One-Pot Synthesis of GABA Amides via the Nucleophilic Addition of Amines to 3,3-Disubstituted Cyclopropenes

ARTICLE *in* ORGANIC & BIOMOLECULAR CHEMISTRY · JULY 2015

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One-pot synthesis of GABA amides *via* the nucleophilic addition of amines to 3,3-disubstituted cyclopropenes†

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Cite this: *Org. Biomol. Chem.*, 2015, **13**, 8993

Received 16th July 2015,
Accepted 29th July 2015

DOI: 10.1039/c5ob01462j

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A one-pot synthesis of various GABA amides has been demonstrated, employing the nucleophilic addition of primary and secondary amines across the double bond of cyclopropene-3-carboxamides, followed by ring-opening of the resulting donor–acceptor cyclopropanes and subsequent *in situ* reduction of enamine (imine) intermediates.

γ-Aminobutyric acid (GABA) is the chief inhibitory neurotransmitter in the mammalian central nervous system playing a principal role in reducing neuronal excitability,[1] and is a species of immense importance for modern bioorganic and medicinal chemistry. This motif is omnipresent in natural products, including Bistramide A[2] and cyclic oligopeptides Microsclerodermins[3] and Unguisins.[4] GABA derivatives are also widely used in numerous over-the-counter and prescription medicinal agents, such as Noofen (Phenibut),[5] Picamilon,[6] Lioresal (Baclophen), Lyrica (Pregabalin)[7] or anti-arthritic drug Trocade (Cipemastat)[8] (Fig. 1).

In our studies[9] of donor–acceptor cyclopropanes (DAC),[10] we investigated the possibility to access substituted GABA derivatives **5** *via* the ring opening of DAC **1** (Scheme 1). The propensity of DACs toward ring cleavage is proportional to polarization of the C–C bond between electron-donating (EDG) and electron-withdrawing (EWG) groups. The requisite polarization is commonly achieved through installation of strong EWGs, typically two ester groups, additionally activated by a Lewis acid ("pull" strategy), which leads to products with an "extra" carboxylate moiety at the α-carbon. In our recent report[9] we proposed the possibility to employ an alternative "push" strategy by taking advantage of our formal nucleophilic substitution methodology that allows for installation of various *N*-moieties in the cyclopropane ring. Herein we demonstrate the proof of concept and employment of this strategy toward synthesis of GABA amide derivatives.

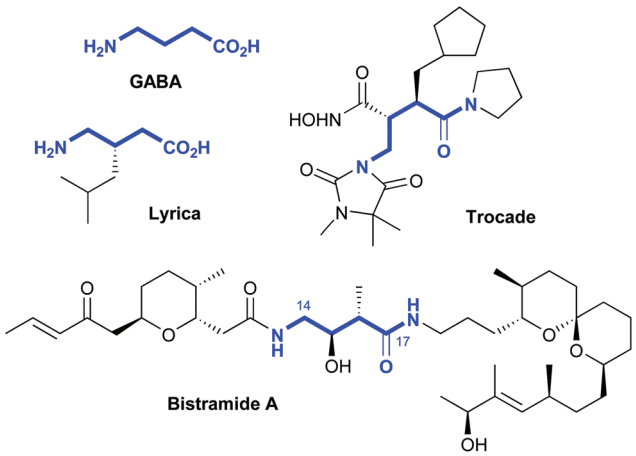
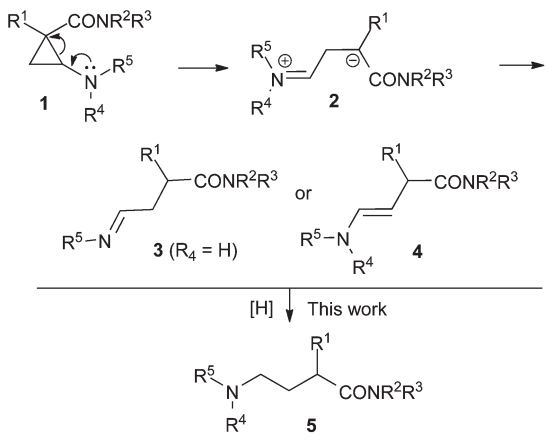


Fig. 1 Biologically active GABA derivatives.



