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# Stereoselective synthesis and applications of nitrogen substituted donor–acceptor cyclopropanes (N-DACs) in the divergent synthesis of azacycles†

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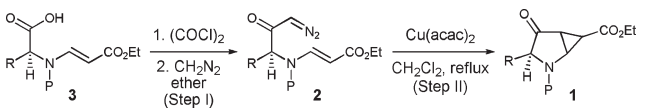
**A new, highly stereoselective intramolecular cyclopropanation of vinylogous carbamates with carbenes in the presence of $Cu(acac)_2$ as the catalyst has been developed for the construction of cyclopropapyrrolidinones. The '*syn*' isomer of N-DAC can be converted to the '*anti*' isomer by simple silica gel treatment. Regioselective cleavage of each of the cyclopropane bonds of these two acceptor substituted N-DACs led to a diverse array of azacycles.**

Recent years have seen the emergence of donor–acceptor substituted cyclopropanes (DACs) as valuable synthons in organic synthesis.[1] Vicinally substituted DACs where an oxygen is the donor substituent have been extensively studied for their reactivity with electrophiles and nucleophiles.[2] These DACs have been used in the synthesis of a variety of natural[3] and un-natural[4] products bearing ether and lactone moieties. In contrast, the majority of the efforts on the synthesis and utility of the corresponding nitrogen substituted DACs (N-DACs) have focused on using them as conformationally restricted *β*-alanine analogues, namely, *β*-aminocyclopropanecarboxylic acids (*β*-ACCs).[5] Surprisingly, the "push–pull" effect present in N-DACs has not been exploited to a significant extent from a synthetic point of view. In this context, some notable examples include deployment of N-DACs as 1,3-dipoles in dipolar cycloaddition reactions, homo-Nazarov cyclization and in ring-opening reactions with various electrophiles and nucleophiles.[6] This interesting reactivity of the N-DACs has also been exploited in the synthesis of natural products.[7] In spite of these developments in this area, some challenges still remain. In many cases, methods developed for the synthesis of N-DACs suffer from limitations such as low yields and/or poor stereoselectivities.[8] Moreover, the N-DACs bearing 1,2-donor–acceptor or 1,1-bisacceptor substituents allow for cleavage of only one of the cyclopropane bonds with very high regioselectivity. A systematic study demonstrating that each of the cyclopropane bonds of N-DACs can be cleaved with complete regiocontrol is conspicuous by its absence. Herein, we describe a highly regio- and stereoselective synthesis of N-DACs employing intramolecular cyclopropanation of vinylogous carbamates. Further, we demonstrate that each of the cyclopropane bonds of these N-DACs can be cleaved with complete regiocontrol, generating a diverse array of azacycles.

Recently, we developed a new method for stereoselective synthesis of the oxygen substituted DACs employing intramolecular cyclopropanation of vinylogous carbonates.[9] These DACs were used in the divergent synthesis of THF, THP and lactone derivatives. In continuation of our interest in using vinylogous functional groups in the synthesis of heterocycles,[10] we envisioned that the N-DAC **1** could be readily assembled by copper(I) catalysed intramolecular cyclopropanation[11] of the vinylogous carbamate moiety in the diazoketone **2** (Scheme 1). The diazoketone **2** could in turn be readily prepared from the acid **3**, which itself is obtained from readily available enantiomerically enriched α-amino acids. The choice of the nitrogen protecting group was previously noted as very important since β-ACCs or N-DACs without an electron withdrawing substituent on nitrogen are extremely susceptible to ring opening reactions.[1] Protecting groups such as tosyl and carbamates were thus chosen for this study.

The diazoketones **2** required for the study were readily prepared from the acids **3**. Reaction of the acid **3a** with oxalyl chloride followed by treatment of the acid chloride with ethereal diazomethane generated the diazoketone **2a**. Decomposition of the diazoketone **2a** in refluxing $CH_2Cl_2$ using $Cu(acac)_2$ as the catalyst furnished the N-DAC **1a** in very good yield with excellent diastereoselectivity (Table 1, entry 1). Delighted by success of this reaction, the scope of this intramolecular cyclopropanation of vinylogous carbamate with carbene was studied with various *N*-carbamate and *N*-tosyl protected diazoketones **2**. The reaction was found to work efficiently with the *N*-carbamate protected diazoketone derivatives **2b–d** as well, which gave rise to




