Unexpected formation of β-lactams and penem isosteres from mesoionics: sequential ring-opening–rearrangement of [3 + 2] cycloadducts

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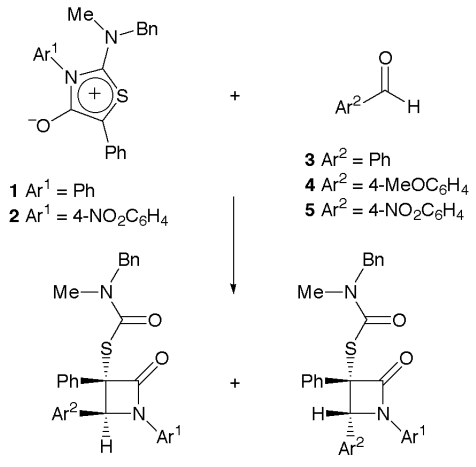
A novel and simple method has been developed to obtain penem analogs with biologically interesting functionalities, which combines aromatic aldehydes with thioisomünchnones, a readily available class of mesoionic heterocycles.

Mesoionics, five-membered aromatic heterocycles that cannot be represented by Lewis forms not involving charge separation, constitute a large and heterogeneous family of masked dipoles.[1] Their [3 + 2] cycloadditions have proven to be a fertile methodology, often encompassing the preparation of naturally-occurring products.[2] The versatility of these synthons can be exemplified in the case of 1,3-thiazolium-4-olates (thioisomünchnones) which have been converted into six-,[3] five-[4] and three-membered[5] functionalized rings by reaction with different dipolarophiles.

In contrast to what was expected, the reactions of 2-aminothioisomünchnones, such as **1** and **2**, with aromatic aldehydes yielded β-lactams, which have hitherto been unknown for this type of mesoionics. These condensations were conducted in anhydrous benzene at reflux and gave rise to a monocyclic β-lactam skeleton in moderate to good yields and without by-products (Scheme 1, Table 1). Besides the crucial importance of β-lactams as antimicrobial agents,[6] monocyclic azetidin-2-ones are potential inhibitors of elastase enzymes.[7] An additional feature of the structures arising from the above-mentioned coupling is the presence of a sulfur-containing side chain, the structural motif encountered in other penem antibiotics such as penicillins and cephalosporins.[8]



Scheme 1

Table 1 Synthesis of β-lactams **6**–**11**

Mesoionic	Aldehyde	*t*/h	Yield (%)[a]		*cis*:*trans*[b]
1	**3**	4	**6a** (41)	**6b** (34)	65:35
1	**4**	10	**7a** (54)	**7b** (20)	70:30
1	**5**	3	**8a** (—)[c]	**8b** (30)	59:41
2	**3**	1	**9a** (35)	**9b** (25)	57:43
2	**4**	6	**10a** (29)	**10b** (20)	60:40
2	**5**	1	**11a** (42)	**11b** (25)	58:42

[a] Yields of the pure isolated *cis* and *trans* isomers. [b] The *cis*:*trans* ratio was determined by ^{1}H NMR (400 MHz). [c] Not isolated.

In every case, β-lactams were formed as a mixture of *cis*- and *trans*-isomers (with respect to the orientation of aryl substituents at C-3 and C-4) and the *cis*:*trans* ratio was established by ^{1}H NMR of crude samples.† Individual diastereomers could be separated either by fractional crystallization or preparative chromatography. Furthermore, the structure of compound *cis*-**7a** was unequivocally confirmed by single-crystal X-ray diffraction analysis (Fig. 1).‡

A plausible rationale to account for the formation of β-lactams is shown in Scheme 2. The tandem process involves first a [3 + 2] cycloaddition in which thioisomünchnone plays the role of the dipole to produce a transient cycloadduct which undergoes a spontaneous C–N bond cleavage, followed by a rearrangement under the reaction conditions. The first step may also be rationalized assuming the stereoelectronic effect provided by the lone pair of the *N*,*N*-dialkylamino nitrogen *via* an intramolecular elimination. The pyramidal configuration of this nitrogen may bring the lone-pair orbital into an *anti* disposition with the leaving group, which competes favorably with the alternative carbon–sulfur scission. The resulting zwitterionic intermediate would largely be stabilized by resonance effects of the substituents on the charged atoms. The