Scheme 1

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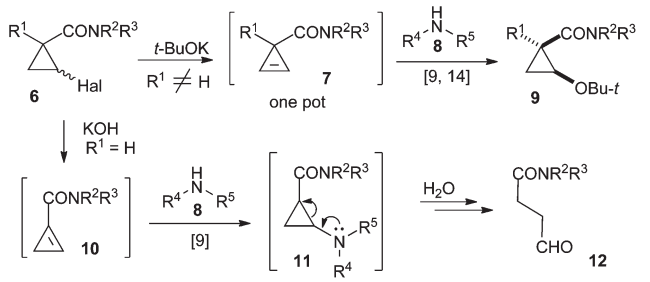
†Electronic supplementary information (ESI) available: Experimental procedures, physico-chemical and spectral data. See DOI: 10.1039/c5ob01462j

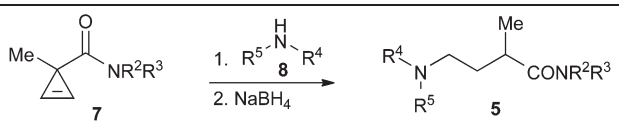
The above-mentioned formal nucleophilic substitution of halocyclopropanes **6**[9] provides convenient access to various cyclopropylamine derivatives **11**, including carboxamides and sulphonamides of *trans*-β-aminocyclopropanecarboxylic acid (β-ACC), *N*-cyclopropylhetaryls and *N*-cyclopropylanilines (Scheme 2).[9,11] These reactions proceed *via* a base-driven nucleophilic addition across the double bond of conjugate cyclopropene **10**.[12,13] However, attempts to isolate hydroamination products resulting from the addition of electron-rich amine derivatives to the *in situ* generated, very electrophilic 1-substituted cyclopropenes **10** were unsuccessful. Small amount of water generated as by-product upon dehydrohalogenation of **6** in the presence of KOH resulted in a rapid, amine-mediated ring-opening hydration of intermediate cyclopropene **10** affording aldehyde **12** (Scheme 2).[9] Furthermore, nitrogen nucleophiles do not easily add to less electrophilic, non-conjugate 3,3-disubstituted cyclopropenes **7** under conditions used for generation thereof.[14] This reaction was totally suppressed by a much more facile addition of an alkoxide (employed as a base for dehydrohalogenation step), to afford cyclopropanol ether **9**. Thus, employment of a stable, isolated cyclopropenes **7**[15] was envisaged as an alternative approach to hydroamination that could be carried out under alcohol- and/or water-free conditions. It was anticipated that the addition of an electron-rich amino group would help trigger the desired bond cleavage in intermediate **1**. The resulting zwitterionic intermediate **2**, in the presence of a proton source, would be stabilized in a form of imine **3** (if derived from primary amine **8**) or enamine **4**, respectively. Species **3** or **4** can subsequently be reduced *in situ* to give GABA amide **5** (Scheme 1), or be employed as electrophilic or nucleophilic moiety in various imine or enamine chemistry.



Scheme 2

Accordingly, we exposed neat *N*,*N*-diethyl-1-methylcycloprop-2-ene-1-carboxamide (**7a**)[15] to diethylamine (**8a**, 3.0 equiv.) at various temperatures to monitor the ring opening. It was found that heating the mixture at 100 °C allowed for complete and clean ring cleavage. GC analysis of crude reaction mixtures showed a single product peak, attributed to enamine **4aa**. Next, the crude mixture was treated with borohydride ($NaBH_4$ or $NaBH(OAc)_3$) in dichloromethane to afford the target amide **5aa** as a single product in good yield (Table 1, entry 1). Interestingly, under similar conditions, diisopropylamine (**8b**) did not react at all, leaving cyclopropene **7a** intact even after extended heating at 125 °C. Apparently, this bulky amine was insufficiently nucleophilic to enable the hydro-

Table 1 Synthesis of GABA amides *via* reductive ring cleavage of cyclopropylamines generated *in situ* upon hydroamination of cyclopropenes



