ORGANIC LETTERS

2008
Vol. 10, No. 18
4081−4084

C−C Bond-Forming Desulfurizations of Sulfoximines

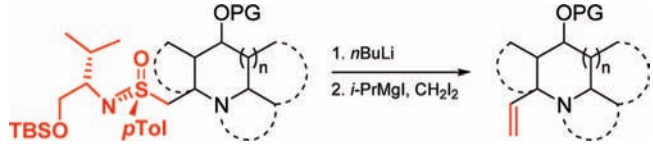
M. Reggelin,*,† S. Slavik,‡ and P. Bühle§

Clemens-Schöpf-Insitut für Organische Chemie and Biochemie, Petersenstrasse 22, Technische Universität, 64287 Darmstadt, Germany, Merck KGaA, Frankfurter Str. 250, 64293 Darmstadt, Germany, and General Motors Europe Engineering, Peter Sander Strasse 43, 55252 Mainz-Kastel, Germany

re@punk.oc.chemie.tu-darmstadt.de

Received July 14, 2008

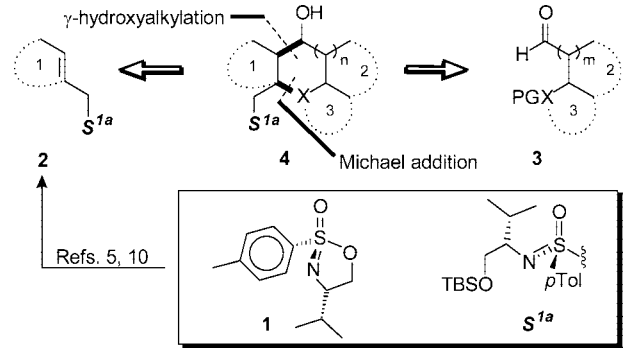
ABSTRACT



Highly substituted, enantiomerically pure azaheterocyclic ring systems play an important role in medicinal chemistry as potential peptide mimetics. Metalated 2-alkenyl sulfoximines offer an efficient entry to this class of compounds. In this paper, we describe a new means to remove the sulfonimidoyl auxiliary with concomitant formation of a C−C double bond.

Since the days of their discovery,[1] sulfoximines have evolved into an important class of compounds.[2] This is true in particular for their application as chiral ligands[3] as well as chiral auxiliaries.[2] Enantiomerically pure 2-alkenyl sulfoximines **2** derived from cyclic sulfonimidates[4] such as **1** have been introduced by us in 1994 as efficient solutions for asymmetric d^3-synthons (Scheme 1).[5] Titanated sulfoximines derived from **2** undergo γ-hydroxyalkylation reactions with

Scheme 1. Overview



α- or β-heteroatom-substituted aldehydes **3** furnishing isomerically pure γ-hydroxy vinylsulfoximines, which in turn cyclize to highly substituted hetero(poly)cyclic ring systems **4** (X = O[6] or X = N[7]).

Based on an alternative classification scheme for β-turn structures proposed by Ball in 1993,[8] we envisaged the

† Technische Universität Darmstadt.
‡ Present affiliation: General Motors Europe Engineering.
§ Present affiliation: Merck KGaA.

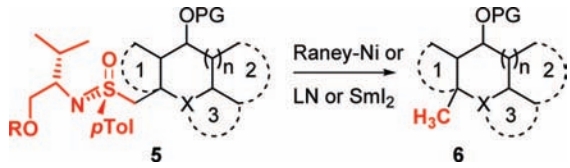
(1) Bentley, H. R.; McDermott, E. E.; Pace, J.; Whitehead, J. K.; Moran, T. *Nature* **1949**, *163*, 675–676.
(2) Gais, H. J. *Heteroatom. Chem.* **2007**, *18*, 472–481. Okamura, H.; Bolm, C. *Chem. Lett.* **2004**, *33*, 482–487. Reggelin, M.; Zur, C. *Synthesis* **2000**, 1–64.
(3) Lu, S.-M.; Bolm, C. *Adv. Synth. Catal.* **2008**, *350*, 1101–1105. Lemasson, F.; Gais, H. J.; Raabe, G. *Tetrahedron Lett.* **2007**, *48*, 8752–8756. Spohr, V.; Kaiser, J. P.; Reggelin, M. *Tetrahedron: Asymmetry* **2006**, *17*, 500–503. Reetz, M. T.; Bondarev, O. G.; Gais, H. J.; Bolm, C. *Tetrahedron Lett.* **2005**, *46*, 5643–5646. Reggelin, M.; Weinberger, H.; Spohr, V. *Adv. Synth. Catal.* **2004**, *346*, 1295–1306. Bolm, C.; Verrucci, M.; Simic, O.; Cozzi Pier, G.; Raabe, G.; Okamura, H. *Chem Commun.* **2003**, 2826–2827. Bolm, C.; Martin, M.; Simic, O.; Verrucci, M. *Org. Lett.* **2003**, *5*, 427–429. Bolm, C.; Simic, O.; Martin, M. *Synlett* **2001**, 1878–1880.
(4) Reggelin, M.; Junker, B. *Chem. Eur. J.* **2001**, *7*, 1232–1239.
(5) (a) Reggelin, M.; Weinberger, H.; Gerlach, M.; Welcker, R. *J. Am. Chem. Soc.* **1996**, *118*, 4765–4777. (b) Reggelin, M.; Weinberger, H. *Angew. Chem., Int. Ed.* **1994**, *33*, 444–446.
(6) Reggelin, M.; Gerlach, M.; Vogt, M. *Eur. J. Org. Chem.* **1999**, 1011–1031. Reggelin, M.; Weinberger, H.; Heinrich, T. *Liebigs Ann. Recl.* **1997**, 1881–1886.

