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A 1,3-dipolar cycloaddition–annulation protocol for the expedient regio-, stereo- and product-selective construction of novel hybrid heterocycles comprising seven rings and seven contiguous stereocentres

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ABSTRACT

An expedient regio-, stereo- and product-selective synthesis of novel hybrid heterocyclic systems comprising [1,2-*c*]oxazolidine, pyrrolidine and piperidine units, in good to excellent yields, has been developed via three-component 1,3-dipolar cycloaddition/annulation domino reactions and concomitant trifluoroacetic acid mediated condensative annulation with paraformaldehyde. These novel structurally complex heterocyclic hybrids, accessed by a two-step protocol, possess seven rings and seven contiguous stereocentres.

A major challenge often encountered in modern drug discovery programmes is the design of highly efficient chemical reaction sequences for accessing structurally complex and diverse compounds, possessing important biological activities, in a minimum number of synthetic steps.[1] One such protocol to realize these goals involves the use of multi-component reactions (MCRs),[2] that enable the creation of several bonds in a single operation and offer remarkable advantages such as convergence, operational simplicity, facile automation, reduction in the number of work-ups and minimization of extraction and purification processes and waste generation rendering the transformations more environmentally friendly. MCRs, besides facilitating expedient creation of chemical libraries of structurally diverse drug-like compounds,[3] play a key role in combinatorial[4] and diversity-oriented synthesis.[5]

Among MCRs, three-component reactions involving the [3+2]-cycloaddition of azomethine ylides to olefinic dipolarophiles[6,7] constitute a facile approach for the efficient assembly of five-membered heterocyclic rings of biological importance. Grigg et al.[8,9] synthesized structurally diverse spirocyclic and bridgehead nitrogen heterocycles through inter- and intramolecular cycloaddition of diverse dipolarophiles with in situ generated azomethine ylides via decarboxylative condensation of carbonyl compounds with secondary amines. Fokas et al.[10] synthesized a huge combinatorial library of diverse spiropyrrolidines, whilst Nair et al.[11] reported a novel reaction of sarcosine with 1,2-cyclic diones leading to spiropyrrolidines. Pyrrolidines are particularly important because of their occurrence in a large number of natural products[12] and their interesting biological properties.[13] Molecules with a piperidine sub-structure[14] display a wide array of biological activity, besides being useful synthons for the construction of naturally occurring alkaloids.[15] In this context, bisarylidenepiperidin-4-ones were used as the dipolarophilic components in many cycloaddition reactions[16] to obtain spiroheterocyclic hybrids comprising piperidine, pyrrolidine and other heterocyclic units.

Our research group has largely been involved in the synthesis of novel spiroheterocyclic hybrids through cycloaddition methodology.[17] In particular, we have investigated the synthesis of hexacyclic ring systems via the 1,3-dipolar cycloaddition reactions of bisarylidenepiperidin-4-ones **3** as dipolarophiles and screened them against acetylchlolinesterase enzyme inhibitory activity, which has brought to light various anti-Alzheimer leads.[18] This prompted the present investigation to explore the synthetic utility of these dipolarophiles in the assembly of biologically relevant more complex heterocyclic hybrids and we report the results in this Letter.

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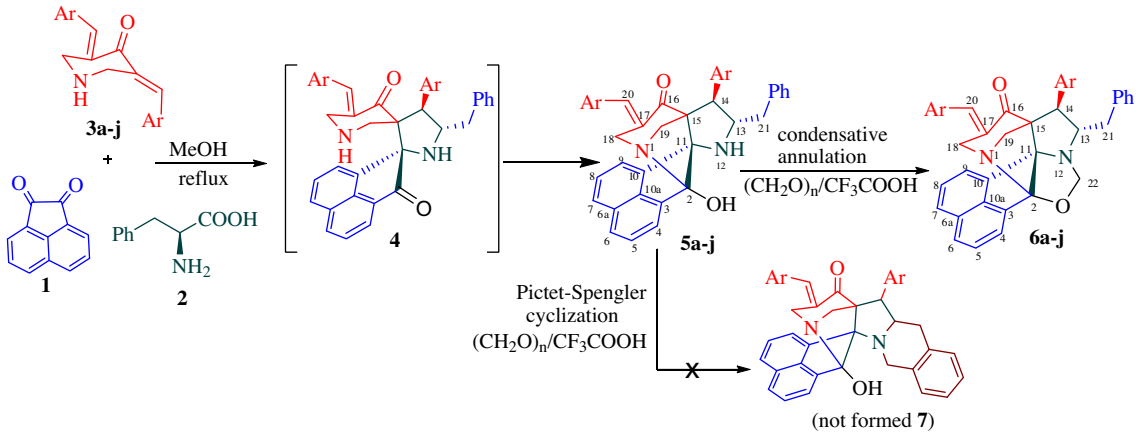

Scheme 1. Stereoselective synthesis of hexa- and heptacyclic hybrid heterocycles **5** and **6**.

