.5 (q, J 129.6); *m*/z 195 (M⁺, 17.8%), 125 (M - 70, 24.5), 97 (59.3), 96 (100), 68 (15.7), 40 (35.8) and 39 (12.0); Found: M⁺, 195.0717. C₁₀H₁₃NOS requires *M*, 195.0718.

(Selenophen-2-yl)(pyrrolidino)methanone 4a. (85%), Mp 64– 66 °C; ν_{max}/cm^{-1} 2969, 2871, 1592 (CO), 1437 and 707; $\delta_{\rm H}$ (200 MHz; CDCl₃) 8.20 (1H, q, *J* 1.1 and 5.6, H-5), 7.73 (1H, q, *J* 1.1 and 4.0, H-3), 7.35 (1H, q, *J* 4.0 and 5.6, H-4), 3.74 (4H, bs, H- α) and 1.99 (4H, bs, H- β); $\delta_{\rm C}$ (50.3 MHz; CDCl₃) 163.9, 139.4, 136.4 (d, *J* 186.5), 132.1 (d, *J* 166.1), 130.3 (d, *J* 167.5), 49.7 (t, *J* 143.4), 48.1 (t, *J* 143.4), 27.0 (t, *J* 133.3) and 24.5 (t, *J* 133.3); *mlz* 229 (M⁺, 45.0%), 159 (M – 70, 100), 131 (13.0), 70 (11.7), 56 (14.2) and 39 (46.6); Found: M⁺, 229.0006.

Methyl 1*H***-1,2,3-triazole-4-carboxylate 6.** (90%), Mp 143–45 °C (lit.,¹⁴ 145 °C); v_{max}/cm^{-1} 3137, 2941, 1732 (CO) and 778; $\delta_{\rm H}$ (200 MHz; acetone-D₆) 8.34 (1H, s, H-5), 3.88 (3H, s, Me); $\delta_{\rm C}$ (50.3 MHz; acetone-D₆) 162.2, 137.3, 133.5 (d, *J* 197.2) and 52.5 (q, *J* 147.4); *m*/*z* 127 (M⁺, 10.9%), 96 (M – OMe, 100), 68 (13.9), 59 (10.2) and 40 (36.0); Found: M⁺, 127.0382. C₄H₅N₃O₂ requires *M*, 127.0382.

Reactions of heteroaroyl azides 1–5 with 5-methylenebicyclo-[2.2.1]hept-2-ene at 25 °C. General procedure

A solution $(2 \times 10^{-3} : 2 \times 10^{-3} \text{ mol}; \text{ exact molar ratio in } 1.0 \text{ cm}^3$ of CDCl₃) of a heteroaroyl azide (1, 0.274; 2, 0.306; 3, 0.334; 4, 0.400; 5, 0.418 g) and 5-methylenebicyclo[2.2.1]hept-2-ene (0.212 g) was allowed to react in a screw-cap tube for the appropriate time (17–25 days). Over time, small aliquots of the solutions were analysed by ¹H-NMR spectroscopy, showing in all cases the decrease of the starting azide and the formation of a fundamental product. After the appropriate time the solution was concentrated by elimination of the solvent under vacuum, and the oily residue was purified, under medium nitrogen pressure, on a 'Florisil' column using dry hexane with increasing amounts of diethyl ether (up to 100%) as eluent. The following (2-heteroaryl)(6-methylene-3-azatricyclo[3.2.1.0^{2,4}]-octan-3-yl)methanones **1b–5b** were characterized by ¹H-NMR, ¹³C-NMR, IR and high-resolution mass spectroscopy.