10.1021/ol8015995 CCC: $40.75
Published on Web 08/20/2008

development of the azapolycyclic systems (**4**, X = N) accessible via 2-alkenyl sulfoximines into *type-III* peptidomimetics.[9] For this to be successful, both the constitutional as well as the configurational scope of the reaction sequence leading to the desired compounds has to be as broad as possible.

Furthermore, a reliable and profitable method to remove the auxiliary has to be found. Whereas the former demand has been shown to be fulfilled,[7,10] the removal of the sulfonimidoyl moiety clearly needed improvement. For the oxacycles (**4**, X = O) and some of the azacycles (**4**, X = N), the application of Raney nickel was successful.[7a] Moreover, reductive desulfurizations with lithium naphthalenide (LN) proved to be an alternative for the azacycles (Scheme 2).[7]

Scheme 2. Nonfunctionalizing Desulfurizations[a]

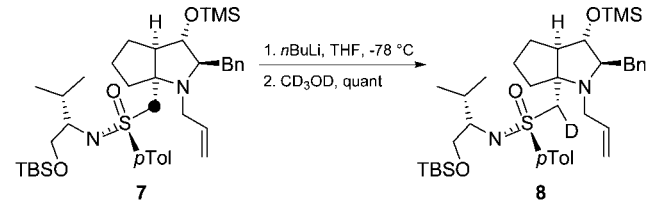


[a]LN: Lithium naphthalenide, R = H or TBS, X = N or O.

Despite these successes, several shortcomings remain. Raney nickel gives reliable results only in the case of the oxacycles; the yields with the azacycles are variable and often unsatisfactory. Desulfurizations with LN require electron-donating substituents at nitrogen and are plagued by β-elimination leading to ring-opened products (with the oxacycles this is the main reaction). The most reliable method until now has been the reduction with SmI_2.[7] For this desulfurization to work, it is necessary to have the nitrogen Boc-protected and the auxiliary deprotected (R = H, Scheme 2). This in turn demands for the absence of ring 3, which is obviously a constitutional drawback. A severe disadvantage of all three variants is the generation of a methyl group which does not allow any further functionalization. On the other hand, in the course of our experiments with 2-oxabicyclo[3.3.0]octanes we developed a sequence to angular vinyl-substituted derivatives.[5a] Unfortunately, this procedure suffers from the instability of the α-methylated allylic sulfoximines used as starting material toward elimination to the corresponding dienes, and even worse, we were not able to apply this chemistry to the azacyclic systems.

For these reasons, we turned our attention to postcyclization modifications. Not unexpectedly, this turned out to be rather difficult (Scheme 3). The carbon next to the sulfonimidoyl moiety (α-carbon) is in a neopentyl position. Therefore, even after electrophilic activation of the latter, nucleophilic substitution should be hampered by steric hindrance.

Scheme 3. Deuteration of the α-Position



●: Neopentyl position

This was found to be the case indeed.[11] Consequently, we next tried to deprotonate the α-position of *N*-donor substituted derivatives like **7**. From deuteration experiments, we learned that carbanion formation takes place but the deuteron was the only electrophile able to attack this position (no reaction occurred with allyl bromide, acrolein and acetaldehyde!). Interestingly, **8** was isolated as a single isomer. At this point, we realized that only a highly reactive, sterically nondemanding reagent might be able to form a bond to this extremely hindered position. These considerations led us to the conclusion to try carbenoids as reaction partners. Theory predicts iodomethyl lithium to be a carbenoid of extraordinary high electrophilicity.[12] On the other hand, due to its pronounced thermal instability,[13] we decided to apply the corresponding magnesium derivative.[14a−c] Following the work of Julia on the olefinating desulfurization of sulfones,[14c,d] we reacted a series of sulfonimidoylmethyl-substituted azacycles with the carbenoid generated from diiodomethane and isopropylmagnesium iodide (Table 1).