**Scheme 1** Intramolecular cyclopropanation of vinylogous carbamate for the synthesis of N-DACs.

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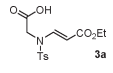
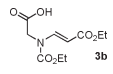
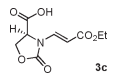
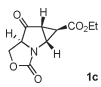
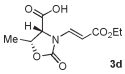
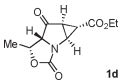
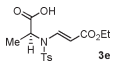
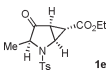
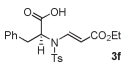
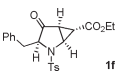
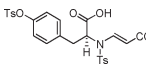
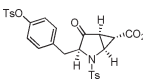
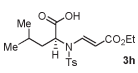
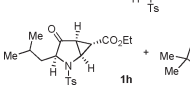
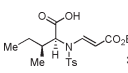
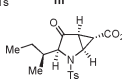
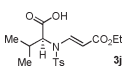
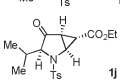
**Table 1** Scope of the intramolecular cyclopropanation of vinylogous carbamates

| Entry | Acid **3** | Yield[a] Step 1 | Yield[a] Step 2 | Product(s) **1**[b] |
|---|---|---|---|---|
| 1 |  **3a** | 71 | 69 |  **1a** |
| 2 |  **3b** | 50 | 78 |  **1b** |
| 3 |  **3c** | 63 | 71 |  **1c** |
| 4 |  **3d** | 76 | 60 |  **1d** |
| 5 |  **3e** | 70 | 75 |  **1e** |
| 6 |  **3f** | 70 | 69 |  **1f** |
| 7 |  **3g** | 52 | 57 |  **1g** |
| 8 |  **3h** | 47 | 75[c] |  **1h** + **4** |
| 9 |  **3i** | 53 | 58 |  **1i** |
| 10 |  **3j** | 48 | 63[d] |  **1j** |

[a] Isolated yield. [b] In all the cases, dr was determined on the crude reaction mixtures by $^1$H NMR and was found to be ≥19:1. [c] Combined yield of the ketones **1h** and **4** (**1h** : **4** = 2 : 1). [d] Reaction was performed at room temperature.

the corresponding cyclopropapyrrolidinone derivatives **1b–d**, respectively, in good yield and excellent '*anti*' diastereoselectivity for **1c–d** (Table 1, entries 2–4). The stereochemistry of these products was assigned on the basis of NOE experiments. This was further confirmed by single crystal X-ray diffraction studies† on the ketone **1c** (Fig. 1).[12] This stereochemical outcome for the formation of N-DAC **1c–d** is consistent with our earlier observations in the case of vinylogous carbonates.[9] Cyclopropanation reactions of the *N*-tosyl protected diazoketones **2e–j** bearing alkyl substitution were particularly interesting. The reaction of the diazoketone **2e** with $Cu(acac)_2$ under optimized conditions followed by purification by flash chromatography on silica gel furnished the N-DAC **1e** in good yield with excellent diastereoselectivity (Table 1, entry 5). However, the stereochemistry obtained was '*syn*' rather than '*anti*' as was observed for the N-DACs **1c–d**. This trend in stereochemical reversal was observed for all other diazoketones **2f–j** bearing *N*-tosyl protection where the corresponding N-DACs **1f–j** were formed in good yields and diastereoselectivities (Table 1, entries 6–10).

Interestingly, when these N-DACs **1e–g** were purified by gravity column using silica gel, the centre α to ketone was found to undergo isomerisation (Table 1, entries 5–8). As a representative example, the $^1$H NMR spectra of the cyclopropapyrrolidinone **1e** recorded under various conditions is depicted in Fig. 2. It could be noted that the $^1$H NMR spectrum of the crude sample suggested the presence of a single diastereomer which was similar to that obtained by flash column. Purification of the sample by gravity column on the other hand showed the presence of a mixture of diastereomers as against the single diastereomer of the crude sample. One set of signals clearly corresponded to the cyclopropapyrrolidinone **1e** obtained from flash column whereas the other set matched with N-DAC **1e′** (*vide infra*). Moreover, the ratio of the diastereomers **1e** and **1e′** varied depending on the amount of the silica gel used and the contact time of the compound with the silica gel. Further, complete isomerisation of the N-DAC **1e** to **1e′** could be effected by its prolonged exposure (~15 days) to the silica gel (Scheme 2). Interestingly, this isomerisation could also be carried out very efficiently within *ca*. 10 min. by treating N-DAC **1e** with a base like DBU in benzene. This feature is particularly attractive as it gives ready access to both the stereoisomers of N-DACs.

