A novel pseudo four component reaction involving homoenolate for the synthesis of γ-aminobutyric acid (GABA) derivatives†

Vijay Nair,*[a] Vimal Varghese,[a] Beneesh P. Babu,[a] C. R. Sinu[a] and Eringathodi Suresh[b]

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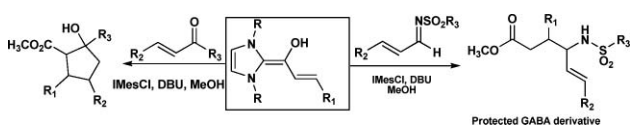
Homoenolate generated from α,β-unsaturated aldehydes by NHC catalysis underwent facile addition to conjugated sulfonimines, generated *in situ*, and subsequent methanolysis to afford protected GABA derivatives stereoselectively and in high yields, thus constituting a novel pseudo four component reaction.

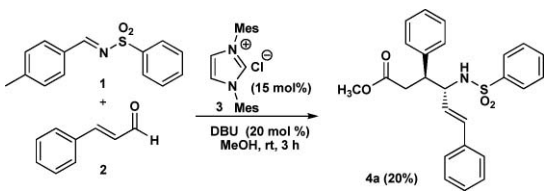
Ever since the original work on homoenolates by Nickon,[1] there has been interest in their utilization as synthons in organic chemistry. Earlier work in this direction, however, was restricted to the use of homoenolate equivalents such as cyclopropanone ketals,[2] acetal appended Grignard reagents[3] and metallated allylic carbamates.[4] The direct generation of homoenolates remained elusive until Bode[5] and Glorius,[6] in their elegant work, independently demonstrated that the reactivity umpolung of aldehydes induced by the addition of nucleophilic heterocyclic carbene (NHC), originally discovered by Breslow,[7] can be extended to α,β-unsaturated aldehydes, thus imparting anionic character to the β-carbon of the latter.[8]

Work by different research groups aimed at harnessing the homoenolate generated by this protocol by various electrophiles has led to the synthesis of a wide range of products including γ-butyrolactones,[5,6] γ-lactams,[9] spiro-γ-lactones,[10] δ-lactones,[11] cyclopentenes,[12] β-lactams,[13] and spirocyclopentanones.[14] Very recently, we have observed that reaction of homoenolate with chalcone in methanol led to the formation of the corresponding methyl β-hydroxycyclo pentane carboxylate instead of the cyclopentene formed in aprotic medium[15,16] (Scheme 1). The success of this reaction prompted us to explore the reactivity of sulfonimines with enals in methanol in anticipation of the formation of novel γ-amino butyric acid (GABA) derivatives. Parenthetically, it may be mentioned that GABA derivatives[17] have assumed great importance due to their exceptional therapeutic potential to alleviate several neurological disorders.[18] In this context, it is noteworthy that Bode has reported a homoenolate annulation, specific to *N*-(4-methoxybenzene) sulfonimine, in *tert*-butanol leading to γ-lactams.[9] Notwithstanding the limited substrate scope for this annulation reported by Bode, we set out to explore homoenolate reaction with sulfonimines in methanol. The preliminary results of our work leading to an efficient synthesis of GABA derivatives *via* a pathway not originally anticipated are reported in this communication.



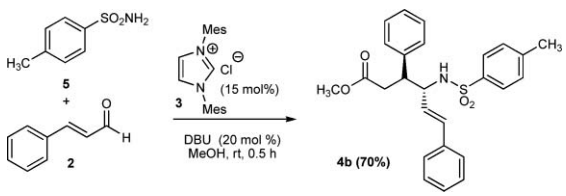
Scheme 1 Background and hypothesis.

The present studies were initiated by exposing a mixture of *p*-tolylbenzenesulfonimine and cinnamaldehyde in methanol to catalytic amount of imidazolium salt (IMesCl) and DBU at room temperature. The product obtained from this reaction in low yield was characterized as **4a** (Scheme 2).



Scheme 2 Attempted homoenolate addition to a pre-formed imine.

This interesting observation can be interpreted by invoking methanolysis of sulfonimine **1** leading to benzene sulfonamide,[19] subsequent formation of the conjugated sulfonimine from the latter and cinnamaldehyde followed by its reaction with homoenolate (*cf* Scheme 5). In view of this observation, we slightly modified the experimental protocol. A solution of *p*-tolylsulfonamide and cinnamaldehyde (4 equiv.) was exposed to IMesCl and DBU in methanol at room temperature. The reaction mixture on usual work up followed by chromatography afforded substituted GABA derivative **4b** in good yield (Scheme 3).



