1,3-Dipolar cycloadditions to methylenespiro[2.2]pentane: a complementary access to spiro cyclopropanated azaheterocycles

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The domino cycloaddition–thermal rearrangement of nitrile oxides and methylenespiro[2.2]pentane gives 5-azaspiro-[2.5]oct-6-en-8-one derivatives; with a nitrone the process complements the one using bi(cyclopropylidene) for the synthesis of α-spiro cyclopropanated heterocyclic ketones.

We have recently reported on the 'domino' cycloaddition–rearrangement process involving 1,3-dipoles such as nitrones **1** or nitrile oxides and bi(cyclopropylidene) **2**.[1] The process, essentially 'one pot', led to new 5-azaspiro[2.5]octan-8-ones **4** with high selectivities and in good yields (Scheme 1). Some of these spirocyclopropanated heterocycles also showed interesting biological activity, as they were found to cleave a DNA plasmid.[2]

However, isoxazolines **5**, derived by addition of **2** to nitrile oxides under the rearrangement conditions did not give the analogous derivatives **6**, instead affording exclusively the 2-substituted dihydrofuro[2,3-*c*]pyridine derivatives **7**[1] due to a non-selective rearrangement of both cyclopropane units in **5** under the required thermolytic conditions (Scheme 2).

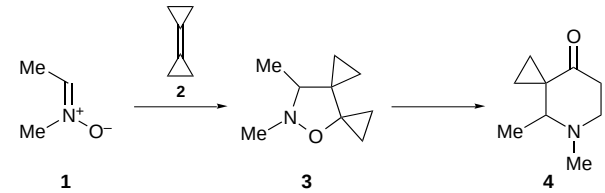
We now report the synthesis of 6-substituted 5-azaspiro-[2.5]oct-6-en-8-ones **11** by a different approach, utilising methylenespiro[2.2]pentane **8** as the dipolarophile (Scheme 3).

Methylenespiro[2.2]pentane **8**,[3,4] easily available from methylenecyclopropane[4a] or by thermal isomerization of bi(cyclopropylidene),[4b] has already been used in [2+1] addition processes for the synthesis of triangulanes.[5] The cycloaddition of benzonitrile oxide **9a**, generated slowly *in situ* at room temperature from the corresponding hydroximoyl chloride, to **8** afforded the isoxazoline **10a** in 64% yield with high regioselectivity, while the stable 2,4,6-trimethylbenzonitrile oxide **9b** gave the corresponding adduct **10b** quantitatively. Compared to bi(cyclopropylidene) **2**,[1] methylenespiro-[2.2]pentane **8** showed higher reactivity towards nitrile oxides, as demonstrated by the milder conditions required for the reaction with the stable nitrile oxide **9b** and the considerable decrease in formation of the undesired side-product generated by dimerization of the unstable nitrile oxide **9a**.

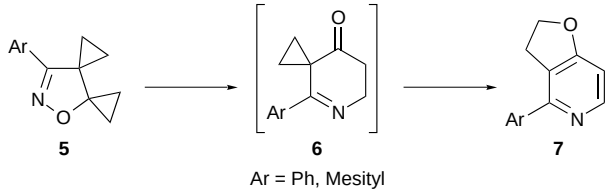
Isoxazolines **10** underwent thermal rearrangement more easily than their counterparts (**5**) from bi(cyclopropylidene)[1] and provided the ketones **11**, which contained a spiro-cyclopropane ring on the pyridone structure (Scheme 3). The structural assignment was based on the observation of characteristic signals in the NMR spectra for the C=C–C=O system, the olefinic proton and the methylene group adjacent to nitrogen. The higher lability of compounds **6** (Scheme 2), where the cyclopropane ring did not survive the rearrangement conditions, can be ascribed to the double spiro-conjugated cyclopropane ring.[6]

The highly regioselective opening of the spiro cyclopropane ring in **10** is noteworthy. This selectivity is opposite to that obtained when the process was applied to alkyl or aryl-substituted methylenecyclopropanes.[7] If a homolytic N–O bond cleavage is involved, as indicated by previous observations,[7a] this selectivity can be explained by the higher preference for the route (*a*) (Scheme 4) with ring opening to the diradical intermediate **A**, where the disubstituted cyclopropane carbon maintains the sp^3-like hybridization lost in intermediate **C** (Scheme 4).

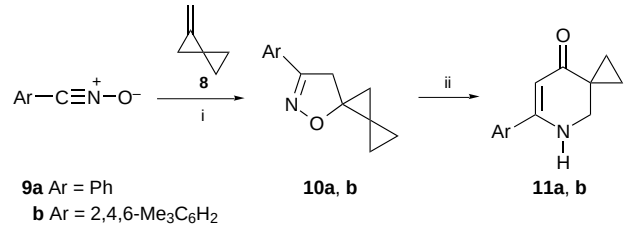
However, cyclopropyl methyl radicals **A** are known to rearrange readily to homoallylic radicals **E**,[8] which would eventually lead to products not observed in our process. This high regio- and chemo-selectivity, therefore, cannot rule out the



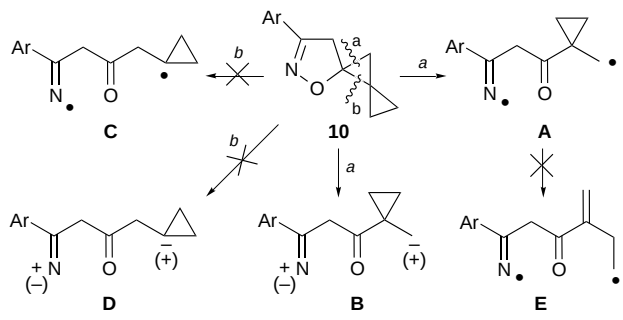
Scheme 1



Scheme 2



Scheme 3 *Reagents and conditions* for **9a**: i, C_6H_6, room temp. 16 h, 64%; ii, *o*-dichlorobenzene, 160 °C, 14 h, 70%; for **9b**: i, C_6H_6, 60 °C, 4 h, 95%; ii, mesitylene, 163 °C, 4 h, 92%



Scheme 4

presence of zwitterionic intermediates such as **B** in the rearrangement of isoxazolines **10**, although a solvent effect on the process could not be observed. Further investigations are required to assess the origin of the high regio- and chemoselectivity observed.

With nitrones the process suffers from low selectivity. For example, heating a solution of nitrone **12** and **8** in *o*-dichlorobenzene at 160 °C for 2 h in a 'one pot' process gives the ketone **13** (30%) as well as the enaminone **14** and the regioisomeric cycloadduct **15** (Scheme 5).[1,5*a*,7] The regioselectivity of the cyclopropane opening was confirmed, but, as expected, besides the product of diradical coupling (**13**), a 1,5-hydrogen shift in the intermediate diradical led to the open-chain isomer **14**, as the major product.[7]

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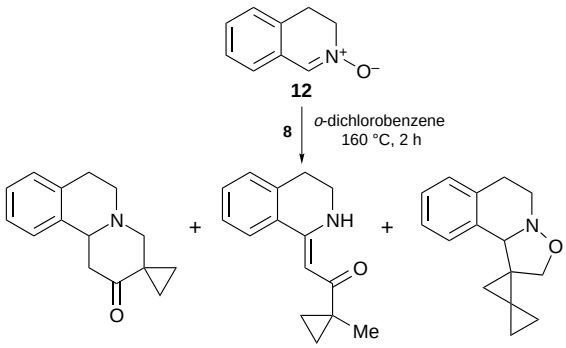

Scheme 5

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