(2-Furyl)(6-methylene-3-azatricyclo[3.2.1.0^{2,4}]octan-3-yl)-

methanones 1b. (75%), Oil; v_{max}/cm^{-1} 3098, 2978, 1663 (CO), 1319, 1167, 884 and 762; $\delta_{\rm H}$ (200 MHz; CDCl₃) 7.55 (1H, q, *J* 0.9 and 1.7, H-5), 7.13 (1H, q, *J* 0.9 and 3.5, H-3), 6.51 (1H, q, *J* 1.7 and 3.5, H-4), 5.01 (1H, s), 4.79 (1H, s), 3.06 (1H, s), 2.96 (1H, d, *J* 5.3), 2.87 (1H, d, *J* 5.3), 2.72 (1H, s), 2.21 (1H, 'd', *J* 15.8), 1.98 (1H, 'd', *J* 15.8), 1.58 (1H, 'd', *J* 10.3) and 1.07 (1H, 'd', *J* 10.3); $\delta_{\rm C}$ (50.3 MHz; CDCl₃) 167.0, 149.6, 148.6, 145.9 ('d', *J* 203.7), 116.7 ('d', *J* 179.2), 112.2 ('d', *J* 177.3), 106.9 ('t', *J* 157.5), 45.8 ('d', *J* 149.2), 39.7 ('d', *J* 182.2), 39.0 ('d', *J* 188.3), 37.2 ('d', *J* 150.5), 34.5 ('t', *J* 130.3) and 29.2 ('t', *J* 135.8); *m/z* 215 (M⁺, 13.9%), 186 (M – 29, 7.6), 104 (59.5), 95 (100), 91 (16.9), 84 (10.4), 77 (14.6), 65 (6.6), 53 (7.3) and 39 (42.7); Found: M⁺, 215.0945. C₁₃H₁₃NO₂ requires *M*, 215.0946. (2-Thienyl)(6-methylene-3-azatricyclo[3.2.1.0^{2,4}]octan-3-yl)methanones 2b. (80%), Oil; v_{max}/cm^{-1} 3091, 2974, 1653 (CO), 1414, 1256, 839 and 720; $\delta_{\rm H}$ (200 MHz; CDCl₃) 7.73 (1H, q, *J* 1.2 and 3.7, H-3), 7.52 (1H, q, *J* 1.2 and 5.0, H-5), 7.10 (1H, q, *J* 3.7 and 5.0, H-4), 5.00 (1H, s), 4.79 (1H, s), 3.05 (1H, s), 2.97 (1H, d, *J* 5.3), 2.88 (1H, d, *J* 5.3), 2.71 (1H, s), 2.20 (1H, 'd', *J* 15.8), 1.98 (1H, 'd', *J* 15.8), 1.61 (1H, 'd', *J* 10.2) and 1.07 (1H, 'd', *J* 10.2); $\delta_{\rm C}$ (50.3 MHz; CDCl₃) 170.5, 149.2, 138.3, 131.6 ('d', *J* 181.1), 131.4 ('d', *J* 169.0), 127.8 ('d', *J* 168.3), 106.5 ('t', *J* 156.6), 45.5 ('d', *J* 149.7), 39.9 ('d', *J* 177.6), 39.2 ('d', *J* 186.6), 36.7 ('d', *J* 148.5), 34.1 ('t', *J* 133.0) and 28.8 ('t', *J* 135.7); *m/z* 231 (M⁺, 7.9%), 202 (M – 29, 5.6), 153 (9.5), 111 (100), 104 (11.5), 91 (7.6), 83 (10.4), 77 (6.4), 70 (7.4), 53 (6.8), 45 (14.0) and 39 (47.5); Found: C, 67.5; H, 5.7; N, 6.1; S, 13.9.

(5-Methyl-2-thienyl)(6-methylene-3-azatricyclo[3.2.1.0²⁴]octan-3-yl)methanones 3b. (75%), Oil; v_{max} /cm⁻¹ 2967, 2921, 1646 (CO), 1457, 1260, 884 and 702; $\delta_{\rm H}$ (300 MHz; CDCl₃) 7.55 (1H, d, J 3.7, H-3), 6.75 (1H, dq, J 1.0 and 3.7, H-4), 5.01 (1H, s), 4.79 (1H, s), 3.03 (1H, s), 2.93 (1H, d, J 5.2), 2.84 (1H, d, J 5.2), 2.69 (1H, bs), 2.51 (3H, s, J 1.0), 2.18 (1H, 'd', J 15.6), 1.97 (1H, 'd', J 15.6), 1.60 (1H, 'd', J 10.3) and 1.05 (1H, 'd', J 10.3); $\delta_{\rm C}$ (75.4 MHz; CDCl₃) 170.7, 149.3, 147.2, 135.6, 135.1, 132.0 (J 168.0), 126.3 (J 156.8), 106.4 ('t', J 155.5), 45.5 (J 149.2), 39.7 (J 181.8), 39.1 (J 195.0), 36.7 (J 145.5), 34.1 ('t', J 131.3), 28.8 ('t', J 139.2) and 15.8 (q, J 129.2); *m*/*z* 245 (M⁺, 5.1%), 216 (M - 29, 9.4), 125 (100), 111 (7.9), 104 (9.0), 96 (5.9), 91 (2.9), 84 (3.4), 77 (13.6), 69 (6.2), 66 (7.4), 53 (28.4) and 39 (17.0); Found: C, 68.6; H, 6.1; S, 13.0. C₁₄H₁₅NOS requires C, 68.5; H, 6.2; S, 13.1.