Scheme 3 Homoenolate addition to sulfonimine formed *in situ*.

The racemic product **4b** was characterized by conventional spectroscopic methods and its structure and relative stereochemistry confirmed by single crystal X-ray data[20] (Fig. 1).

A number of commonly used NHC catalysts were screened for assessing their utility in optimising this reaction and the results are summarized in Table 1. Triazolium catalysts were found

[a]*Organic Chemistry Section, National Institute for Interdisciplinary Science and Technology (CSIR), Trivandrum, 695 019, India. E-mail: vijaynair_2001@yahoo.com*
[b]*Central Salt and Marine Chemicals Research Institute, Bhavnagar, 364002, India*

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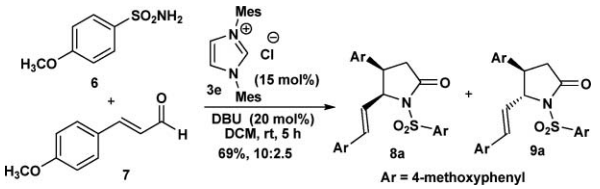
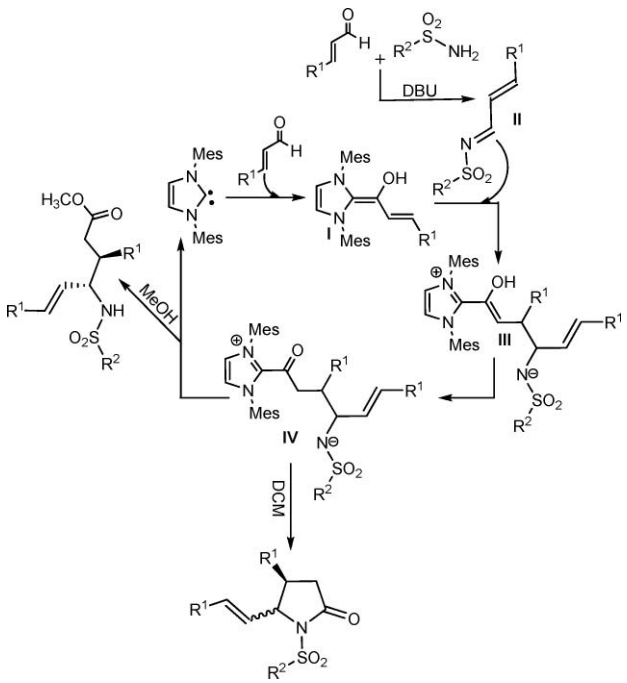


Scheme 4 Homoenolate annulation in dichloromethane.



Scheme 5 Postulated catalytic cycle.

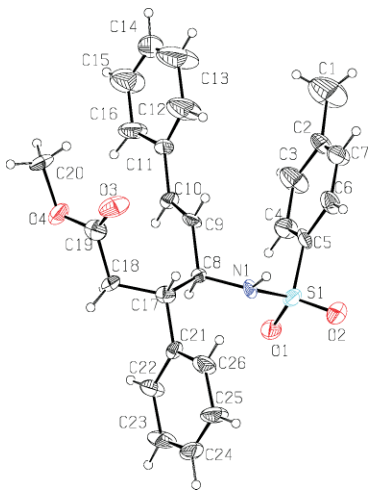
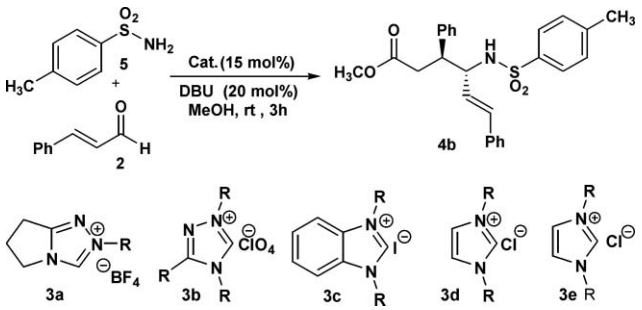


Fig. 1 Single crystal X-ray structure of **4b** (30% probability factor for the thermal ellipsoids).

to be ineffective in this reaction while imidazolium catalyst **3d** afforded the product in low yield. Among the various catalysts screened, **3e** was found to give the best results, in methanol at room temperature.

