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A novel class of azatricyclononanes: pentasubstituted cyclopropanes from an uncatalysed reaction

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This paper is dedicated to Professor George Fleet, on the occasion of his 65th birthday

ABSTRACT

The direct and versatile stereoselective synthesis of a novel class of cyclopropyl derivatives of pyroglutamic acid is reported, using substituted diaryldiazo compounds. The course of the reaction has been investigated, and yields of substituted fluorenylcyclopropanes are greater than those of diphenylmethylcyclopropane analogues.

1. Introduction

We have shown that pyroglutamic acid derivatives provide useful templates for the effective preparation of compound libraries with diverse functionality and controlled stereochemistry by alkylation reactions at the α-position[1–5] and conjugate additions of carbon, oxygen and nitrogen nucleophiles at the β-position[6–10] of the lactam carbonyl; these substrates may also undergo fully stereoselective cycloaddition reactions.[4] We have demonstrated that this approach provides access to novel kainoid and amino acid analogues[1,3,11,12] and conformationally well-defined amino acid analogues,[10] and of interest to us was the possibility that this approach might be extendable to even more conformationally restricted systems. The cyclopropyl unit is an important means for the introduction of rigidity, and conformationally well-defined amino acids[13] and peptides[14,15] and analogues of cytosine[16] have been identified. Recently, cyclopropyl annulated prolines have been shown to possess antibacterial activity,[17] and of interest to us was the development of methodology for the rapid access to cyclopropyl derivatives of pyroglutamate and proline. Literature precedent clearly indicated that these compounds might be of interest, which have been accessed by Madalengoitia using sulfur ylid additions.[18–22] Herein we report that azabicyclo[3.1.0]hexanes may be formed by the direct cyclopropanation of pyroglutamate derivatives using substituted diaryldiazo compounds and without metal catalysis; this process is highly stereoselective.

2. Results and discussion

Our approach commences from the unsaturated lactams **1a,b** (Schemes 1 and 2), prepared as previously reported.[4,3] The required diaryl diazomethanes **2a–d** and 9-diazo-9*H*-fluorenes **3a–f** (Scheme 2) were easily generated by conversion of the corresponding ketone either to the hydrazone followed by yellow mercuric oxide oxidation, or to the tosylhydrazone followed by basic elimination. Upon reaction of enone **1a** with diphenyldiazomethane **2c** in acetone solvent at reflux, we found that cyclopropane product **4** was obtained in 23% yield, along with the olefin product **6**, in 26% yield.[23] Also isolated was pyrazoline **5** in 26% yield, which is indefinitely stable at room temperature; however heating at reflux in toluene quantitatively yielded cyclopropane **4**; the alternative pyrazoline was not isolated. Similar reaction of diazofluorene **3** gave cyclopropyl adduct **7** in good yield (66%).

A range of substituted diazo compounds were reacted with activated enone **1b** (Scheme 2);[23] it should be noted that **1b** is very much prone to dimerisation (with **10** obtained as a single diastereomer), and needs to be used immediately after preparation. With both the diphenylmethyl-**2a–d** and fluorenyl-series **3a–f** of diazo compounds, the reactions were found to be significantly faster than for lactam **1a**, and no pyrazoline adducts analogous to **5** were isolated. An increase in the electron density in the diazo series **2** (**2a**→**2d**) gives significantly increased yields of cyclopropyl **8** relative to enone **9**, so that for example, diazo **2d** gave cyclopropane **8d** in 64% yield, along with only 16% of **9d** (Table 1). Olefin substitution products **9c,d** were obtained with diazo compounds **2c** and **2d** in 46% and 16% yields, respectively. Notably, only dimerised starting material **10** was isolated on reaction with diazo **8a**, indicating that this cycloaddition process is not without synthetic limitation. It should be noted that the reaction of enone **1b** with a range of substituted diazofluorenes yielded the cyclopropane products exclusively (Table 2), in yields ranging from 41% for **3f** (unoptimised) to 97% (optimised) for **3e**, and this was a significantly superior outcome to the diphenylmethyl series.

