Pergamon

SCIENCE DIRECT®

Tetrahedron Letters 44 (2003) 523–525

TETRAHEDRON LETTERS

Synthesis and 1,3-dipolar cycloadditions of a new enantiopure cyclic nitrone

Ramón Alibés,[a] Pilar Blanco,[a] Pedro de March,[a] Marta Figueredo,[a,*] Josep Font,[a] Ángel Álvarez-Larena[b] and Juan F. Piniella[b]

[a]*Departament de Química, Universitat Autònoma de Barcelona, E-08193 Bellaterra, Spain*
[b]*Unitat de Cristal·lografia, Universitat Autònoma de Barcelona, E-08193 Bellaterra, Spain*

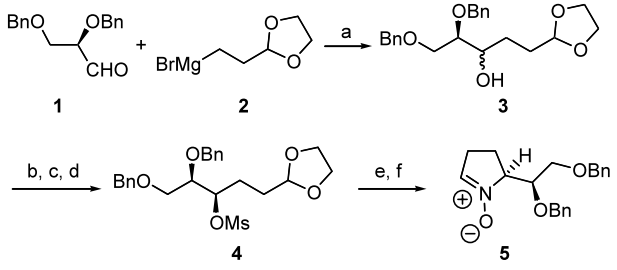
Received 4 November 2002; accepted 14 November 2002

Abstract—A new enantiopure cyclic nitrone has been efficiently synthesized from a D-glyceraldehyde derivative. It's 1,3-dipolar cycloaddition to different classes of dipolarophiles show complete antifacial selectivity, furnishing highly functionalized enantiopure bicyclic isoxazolidines.

The utility of nitrones in synthetic organic chemistry has been widely illustrated.[1] The main reactions involving such compounds are nucleophilic addition, and 1,3-dipolar cycloaddition to olefins and acetylenes. Both of these processes have been used as key steps in the preparation of diverse target molecules containing nitrogen. A very important aspect of these reactions is the control of the configuration of the newly generated stereogenic centers and, although noticeable efforts have been devoted to this end,[2] there is still a need for further practical solutions in this field.

Up to now, the enantioselective catalysis in reactions involving nitrones[2,3] has reached quite limited success and good results have been found mainly in reactions involving aromatic nitrones as substrates. Alternatively, preparations of several enantiopure nitrones from starting materials of the chiral pool have been described,[2a,b,4] and currently the use of such substrates seems the most practical choice for nitrone based stereoselective synthesis. Among them, five membered cyclic nitrones have received particular attention, principally due to their utility as precursors of pyrrolizidine alkaloids, and several groups including ours have developed methodologies to access differently substituted pyrrolidine *N*-oxides in enantiopure form.[4a,b,e,f,g,j,k,5] Here we present a very efficient and stereoselective synthesis of the new nitrone **5** and an overview of it's 1,3-dipolar cycloaddition to several kind of dipolarophiles.

The synthesis of nitrone **5**, outlined in Scheme 1, starts from di-*O*-benzyl-D-glyceraldehyde, **1**, which can be readily prepared from D-mannitol.[6] Reaction of **1** with the Grignard reagent **2**[7] furnishes a ca. 1:1 mixture of the *syn* and *anti* alcohols **3** in 67% yield. The proportion of the *syn* isomer can be increased by in situ generation of the corresponding cuprate species,[8] but the inability of separating the diastereomeric alcohols makes it more practical to oxidize the mixture and then reduce the resulting ketone with L-Selectride®. This procedure renders exclusively the alcohol *syn*-**3** in 55% overall yield from **1**. Mesylation of *syn*-**3**, followed by hydrolysis of the acetal and then treatment with hydroxylamine provides the target nitrone **5**, $[\alpha]_D = -37$



Scheme 1. *Reagents and conditions*: (a) THF, rt, 4 h, 67%; (b) Dess–Martin, CH_2Cl_2, 2 h, 95%; (c) L-Selectride®, THF, −78°C, 87%; (d) MsCl/pyr., CH_2Cl_2, rt, 3 days, 89%; (e) 2 M HCl/THF, 50°C, 16 h, 96%; (f) $NH_2OH{\cdot}HCl$/pyr., ^{t}BuOH, 80°C, 4 days, 67%.