The reaction was extended to a number of enals and sulfonamides and the results are presented in Table 2.

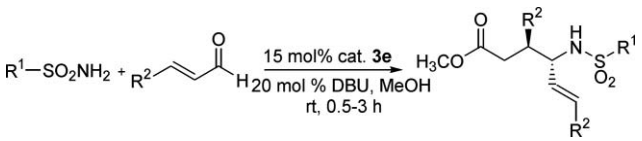
Table 1 Catalyst screening



Entry	Catalyst	Conditions[a]	Yield (%)[b]
1	**3a**	Methanol, rt, 24 h	—
2	**3b**	Methanol, rt, 24 h	—
3	**3c**	Methanol, rt, 24 h	—
4	**3d**	Methanol, rt, 24 h	19
5	**3e**	Methanol, rt, 0.5 h	70

[a] With one equiv. of sulfonamide and four equiv. of aldehyde 2. [b] Isolated yield, **3a** : R = pentaflourophenyl, **3b** : R = phenyl, **3c** : R = ethyl, **3d** : *R* = 2,6-diisopropylphenyl, **3e** : *R* = 2,4,6-trimethylphenyl.

Table 2 Substrate scope



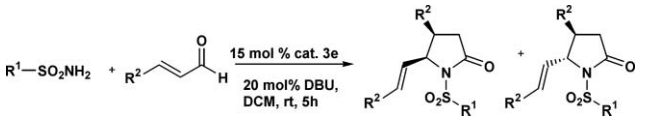
Entry	R^1	R^2	Product	Time/h	Yield (%)[a]
1	Phenyl	Phenyl	**4a**	0.5	97
2	4-Methoxyphenyl	Phenyl	**4c**	1	80
3	4-Methoxyphenyl	2-Methoxyphenyl	**4d**	1.5	91
4	4-Methylphenyl	3-Chlorophenyl	**4e**	3	65
5	4-Methoxyphenyl	3-Chlorophenyl	**4f**	3	74
6	4-Methylphenyl	2-Methoxyphenyl	**4g**	1	75
7	Phenyl	2-Methoxyphenyl	**4h**	1	95
8	4-Methylphenyl	4-Methoxyphenyl	**4i**	2	93
9	4-Methoxyphenyl	4-Methoxyphenyl	**4j**	2	97
10	Phenyl	4-Methoxyphenyl	**4k**	1.5	81
11	4-Methylphenyl	2-Thienyl	**4l**	3	72
12	4-Methoxyphenyl	2-Thienyl	**4m**	3	67

[a] Isolated yield.

While contemplating on a mechanistic postulate (Scheme 5) for this reaction and the role of methanol in delivering the final product, it occurred to us that in the absence of methanol, the intermediate **IV**, with no opportunity to undergo protonation would cyclize on to the carboxy surrogate to afford a γ-lactam and in the process will regenerate the NHC catalyst. In the event, when 4-methoxybenzene sulfonamide and 4-methoxy cinnamaldehyde were treated with IMesCl and DBU in dichloromethane, a mixture of γ-lactams **8a** and **9a** was obtained in good diastereomeric ratio (Scheme 4).

The products were characterized by spectroscopic analysis. Conclusive evidence for the structure and relative stereochemistry was obtained by single crystal X-ray analysis of the racemic compound **8a** (Fig. 2).

Table 3 Substrate scope



Entry	R^1	R^2	Products	Ratio	Yield (%)[a]
1	4-Methoxyphenyl	4-Methoxyphenyl	**8a** & **9a**	10 : 2.5	69
2	4-Methylphenyl	4-Methoxyphenyl	**8b** & **9b**	10 : 1.5	69
3	4-Methylphenyl	Phenyl	**8c** & **9c**	10 : 3	65
4	4-Methoxyphenyl	Phenyl	**8d** & **9d**	10 : 1.5	55
5	4-Methylphenyl	2-Methoxyphenyl	**8e** & **9e**	10 : 2	62
6	4-Methoxyphenyl	2-Methoxyphenyl	**8f** & **9f**	10 : 1	53
7	Phenyl	2-Methoxyphenyl	**8g** & **9g**	10 : 1.2	54
8	Phenyl	4-Methoxyphenyl	**8h** & **9h**	10 : 1	53
9	Phenyl	Phenyl	**8i** & **9i**	10 : 1.5	60

[a] Overall Yield.