The stereochemistry of these isomerised N-DACs **1e′**–**g′** was confirmed by NOE experiments. Further unambiguous confirmation was obtained by subjecting the N-DAC **1g′** to single crystal X-ray diffraction† studies (Fig. 1).[12] Based on the crystal structure of the N-DACs obtained upon isomerisation, it is clear

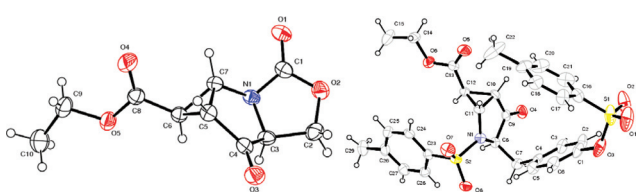


**Fig. 1** ORTEP diagrams for the N-DAC **1c** and **1g′**.

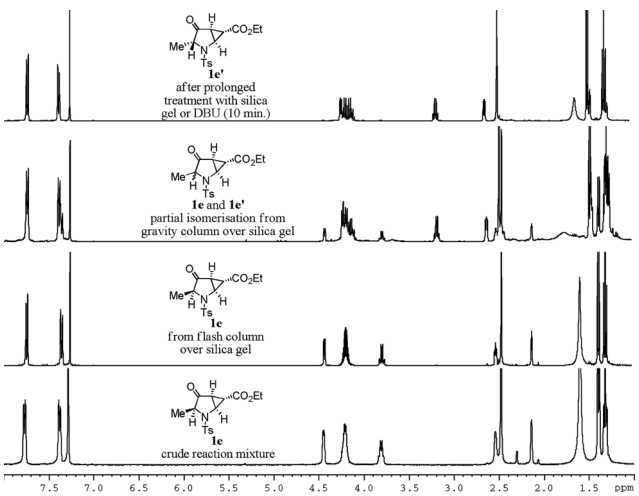
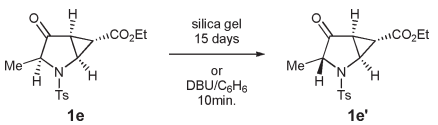



**Fig. 2** $^1$H NMR spectra of the ketones **1e** and **1e′**.



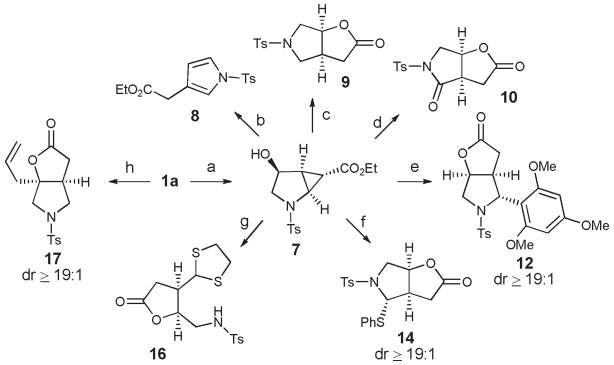

**Scheme 2** Isomerisation studies on the N-DAC **1e**.

that the '*anti*' isomer will be thermodynamically more stable compared to the '*syn*' isomer. This is due to the steric interaction between the alkyl substituent and the cyclopropane proton α to the ester in the '*syn*' isomer, which will be absent in the '*anti*' isomer. Formation of the less stable '*syn*' isomer in the case of N-DACs bearing tosyl protection is clearly an outcome of kinetic control, though its origin is not completely understood at this juncture. It was also interesting to note that this isomerisation on silica gel was neither observed for the N-DACs **1i–j** nor for the N-DACs **1c–d**, perhaps due to the branching on the alkyl group in the former case and the relatively lower acidity of the proton α to the carbonyl group in the latter case.

It is pertinent to mention here that in the case of the diazoketone **2h**, along with the N-DAC **1h**, ketone **4** was formed as a by-product *via* C–H insertion of carbene into the methine of the isobutyl group (Table 1, entry 8). Again, this was contrary to our observation in the case of intramolecular cyclopropanation of vinylogous carbonates where analogous substrate did not give any of the C–H insertion product while using copper salts as the catalyst.[9]