Keywords: enantiopure cyclic nitrone; dipolar cycloaddition; facial selectivity.

* Corresponding author. Tel.: +34-93-5811853; fax: +34-93-5811265; e-mail: marta.figueredo@uab.es

0040-4039/03/$ - see front matter
PII: S0040-4039(02)02587-X

(c 1.8, $CHCl_3$), in 57% yield. This sequence may be easily performed in a multi-gram scale and batches of up to 4 g of **5** have been prepared in a single operation.

The enantiomeric purity of alcohol *syn*-**3** was established by ^1H NMR analysis of the diastereomeric corresponding Mosher esters, while the absolute configuration of nitrone **5** was confirmed by X-ray analysis of a derivative (vide infra).

The 1,3-dipolar cycloaddition of **5** to a series of dipolarophiles **6**–**11** (Fig. 1) was then investigated, with the aim of determining the scope of this chiral nitrone as asymmetric inductor in such processes. The results of this study are summarized in Table 1.

The relative configuration of the newly generated stereogenic centers in the isolated cycloadducts was determined by ^1H NMR analyses, including NOE experiments, while an X-ray analysis of a single crystal of compound **14**[9] (Fig. 2) provided evidence for the relative configuration of the chiral centers already present in the starting nitrone. Consequently, the absolute stereochemistry of all the new compounds **3**–**5** and **12**–**20** was undoubtedly secured.

The *endo*/*exo* selectivity followed the expected bias[1,2a,b] and it was very high in all cases, except for vinylene carbonate, **11**, which showed a moderate preference for the *exo* reaction course. Among the cases studied, this dipolarophile was also the single one to afford a

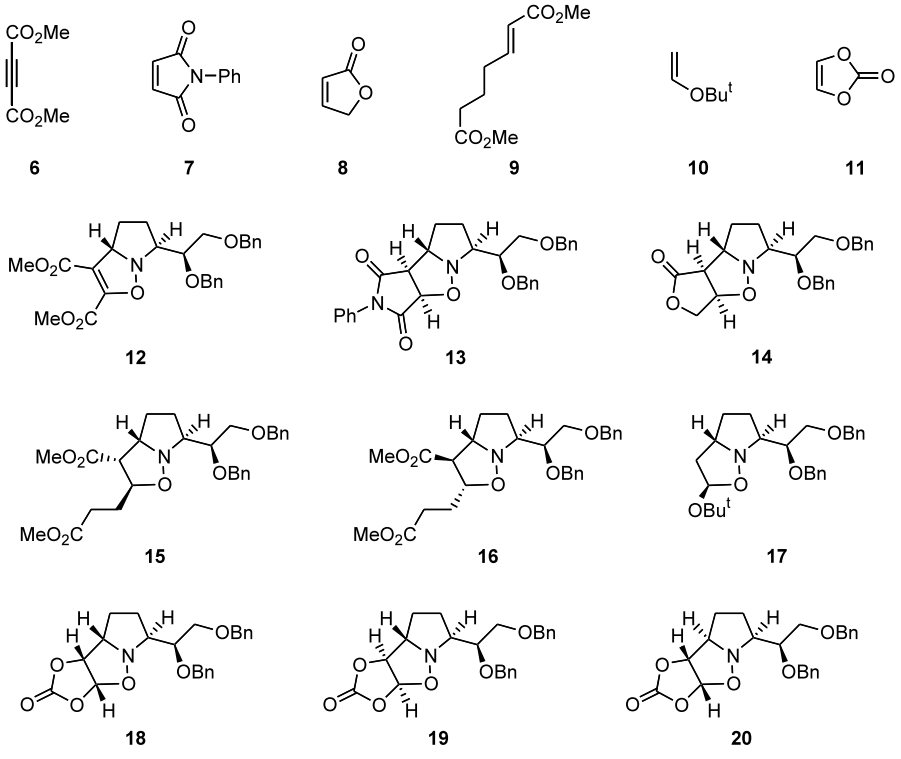


Figure 1. Compounds **6**–**11** were used as dipolarophiles in cycloaddition reactions to the enantiopure nitrone **5**. The cycloadducts **12**–**20** were isolated from these reactions.