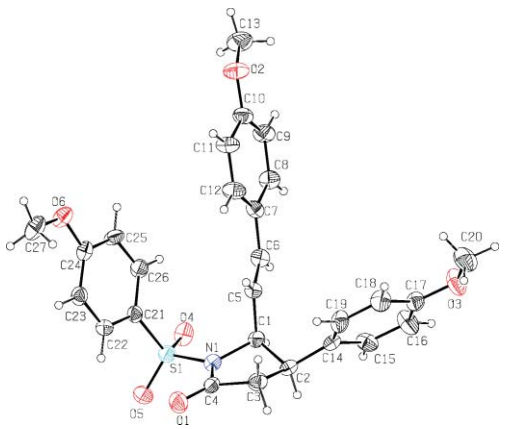


Fig. 2 Single crystal X-ray structure of **8a** (30% probability factor for the thermal ellipsoids).

The reaction was found to be general with a variety of sulfonamides and cinnamaldehydes. The results are summarized in Table 3.

A mechanistic rationalization for the reaction sequences leading to GABA derivative or the γ-lactam depending on the solvent used is presented in Scheme 5. The ease of methanolysis[21] of **IV** *vis a vis* its ring closure may be attributed to the higher efficiency in the formation of GABA derivative. The slower reaction of **IV** in DCM as well as its equilibration may be invoked to account for the formation of diastereomeric mixture in this case. The role played by solvent also cannot be ruled out. The intermediacy of lactam and its methanolysis leading to the formation of the open chain GABA derivative **4g**, however, can be ruled out by the failure of γ-lactam **8e** to afford even a trace of **4g**, when the former was subjected to the experimental conditions shown in Scheme 3.

In conclusion, we have chanced upon a versatile homoenolate reaction with sulfonimine leading to an efficient synthesis of novel GABA derivatives or γ-lactams. The formation of sulfonimine *in situ* as well as the high diastereoselectivity of the reaction, proceeding *via* twin pathways, is noteworthy.