#	7	8 (equiv.)	5	R^2	R^3	R^4	R^5	*T*, °C (time, h)	Yield,[a] %
1	**7a**	**8a** (3.0)	**5aa**	Et	Et	Et	Et	100 (1)	66
2	**7a**	**8b** (3.0)	**5ab**	Et	Et	i-Pr	i-Pr	125 (3)	NR
3	**7a**	**8c** (3.0)	**5ac**	Et	Et	$-(CH_2)_4-$		100 (1)	71
4	**7a**	**8d** (1.5)	**5ad**	Et	Et	$-(CH_2)_2O(CH_2)_2-$		100 (1)	68
5	**7a**	**8e** (1.5)	**5ae**	Et	Et	$-(CH_2)_2N(Et)(CH_2)_2-$		100 (1)	72
7	**7a**	**8f** (1.5)	**5af**	Et	Et	$-(CH_2)_2N(Bn)(CH_2)_2-$		100 (1)	75
7	**7b**	**8a** (3.0)	**5ba**	i-Pr	i-Pr	Et	Et	100 (1)	71
8	**7b**	**8c** (3.0)	**5bc**	i-Pr	i-Pr	$-(CH_2)_4-$		100 (1)	73
9	**7b**	**8d** (1.5)	**5bd**	i-Pr	i-Pr	$-(CH_2)_2O(CH_2)_2-$		100 (1.5)	66
10	**7c**	**8a** (3.0)	**5ca**	$-(CH_2)_4-$		Et	Et	100 (1)	65
11	**7c**	**8c** (3.0)	**5cc**	$-(CH_2)_4-$		$-(CH_2)_4-$		100 (1)	73
12	**7c**	**8d** (1.5)	**5cd**	$-(CH_2)_4-$		$-(CH_2)_2O(CH_2)_2-$		100 (1)	68
13	**7a**	**8g** (1.5)	**5ag**	Et	Et	$PhCH_2CH_2$	H	100 (2)	75
14	**7a**	**8h** (2.0)	**5ah**	Et	Et	$PhCH_2$	H	115 (2)	65
15	**7a**	**8i** (1.3)	**5ai**	Et	Et	Ph	H	140 (5)	68
16	**7b**	**8g** (1.5)	**5bg**	i-Pr	i-Pr	$PhCH_2CH_2$	H	100 (2)	76
17	**7b**	**8h** (1.3)	**5bh**	i-Pr	i-Pr	$PhCH_2$	H	100 (2)	68
18	**7b**	**8j** (3.0)	**5bj**	i-Pr	i-Pr	*n*-Bu	H	100 (1)	76
19	**7c**	**8h** (1.3)	**5ch**	$-(CH_2)_4-$		$PhCH_2$	H	100 (2)	65
20	**7a**	**8k** (1.5)	**5ak**	Et	Et	PhCHMe	H	100 (3)	65 (1 : 1)[b]

[a] Isolated yields of purified products are listed. [b] Diastereomeric ratio measured by GC of crude reaction mixture is shown in parentheses.

amination step (entry 2). In contrast, cyclic secondary amines, such as pyrrolidine (**8c**), morpholine (**8d**), *N*-ethyl- (**8e**), and *N*-benzylpiperazines (**8f**) afforded GABA amides **5ad–5af** in good yields (entries 3–6). *N*,*N*-Diisopropyl-1-methylcycloprop-2-ene-1-carboxamide (**7b**)[15] and (1-methylcycloprop-2-en-1-yl)(pyrrolidin-1-yl)methanone (**7c**)[15] proved to be similarly efficient as **7a** with a number of secondary amines (entries 7–12). Reaction with primary amines, such as phenethylamine (**8g**), benzylamine (**8h**), and *n*-butylamine (**8j**), also proceeded uneventfully, although somewhat more sluggishly (entries 13, 14, 16–19). It was also necessary to raise the temperature to 140 °C to drive the reaction with aniline (**8i**) to complete conversion (entry 15).

Finally, a possibility to induce a diastereoselective ring cleavage upon addition of chiral amines was probed by reacting cyclopropene **7a** with α-phenylethylamine (**8k**). Unfortunately, transfer of asymmetric information from a remote stereogenic center was not efficient, and the corresponding adduct **5ak** was produced as a 1 : 1 mixture of two diastereomers (entry 20).

Conclusions

In conclusion, we have successfully employed an alternative "push" strategy for ring opening of "push–pull" cyclopropanes generated *in situ via* the unassisted nucleophilic addition of electron-rich amines across the double bond of cyclopropene-3-carboxamides. This concept was utilized in efficient one-pot synthesis of GABA derivatives. Further investigations of this transformation are currently underway in our laboratories, which include (a) exploring the possibility of controlling the diastereoselectivity of small ring cleavage upon addition of chiral amines, assisted by Lewis acidic chelating agents; (b) investigating regio- and stereoselectivity of ring cleavage in 1,3,3-trisubstituted chiral cyclopropenes en route to chiral GABA derivatives possessing several contiguous stereogenic centers; (c) intercepting imine species **3** in diastereoselective reactions with C-nucleophiles. The results on these studies will be reported in due course.

This work was financed through the International Collaboration Program, supported by the Ministry of Education and Science of the Russian Federation and the Ministry of Education of Perm Krai. We are also grateful for the financial support by the Russian Foundation for Basic Research (grant #15-03-02661). Support for NMR instruments used in this project was provided by NIH Shared Instrumentation Grant #S10RR024664 and NSF Major Research Instrumentation Grant #0329648.

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