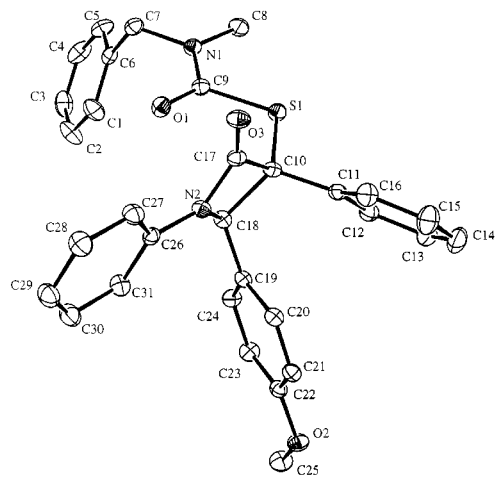
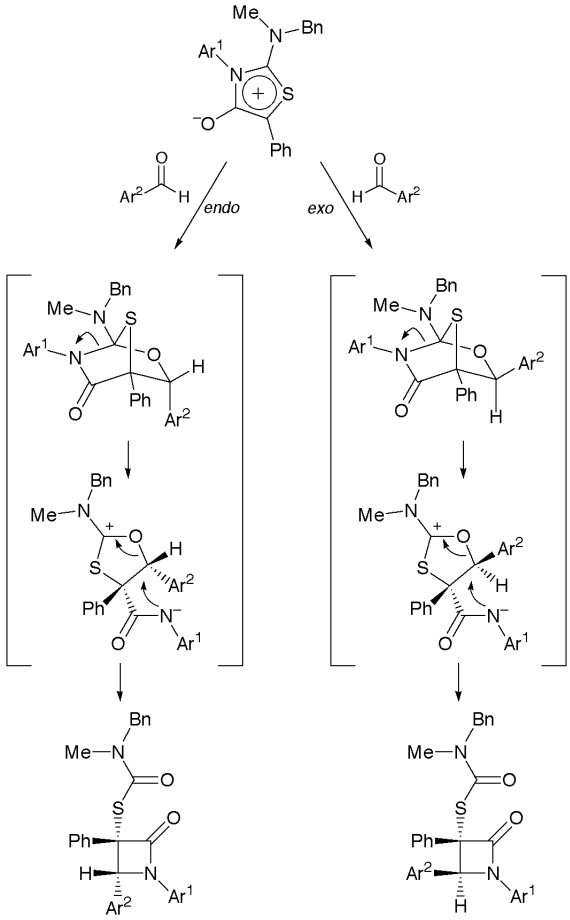


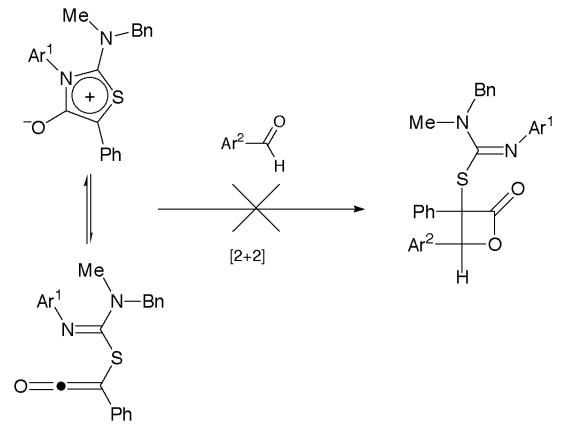
Fig. 1 Solid-state structure of compound **7a**.



Scheme 2

formation of *cis*- and *trans*-diastereomers results from *exo* and *endo* approaches to the mesoionic ring.