The best yields were obtained using the more electron-rich diazofluorene systems **3a,b**, in reactions which were also notable for

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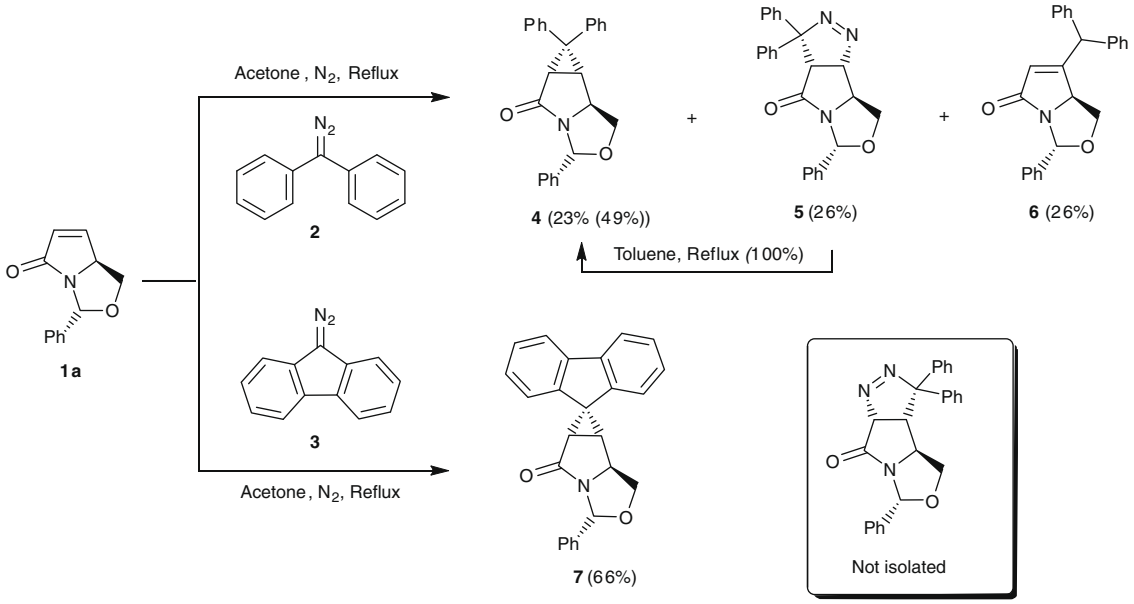
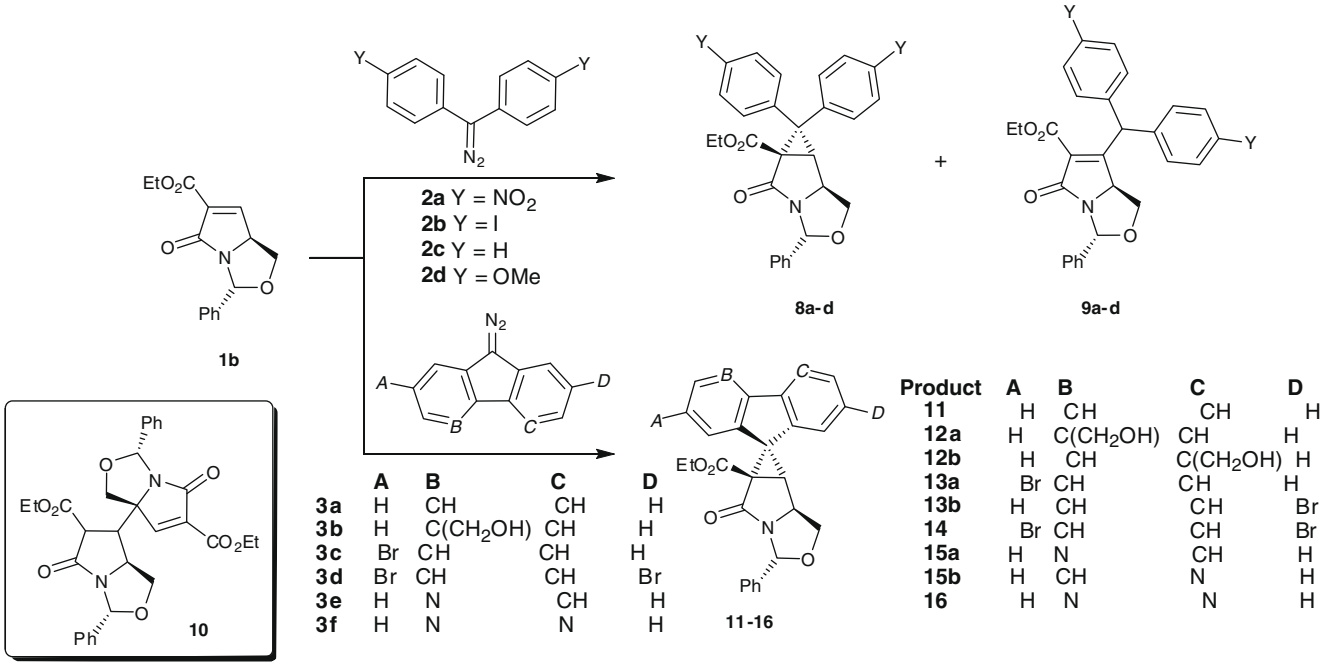