Table 1. 1,3-Dipolar cycloaddition of nitrone **5** to dipolarophiles **6**–**11**

Dipolarophile[a]	Solvent[b]	Time[c]	*endo*–*anti*[d]	*exo*–*anti*[d]	*exo*–*syn*[d]
6	$CHCl_3$	30 min	**12** (89%)[e]	**12** (89%)[e]	–
7	Toluene	2 h	–	**13** (87%)	–
8	Toluene	2 h	–	**14** (89%)	–
9	Toluene	2 h	**15** (83%)[f]	**16** (7%)	–
10	$CHCl_3$	4 h	–	**17** (89%)	–
11	Toluene	20 h	**18** (23%)	**19** (36%)	**20** (11%)

[a] A 10% excess of dipolarophile was used in all runs, except for **11** which was used in a five molar excess.
[b] The reactions were performed at the reflux temperature.
[c] The reactions were run until complete consumption of nitrone **5** according to TLC analysis.
[d] Yields are referred to isolated pure products.
[e] *endo*/*exo* selectivity does not apply to this case.
[f] *endo* related to the ester substituent of the starting olefin.

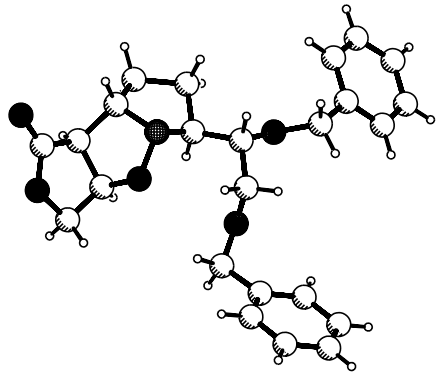


Figure 2. Molecular structure of **14**.

detectable amount of a cycloadduct derived from a synfacial approach.

In conclusion, we have accomplished a very efficient synthesis of the new enantiopure pyrrolidine *N*-oxide **5**, through a very practical sequence, easily scalable, and we have studied its 1,3-dipolar activity towards diversely substituted dipolarophiles. The cycloaddition reactions of nitrone **5** occur with very high yields and stereoselectivity, providing access to a series of densely functionalized enantiopure compounds, demonstrating its high potential in asymmetric synthesis.

Acknowledgements

We thank Generalitat de Catalunya for the award of predoctoral fellowships to P.B. This research was supported by the DGES (project BQU2001-2600) and the CIRIT (project 2001SGR 00178).