It is fair to say that another mesoionic system, 1,3-oxazolium-5-olate, denoted colloquially as münchnone and containing an azomethine ylide dipole, also affords β-lactams by reaction with imines.[9] This formal [2 + 2] cycloaddition has been rationalized assuming that münchnones exist in equilibrium with their ketene-type valence tautomers, which would ultimately be the reactive species. However, there is no spectroscopic evidence of such tautomers, albeit this might be accounted for by a weak equilibrium in solution or a very short lifetime of the latter species. Since β-lactams have now been obtained from thioisomünchnones, for which putative valence tautomers would otherwise lead to a different four-membered ring (Scheme 3), the hypothesis of ketene reagents for münchnone cycloadditions should be revisited. In fact, it is also plausible for a stepwise reaction mechanism combining a [3 + 2] cycloaddition and rearrangement to afford the desired β-lactams. Even though further studies are required, our results represent a step in a direction that has been overlooked. It thus seems likely that münchnones do not behave like ketenes, a belief held for almost three decades.



Scheme 3

To sum up, a concise and novel approach to β-lactams has been developed. The strategy may provide an exciting and growing interest in mechanistic and synthetic chemistry with mesoionic systems.

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Notes and references

† *Selected data* for **6a**: recrystallized from EtOH, mp 147 °C; δ_H(400 MHz, $CDCl_3$) 7.90–6.80 (m, Ar), 5.89 (s, H-4), 4.54 (m, Ph-CH_2), 2.89 (br s, N-CH_3); δ_C(100 MHz, $CDCl_3$) 166.3 (S-CO-N), 164.6 (C-2), 137.7, 136.2, 134.5, 133.5, 129.0, 128.7, 128.6, 128.3, 128.2, 128.0, 127.9, 127.6, 127.2, 124.1, 117.8 (Ar), 69.0 (C-4), 68.3 (C-3), 53.9, 51.9 (Ph-CH_2, two resonances due to restricted rotation), 34.3 (N-CH_3) (Calc. for $C_{30}H_{26}N_2O_2S$: C, 75.29, H, 5.48, N, 5.85, S, 6.70; found: C, 75.18, H, 5.51, N, 5.89, S, 6.65%). For **6b**: recrystallized from CH_2Cl_2–EtOAc–Et_2O, mp 203 °C; δ_H(400 MHz, $CDCl_3$) 7.91–6.78 (m, Ar), 5.83 (s, H-4), 4.13 (d, Ph-CH_2), 2.55 (s, N-CH_3); δ_C(100 MHz, $CDCl_3$) 164.1 (S-CO-N), 163.5 (C-2), 137.6, 137.2, 135.7, 133.7, 129.1, 129.0, 128.4, 128.3, 128.0, 127.7, 127.4, 126.9, 124.1, 117.5 (Ar), 69.7 (C-4), 66.6 (C-3), 52.6 (Ph-CH_2), 34.1 (N-CH_3) (Calc. for $C_{30}H_{26}N_2O_2S$: C, 75.29, H, 5.48, N, 5.85, S, 6.70; found: C, 75.02, H, 5.44, N, 5.86, S, 6.82%).

‡ *Crystal data* for *cis*-**7a**: $C_{31}H_{28}N_2O_3S$, M_r = 508.6, T = 150(2) K, monoclinic, space group $P2_1/c$, a = 11.3385(3), b = 22.6660(7), c = 10.2516(4) Å, β = 92.1722(18)°, V = 2632.75(15) Å^3, ρ_{calc} = 1.283 g cm^{-3}, μ = 0.158 mm^{-1}, Z = 4, reflections collected: 24655, independent reflections: 5299 (R_{int} = 0.0633), final R indices [$I > 2\sigma(I)$]: $R1$ = 0.0443, $wR2$ = 0.1031, R indices (all data): $R1$ = 0.0675, $wR2$ = 0.1171. CCDC 182/1327. See http://www.rsc.org/suppdata/cc/1999/1589 for crystallographic data in .cif format.

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