Scheme 1.



Scheme 2.

Table 1
Reactions of lactam **1b** with diazo compounds **2a–d**

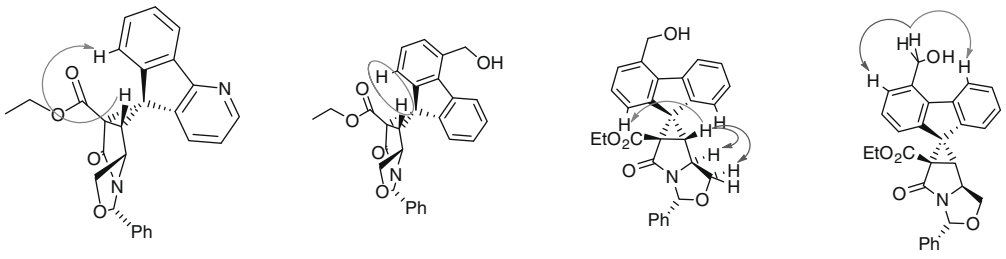
Diazo	Y	Yield product (%)	Yield product (%)	Dimer isolated
2a	NO_2	**8a** (0)	—	Yes
2b	I	**8b** (19)	—	Yes
2c	H	**8c** (29)	**9c** (46)	—
2d	OMe	**8d** (64)	**9d** (16)	—

the absence of products of type **9**. We also noted the higher stability of diazofluorenones over diphenyldiazomethanes under these reaction conditions (unreacted diazofluorenone was frequently obtained at the end of the reaction) and the former are therefore

Table 2
Reactions of lactam **1b** with diazo compounds **3a–f**

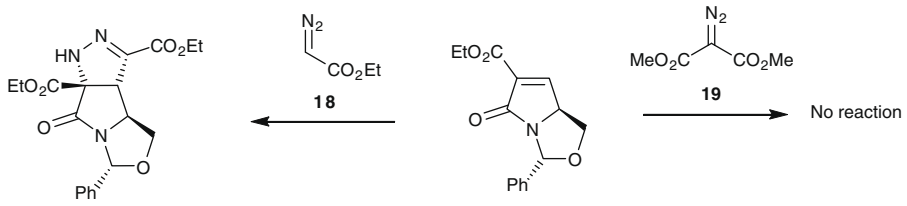
Diazo	Product	Yield of diastereomer (%)
3a	**11**	95
3b	**12a**	36[a]
	12b	36[a]
3c	**13a**	45
	13b	24
3d	**14**	64
3e	**15a**	58
	15b	39
3f	**16**	41

[a] Low overall yield due to the need for extensive chromatography to separate diastereomers.



15b 12a

Figure 1.



17 1b

Scheme 3.

more likely to be longer lived under the reaction conditions, giving rise to higher overall yield.