References

1. (a) Tufariello, J. J. In *1,3-Dipolar Cycloaddition Chemistry*; John Wiley & Sons: New York, 1984; Vol. 2, Chapter 9; (b) Torssell, K. B. G. In *Nitrile Oxides, Nirones, and Nitronates in Organic Synthesis*; VCH Verlagsgesellschaft: Weinheim, 1988; (c) Bloch, R. *Chem. Rev.* **1998**, *98*, 1407–1438.
2. (a) Frederickson, M. *Tetrahedron* **1997**, *53*, 403–425; (b) Gothelf, K. V.; Jørgensen, K. A. *Chem. Rev.* **1998**, *98*, 863–909; (c) Gothelf, K. V.; Jørgensen, K. A. *Chem. Commun.* **2000**, 1449–1458; (d) Merino, P.; Franco, S.; Merchan, F. L.; Tejero, T. *Synlett* **2000**, 442–454; (e) Lombardo, M.; Trombini, C. *Synthesis* **2000**, 759–774.
3. (a) Bayón, P.; de March, P.; Espinosa, M.; Figueredo, M.; Font, J. *Tetrahedron: Asymmetry* **2000**, *11*, 1757–1765; (b) Bayón, P.; de March, P.; Figueredo, M.; Font, J.; Medrano, J. *Tetrahedron: Asymmetry* **2000**, *11*, 4269–4278; (c) Jensen, K. B.; Roberson, M.; Jørgensen, K. A. *J. Org. Chem.* **2000**, *65*, 9080–9084; (d) Ding, X.; Taniguchi, K.; Ukaji, Y.; Inomata, K. *Chem. Lett.* **2001**, 468–469; (e) Mita, T.; Ohtsuki, N.; Ikeno, T.; Yamada, T. *Org. Lett.* **2002**, *4*, 2457–2460; (f) Lo, M. M.-C.; Fu, G. C. *J. Am. Chem. Soc.* **2002**, *124*, 4572–4573; (g) Viton, F.; Bernardinelli, G.; Kündig, E. P. *J. Am. Chem. Soc.* **2002**, *124*, 4968–4969.
4. (a) Hall, A.; Meldrum, K. P.; Therond, P. R.; Wightman, R. H. *Synlett* **1997**, 123–125; (b) Closa, M.; de March, P.; Figueredo, M.; Font, J. *Tetrahedron: Asymmetry* **1997**, *8*, 1031–1037; (c) Merino, P.; Franco, S.; Merchan, F. L.; Tejero, T. *Tetrahedron: Asymmetry* **1997**, *8*, 3489–3496; (d) Closa, M.; Wightman, R. H. *Synth. Commun.* **1998**, *28*, 3443–3450; (e) Murahashi, S.-I.; Ohtake, H.; Imada, Y. *Tetrahedron Lett.* **1998**, *39*, 2765–2766; (f) Cicchi, S.; Nunes, J., Jr.; Goti, A.; Brandi, A. *Eur. J. Org. Chem.* **1998**, 419–421; (g) Goti, A.; Cacciarini, M.; Cardona, F.; Brandi, A. *Tetrahedron Lett.* **1999**, *40*, 2853–2856; (h) Chiacchio, U.; Corsaro, A.; Gumina, G.; Rescifina, A.; Iannazzo, D.; Piperno, A.; Romeo, G.; Romeo, R. *J. Org. Chem.* **1999**, *64*, 9321–9327; (i) Carda, M.; Portolés, R.; Murga, J.; Uriel, S.; Marco, J. A.; Domingo, L. R.; Zaragozá, R. J.; Röper, H. *J. Org. Chem.* **2000**, *65*, 7000–7009; (j) Cordero, F. M.; Gensini, M.; Goti, A.; Brandi, A. *Org. Lett.* **2000**, *2*, 2475–2477; (k) Busqué, F.; de March, P.; Figueredo, M.; Font, J.; Gallagher, T.; Milán, S. *Tetrahedron: Asymmetry* **2002**, *13*, 437–445.
5. (a) Golik, J.; Wong, H.; Krishnan, B.; Vyas, D. M.; Doyle, T. W. *Tetrahedron Lett.* **1991**, *32*, 1851–1854; (b) Ballini, R.; Marcantoni, E.; Petrini, M. *J. Org. Chem.* **1992**, *57*, 1316–1318; (c) Oppolzer, W.; Bochet, C. G.; Merifield, E. *Tetrahedron Lett.* **1994**, *35*, 7015–7018; (d) Cicchi, S.; Goti, A.; Brandi, A. *J. Org. Chem.* **1995**, *60*, 4743–4748; (e) Ishikawa, T.; Tajima, Y.; Fukui, M.; Saito, S. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1863–1864.
6. Ashton, W. T.; Canning, L. F.; Reynolds, G. F.; Tolman, R. L.; Karkas, J. D.; Liou, R.; Davies, M.-E. M.; DeWitt, C. M.; Perry, H. C.; Field, A. K. *J. Med. Chem.* **1985**, *28*, 926–933.
7. Büchi, G.; Wüest, H. *J. Org. Chem.* **1969**, *34*, 1122–1123.
8. Mead, K.; MacDonald, T. L. *J. Org. Chem.* **1985**, *50*, 422–424.
9. Crystallographic data (excluding structure factors) for the structure have been deposited within the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 196484.