Acknowledgements

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Notes and references

1 A. Nickon and J. L. Lambert, *J. Am. Chem. Soc.*, 1962, **84**, 4604–4605.
2 (*a*) E. Nakamura and I. Kuwajima, *J. Am. Chem. Soc.*, 1977, **99**, 7360–7362; (*b*) I. Kuwajima and E. Nakamura, *Comprehensive Organic Synthesis*, Ed., B. M. Trost and I. Fleming, Pergamon, New York, 1991, vol. 2, p. 441; (*c*) M. T. Crimmins, P. G. Nantermet, B. W. Trotter, I. M. Vallin, P. S. Watson, L. A. McKerlie, T. L. Reinhold, A. W.-H. Cheung, K. A. Stetson, D. Dedopoulou and J. L. Gray, *J. Org. Chem.*, 1993, **58**, 1038–1047.
3 (*a*) A. S. Bal, A. Marfat and P. Helquist, *J. Org. Chem.*, 1982, **47**, 5045–5050; (*b*) L. C. Pattenden, R. A. J. Wybrow, S. A. Smith, P. A. Joseph and J. P. A. Harrity, *Org. Lett.*, 2006, **8**, 3089–3091.
4 (*a*) D. Hoppe, *Angew. Chem., Int. Ed. Engl.*, 1984, **23**, 932–948; (*b*) Review: D. Hoppe, *Synthesis*, 2009, 43–61.
5 S. S. Sohn, E. L. Rosen and J. W. Bode, *J. Am. Chem. Soc.*, 2004, **126**, 14370–14371.
6 (*a*) C. Burstein and F. Glorius, *Angew. Chem., Int. Ed.*, 2004, **43**, 6205–6208; (*b*) C. Burstein, S. Tschan, X. Xie and F. Glorius, *Synthesis*, 2006, 2418–2439.
7 R. Breslow, *J. Am. Chem. Soc.*, 1958, **80**, 3719–3726.
8 For recent reviws on NHC catalysis, see: (*a*) D. Enders, O. Niemeier and A. Henseler, *Chem. Rev.*, 2007, **107**, 5606–5655; (*b*) Homoenolate chemistry, see:V. Nair, S. Vellalath and B. P. Babu, *Chem. Soc. Rev.*, 2008, **37**, 2691–2698.
9 M. He and J. W. Bode, *Org. Lett.*, 2005, **7**, 3131–3134.
10 (*a*) V. Nair, S. Vellalath, M. Poonoth, R. Mohan and E. Suresh, *Org. Lett.*, 2006, **8**, 507–509; (*b*) V. Nair, S. Vellalath, M. Poonoth, E. Suresh and S. Viji, *Synthesis*, 2007, 3195–3200.
11 V. Nair, M. Poonoth, S. Vellalath, E. Suresh and R. Thirumalai, *J. Org. Chem.*, 2006, **71**, 8964–8965.
12 V. Nair, S. Vellalath, M. Poonoth and E. Suresh, *J. Am. Chem. Soc.*, 2006, **128**, 8736–8737.
13 M. He and J. W. Bode, *J. Am. Chem. Soc.*, 2008, **130**, 418–419.
14 V. Nair, B. P. Babu, S. Vellalath and E. Suresh, *Chem. Commun.*, 2008, 747–749.
15 V. Nair, B. P. Babu, S. Vellalath, V. Varghese, A. E. Raveendran and E. Suresh, *Org. Lett.*, 2009, **11**, 2507–2510.
16 For the original reports on protonation of homoenolates, see: (*a*) A. Chan and K. A. Scheidt, *Org. Lett.*, 2005, **7**, 905–908; (*b*) B. E. Maki, A. Chan and K. A. Scheidt, *Synthesis*, 2008, 1306–1315; (*c*) S. S. Sohn and J. W. Bode, *Org. Lett.*, 2005, **7**, 3873–3876.
17 For selected references to the synthesis of GABA derivatives, see: (*a*) P. Wipf and C. R. J. Stephenson, *Org. Lett.*, 2005, **7**, 1137–1140; (*b*) F. Royer, F.-X. Felpin and E. Doris, *J. Org. Chem.*, 2001, **66**, 6487–6489; (*c*) R. B. Silverman, R. Andruszkiewicz, S. M. Nanavati, C. P. Taylor and M. G. Vartanian, *J. Med. Chem.*, 1991, **34**, 2295–2298; (*d*) C. G. Wermuth, A. Mann, A. Schoenfelder, R. A. Wright, B. G. Johnson, J. P. Burnett, N. G. Mayne and D. D. Schoepp, *J. Med. Chem.*, 1996, **39**, 814–816.
18 (*a*) O. A. Petroff, *Neuroscientist*, 2002, **8**, 562–573; (*b*) K. Li and I. Xu, *Neuroscience Bulletin*, 2008, **24**, 195–200.
19 Independent experiments in our laboratory have clearly shown that *p*-tolyl benzene sulfonimine when stirred in methanol with catalytic amount of DBU underwent rapid methanolysis to afford *p*-tolualdehyde dimethyl acetal and benzene sulfonamide. In the absence of DBU this reaction is very slow.
20 Crystal structure of compound **4b** and **8a** have been deposited at the Cambridge Crystallographic Data Centre and allocated reference no. are CCDC 737837 and CCDC 737838. Crystal data for compound

4b: $C_{26}H_{27}NO_4S$, $M = 449.55$, Monoclinic, $a = 43.586(9)$ Å, $\alpha = 90°$, $b = 5.4702(12)$ Å, $\beta = 117.916(4)°$, $c = 22.829(5)$ Å, $\gamma = 90°$, $V = 4809.7(18)$ Å^3, $T = 293(2)$ K, Space group = $C2/c$, $Z = 8$, Number of reflections = 8857, Independent reflections = 3116 [R(int) = 0.0782], Final R indices [$I > 2\sigma(I)$] $R_1 = 0.1650$, w$R_2 = 0.3653$, R indices (all data) $R_1 = 0.1986$, w$R_2 = 0.3815$. Crystal data for compound **8a**: $C_{27}H_{27}NO_6S$, $M = 493.56$, Monoclinic, $a = 18.498(11)$ Å, $\alpha = 90°$, $b = 6.806(4)$ Å, $\beta = 108.307(11)°$, $c = 20.715(13)$ Å, $\gamma = 90°$, $V = 2476(3)$ Å^3, $T = 293(2)$ K, Space group = P21/n, $Z = 4$, Number of reflections = 9340, Independent reflections = 3239 [R(int) = 0.0482], Final R indices [$I > 2\sigma(I)$] $R_1 = 0.1000$, w$R_2 = 0.1725$, R indices (all data) $R_1 = 0.1142$, w$R_2 = 0.1783$.

21 Conceivably, the initial protonation may occur with the aid of the protonated DBU.