The *exo*-stereochemistry of the cyclopropane products was confirmed by single crystal X-ray analysis for **4**, **7**, **8b–d**, **11**, **14** and **15b**,[24] which is consistent with a sterically preferred outcome). It should be noted that in the ^{1}H NMR spectrum, the signal at ca. δ 3.5, diagnostic of H-6, always occurred as a singlet, as a result of its orthogonal relationship to H-5; a similar structural feature has been previously reported.[14] With unsymmetrical diazo compounds **3b,c,e**, two diastereomeric *exo*-cyclopropanes were obtained (Table 2). Although the determination of the stereochemistry of **15b** was readily possible by NOE irradiation of the H-6 proton, giving an enhancement to a single identifiable aromatic proton, and this stereochemical outcome confirmed by X-ray analysis, the two non-crystalline diastereomers **12a,b** were separable and distinguishable by ^{1}H NMR spectroscopy only with difficulty. The assignment of stereochemistry in this case required a series of NOE and TOCSY experiments (Fig. 1), utilising firstly, the existence of the key NOE enhancement observed via irradiation of the δ 3.5 singlet for H-6 to identify the proximal aromatic hydrogen, secondly NOE from the aromatic CH_2OH to flanking hydrogens, and a TOCSY to identify which of the three possible aromatic rings on which these hydrogens were located (Fig. 1).

In contrast to the reactivities of diaryldiazomethanes and fluorenyldiazomethanes towards **1b**, ethyl diazoacetate **18** furnished 2-pyrazoline **17**, which is presumably the most stable tautomer, and whose regiochemistry was established on the basis of careful analysis of ^{13}C shift data (Scheme 3). This is a similar outcome to the cycloaddition reaction with 4-naphthoxybutenolide.[25] However, dimethyl diazomalonate **19** gave no such reaction, even when used as the solvent, and only **10** was formed.

Mechanistically, this reaction may be considered to proceed via carbene (singlet or triplet) insertion or cycloaddition (pyrazoline formation) processes. We believe that the former is unlikely, since the majority of reactions are conducted with excess diazo compound in refluxing acetone, well below the decomposition temperature for diazofluorene and diphenylmethyldiazo compounds (we have recently established by thermal gravimetric analysis that these compounds decompose at >120 °C, and some are stable even to >165 °C). In favourable cases (e.g., **3b,c,e**), unreacted diazoalkane may even be isolated in pure form from the reaction mixture. Furthermore, the rate of reaction of enone **1b** is greater than **1a**, consistent with a concerted pathway, in which formation of one regioisomer of the pyrazoline product as a result of steric and/or electronic factors is preferred, and that this immediately collapses leading to the formation of the observed products **8** and **9**. In the case of **1a**, both pyrazolines are formed, one of which immediately collapses to the products **4** and **6**, and the other **5** (which can easily be isolated) only does so at elevated temperature. The collapse of pyrazolines to cyclopropanes has been investigated in detail.[26] The formation of both pyrazoline and cyclopropyl products has been observed in the reactions of diazo compounds with unsaturated maleimide systems.[27]

3. Conclusion

We have demonstrated that direct cyclopropanation of electronrically activated unsaturated pyrrolidinones using diaryl diazo compounds allows stereoselective access to conformationally well-defined structures. These compounds are likely to find application in diverse areas. This work complements work recently reported by Fleet et al., who demonstrated novel methodology for the protection of carbohydrates using diaryldiazomethanes, highlighting the importance of these under-utilised reagents.[30]

Acknowledgements

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23. General method: **1a** or **1b** (1 equiv) and 1.5–2.5 equiv of diazo compound were dissolved in acetone (5–10 mL per mmol), degassed with N_2 and heated at reflux. After completion, the reaction mixture was concentrated and purified by column chromatography.
24. Crystal structures were determined using low temperature data collected using a Nonius Kappa-CCD, solved using SIR92[28] software suite[29] and refined using the CRYSTALS software suite. Crystallographic data (excluding structure factors) for all structures have been deposited with the Cambridge Crystallographic Data Centre (CCDC 718621–718628) and copies of these data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif.
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