After the successful stereoselective synthesis, attention was turned towards studying the reactivity of the synthesised N-DACs. The reactivity of these N-DACs paralleled that observed for oxygen substituted DACs in our earlier studies. Thus, treatment of cyclopropapyrrolidinones **1a**, **1c** and **1e** with tributyltinhydride and AIBN in refluxing benzene furnished the corresponding pyrrolidinone derivatives **5a**, **5c** and **5e**, respectively, in excellent yield (Scheme 3).[13] On the other hand, their reaction with TMSOTf furnished the corresponding piperidinone derivatives **6** *via* preferentially coordinating with the ketone rather than the ester leading to the formation of iminium ion followed by elimination of *β*-proton. The piperidinone derivatives **6** are complementary to those described by Georg *et al.* recently using trapping of ketene with vinylogous carbamates.[14]

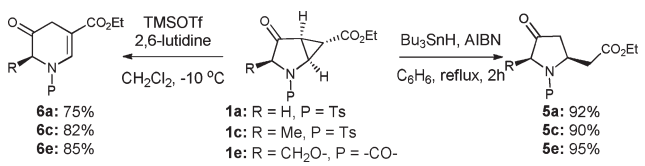
Regioselective cleavage of the third cyclopropane bond of N-DAC required activation of the carbonyl of the ester moiety with Lewis or Brønsted acid. Towards this end, the ketone **1a** was chemo- and stereoselectively reduced using lithium aluminium hydride to furnish the alcohol **7** (Scheme 4). The cyclopropane bond of the alcohol **7** could be cleaved under a variety of conditions leading to a diverse array of heterocyclic skeletons. Thus, reaction of the alcohol **7** in methanol in the presence of a catalytic amount of sulfuric acid furnished the pyrrole derivative **8**. The iminium ion intermediate generated by reaction of the alcohol **7** with TMSOTf could be reduced with $Et_3SiH$ or oxidised with *m*-CPBA along with concomitant lactonization to give lactone **9** and furopyrrolodione **10**, respectively. The intermediate iminium ion could be trapped even with a carbon nucleophile like 1,3,5-trimethoxybenzene (**11**) leading to the arylated furopyrrolone **12** in very good yield with excellent diastereoselectivity. The iminium ion intermediate trapping with sulfur nucleophiles was found to be particularly interesting. Thiophenol (**13**), when used as nucleophile, led to the formation of the lactone **14**. On the other hand using ethanedithiol (**15**) as the nucleophile furnished the γ-butyrolactone derivative **16** by tandem ring opening–iminium ion trapping with ethanedithiol, thioacetalization and subsequent lactonization. Finally, the tertiary alcohol intermediate generated by allylation of the ketone **1a** using TMSOTf and allyltributyltin could be further reacted with triethylsilane *in situ* to furnish the substituted lactone derivative **17**. This study thus unambiguously demonstrated that the N-DACs can give rise to a diverse array of azacycles.




**Scheme 4** Tandem regioselective ring opening–lactonization of N-DACs. Reagents and conditions: (a) LAH, THF, −78 °C, 75%; (b) $H_2SO_4$, MeOH, 0 °C–rt, 64%; (c) TMSOTf, $Et_3SiH$, $CH_2Cl_2$, −10 °C–rt, 92%; (d) TMSOTf, *m*-CPBA, $CH_2Cl_2$, −10 °C–rt, 74%; (e) TMSOTf, 1,3,5-$(MeO)_3C_6H_3$ (**11**), $CH_2Cl_2$, −10 °C–rt, 91%; (f) TMSOTf, PhSH (**13**), $CH_2Cl_2$, −10 °C–rt, 91%; (g) TMSOTf, $HS(CH_2)_2SH$ (**15**), $CH_2Cl_2$, −10 °C–rt, 70%; (h) $^n$$Bu_3SnAllyl$, TMSOTf, $CH_2Cl_2$, −10 °C, then $Et_3SiH$, 67%.

## Conclusions

We have developed a highly stereoselective synthesis of N-DACs employing intramolecular cyclopropanation of vinylogous carbamates with carbenes in the presence of $Cu(acac)_2$ as the catalyst. Stereochemical assignment of these cyclopropapyrrolidinones **1** was done with the help of NOE and X-ray diffraction studies. The reactivity of two acceptor substituted N-DACs allowed for the regioselective cleavage of each of the cyclopropane bonds by an appropriate choice of reagents, leading to the divergent synthesis of azacycles.




**Scheme 3** Ring opening of N-DAC **1** for the synthesis of pyrrolidin-3-ones and piperidin-3-one.

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12 CCDC 826028 (**1c**) and CCDC 826029 (**1g′**) contain the supplementary crystallographic data for this paper.† These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif

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