For the first time, we have employed the 1,3-dipolar cycloaddition reaction of bisarylidenepiperidin-4-ones with the hitherto unexplored azomethine ylide generated in situ from acenaphthenequinone and L-phenylalanine, which furnished novel hexacyclic ring systems **5** (Scheme 1). The choice of L-phenylalanine for reaction with acenapthequinone, which has not been used so far for the preparation of azomethine ylides, was triggered by the consideration that the initially formed hexacyclic ring system **5** can participate in two competitive annulation pathways on reaction with formaldehyde in the presence of an acid catalyst: (i) formation of oxazolidines **6** comprising [1,2-*c*]oxazolidine, pyrrolidine and piperidine moieties by condensative annulation and (ii) Pictet–Spengler annulation involving the phenyl ring of **5** originating from phenylalanine (Scheme 1) furnishing novel heterocycles **7**. Of these possibilities, the reaction of **5** with paraformaldehyde proceeded in a highly product-selective manner furnishing solely the heptacyclic ring system **6**.

In the present study, the hexacyclic compounds **5a–j** were obtained in good to excellent yields (83–97%) from the 1,3-dipolar cycloaddition reaction of the azomethine ylide generated in situ from equimolar amounts of acenapthenequinone (**1**) and L-phenylalanine (**2**), with a series of bisbenzylidenepiperidin-4-ones **3** in methanol under heating at reflux. Initially, choosing a model three-component reaction of an equimolar mixture of 3,5-dibenzylidenepiperidin-4-one (**3a**), acenapthenequinone (**1**) and L-phenylalanine (**2**), a solvent-screen for this domino protocol was investigated employing methanol, ethanol, acetonitrile, 1,4-dioxane and 1,4-dioxane-methanol (1:1 v/v) mixture (Table 1) under reflux (on a water bath). After completion of the reaction (TLC), the product **5a** was obtained in the pure state by purification through column chromatography. The best yield of **5a** was obtained in methanol under reflux in a short reaction time of two hours (Table 1, entry 1). Hence, all the subsequent reactions were carried out by heating to reflux an equimolar mixture of the reactants in methanol on a water bath for two hours.

Table 1
Solvent-screen for the synthesis of heterocyclic hybrid **5a**

Entry	Solvent	Reaction time (h)	Yield[a,b] (%)
1	MeOH	2.0	97
2	EtOH	4.0	65
3	MeCN	5.0	55
4	1,4-Dioxane	3.5	69
5	1,4-Dioxane–MeOH (1:1 v/v)	3.0	80

[a] Isolated yield after purification by column chromatography.
[b] Reaction performed under heating at reflux.

The structures of hexacyclic hybrid heterocycles **5** were elucidated by elemental analysis and NMR spectroscopic techniques.[19] In the ^{1}H NMR spectrum of **5a**, the arylmethylidene proton appeared as a singlet at δ 6.30, unusually appearing upfield, being explicable by its presence in the shielding zone of the acenaphthene ring system. This proton showed H,H-COSY correlations with the 18-CH_2 hydrogens occurring at δ 3.40 (J = 17.6 Hz) and δ 3.68 (J = 17.6, 2.2 Hz), presumably due to allylic coupling. The other methylene hydrogens of the piperidone ring (19-CH_2) gave a doublet at δ 3.01 (J = 12.4 Hz) and a multiplet at δ 4.21–4.35. The two doublet of doublets at δ 2.86 (J = 14.6, 5.1 Hz) and δ 3.15 (J = 13.9, 3.6 Hz) were due to the benzylic hydrogens of the pyrrolidine ring, the large J value arising from geminal coupling between the 21-CH_2 hydrogens, and the small J value due to vicinal coupling with the adjacent methine hydrogen, next to NH, that appeared as a multiplet in the region of δ 4.21–4.35. In the ^{13}C NMR spectrum of **5a**, C-13 and C-14 showed signals at δ 51.2 and 62.0, the three

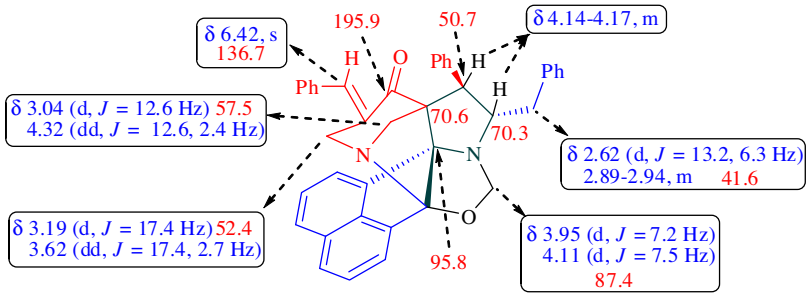

Figure 1. Selected ^{1}H and ^{13}C NMR chemical shifts of **6a**.