(Selenophen-2-yl)(6-methylene-3-azatricyclo[3.2.1.0^{2,4}]octan-3-yl)methanones 4b. (73%), Oil; v_{max}/cm^{-1} 3065, 2975, 1645 (CO), 1427, 1298, 886 and 700; $\delta_{\rm H}$ (200 MHz; CDCl₃) 8.24 (1H, q, J 1.1 and 5.5, H-5), 7.94 (1H, q, J 1.1 and 3.9, H-3), 6.51 (1H, q, J 3.9 and 5.5, H-4), 4.98 (1H, s), 4.78 (1H, s), 3.03 (1H, s), 2.96 (1H, d, J 5.3), 2.87 (1H, d, J 5.3), 2.69 (1H, s), 2.21 (1H, 'd', J 15.7), 1.96 (1H, 'd', J 15.7), 1.60 (1H, 'd', J 10.3) and 1.07 (1H, 'd', J 10.3); $\delta_{\rm C}$ (50.3 MHz; CDCl₃) 171.8, 148.9, 137.5 ('d', J 186.7), 136.5, 133.6 ('d', J 166.8), 130.2 ('d', J 167.0), 106.4 ('t', J 157.3), 45.3 ('d', J 148.7), 39.9 ('d', J 181.1), 39.2 ('d', J 185.2), 36.6 ('d', J 148.9), 33.9 ('t', J 131.3) and 28.6 ('t', J 137.9); m/z 279 (M⁺, 12.3%), 250 (M – 29, 3.6), 159 (100), 131 (10.8), 104 (32.8), 91 (15.0), 78 (12.4), 77 (28.0), 65 (14.1), 53 (19.5), 41 (18.1) and 39 (80.6); Found: M⁺, 279.0162. C₁₃H₁₃NOSe requires *M*, 279.0162.

(6-Methylene-3-azatricyclo[3.2.1.0^{2,4}]octan-3-yl)(thieno-

[3,2-*b***]thiophen-2-yl)methanone 5b.** (85%), Resinous, dark compound; v_{max}/cm^{-1} 3083, 2978, 1647 (CO), 1501, 1363, 1333, 885 and 712; $\delta_{\rm H}$ (200 MHz; CDCl₃) 7.91 (1H, s, H-3), 7.56 (1H, d, *J* 5.3, H-5), 6.51 (1H, d, *J* 5.3, H-6), 5.00 (1H, s), 4.79 (1H, s), 3.08 (1H, s), 3.01 (1H, d, *J* 5.5), 2.92 (1H, d, *J* 5.5), 2.73 (1H, s), 2.21 (1H, 'd', *J* 15.8), 1.98 (1H, 'd', *J* 15.8), 1.61 (1H, 'd', *J* 10.3); $\delta_{\rm C}$ (50.3 MHz; CDCl₃) 171.0, 149.0, 140.0, 136.5, 134.3, 131.5 ('d', *J* 186.5), 123.7 (d, *J* 172.3), 119.7 ('d', *J* 174.2), 106.5 ('t', *J* 156.7), 45.4 ('d', *J* 146.9), 40.0 ('d', *J* 180.4), 39.4 ('d', *J* 185.0), 36.7 ('d', *J* 150.8), 34.0 ('t', *J* 129.7) and 28.7 ('t', *J* 137.7); *m/z* 287 (M⁺, 11.3%), 258 (M – 29, 6.0), 167 (100), 139 (14.7), 104 (8.9), 95 (6.0), 93 (6.3), 79 (11.8), 77 (10.0), 69 (6.6), 53 (5.5) and 39 (7.8); Found: M⁺, 287.0439. C₁₅H₁₃NOS₂ requires *M*, 287.0439.

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