These experiments were performed using two flasks connected by a glass capillary (see the Supporting Information). The whole assembly was immersed in a dry ice−acetone bath, and one flask contained the deprotonated sulfoximine and the other one the carbenoid solution prepared by adding diiodomethane to the Grignard reagent. After 1 h at −78 °C, the α-deprotonated azacycle was added dropwise to the carbenoid solution under isothermal conditions using the

(7) (a) Reggelin, M.; Junker, B.; Heinrich, T.; Slavik, S.; Bühle, P. *J. Am. Chem. Soc.* **2006**, *128*, 4023–4034. (b) Reggelin, M.; Heinrich, T. *Angew. Chem., Int. Ed.* **1998**, *37*, 2883–2886.

(8) Ball, J. B.; Hughes, R. A.; Alewood, P. F.; Andrews, P. R. *Tetrahedron* **1993**, *49*, 3467–3478.

(9) Rich, D. H.; Ripka, A. S. *Curr. Opin. Chem. Biol.* **1998**, *2*, 441–452.

(10) Reggelin, M.; Kühl, J.; Kaiser, J. P.; Bühle, P. *Synthesis* **2006**, 2224–2232.

(11) Nevertheless, with *N*-methyl-substituted sulfoximines this has been shown to be possible. Rajender, A.; Gais, H. J. *Org. Lett.* **2007**, *9*, 579–582. Gais, H.-J.; Loo, R.; Roder, D.; Das, P.; Raabe, G. *Eur. J. Org. Chem.* **2003**, 1500–1526. Kohler, F.; Gais, H. J.; Raabe, G. *Org. Lett.* **2007**, *9*, 1231–1234. Adrien, A.; Gais, H. J.; Kohler, F.; Runsink, J.; Raabe, G. *Org. Lett.* **2007**, *9*, 2155–2158.

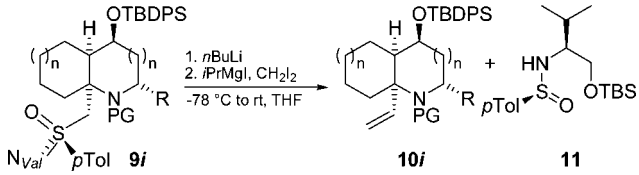
(12) (a) Zhou, Y. B.; Cao, F. L. *J. Organomet. Chem.* **2007**, *692*, 3723–3731. (b) Boche, G.; Lohrenz, J. C. W. *Chem. Rev.* **2001**, *101*, 697–756.

(13) Köbrich, G. *Angew. Chem., Int. Ed.* **1972**, *11*, 473–485. Köbrich, G.; Von Nagel, R. *Chem.-Ztg.* **1970**, *94*, 984–985.

(14) (a) Villieras, J. *Bull. Soc. Chim. Fr.* **1967**, 1520–1532. (b) Hahn, R. C.; Tompkins, J. *Tetrahedron Lett.* **1990**, *31*, 937–940. (c) De Lima, C.; Julia, M.; Verpeaux, J. N. *Synlett* **1992**, 133–134. (d) Charreau, P.; Julia, M.; Verpeaux, J.-N. *J. Organomet. Chem.* **1989**, *379*, 201.

(15) (a) Plietker, B.; Seng, D.; Fröhlich, R.; Metz, P. *Eur. J. Org. Chem.* **2001**, 3669–3676. (b) Plietker, B.; Metz, P. *Tetrahedron Lett.* **1998**, *39*, 7827–7830. (c) Pearlman, B. A.; Putt, S. R.; Fleming, J. A. *J. Org. Chem.* **2006**, *71*, 5646–5657.

Table 1. Desulfurization Experiment



entry	n	PG	R	*i*	yield [%]			method
					9*i*	**10*i***	**11**	
1	**1**	**Me**	**H**	**a**	46	**26**	26	a)
2	**1**	**Allyl**	**H**	**b**	12	**75**	32	a)
3	**1**	**Bn**	**H**	**c**	25	**66**	36	a)
4	**0**	**PMB**	**Ph**	**d**	17	**50**	35	a)
5	**0**	**Allyl**	**Ph**	**e**	5	**83**	34	a)
6	**0**	**Bn**	**Ph**	**f**	37	**63**	38	a)
7	**1**	**Bn**	**H**	**c**	77	**14**	-	b)
8	**1**	**Bn**	**H**	**c**	35	**60**	24	c)
9	**1**	**Bn**	**H**	**c**	53	**27**	34	d)
10	**1**	**Boc**	**H**	**g**	0[e]	**0**[e]	0[e]	a)

[a] *n*-BuLi (1 equiv), *i*-PrMgI, and CH_2I_2 (10 equiv each). [b] One-pot protocol: *n*-BuLi (1 equiv), CH_2I_2 (10 equiv), *i*-PrMgI (10 equiv). [c] Same as (a) but 12 h at −78 °C, quench at −78 °C. [d] Same as (c) but only 1 h reaction time. [e] Ring-opened product **16** was formed (Scheme 5).

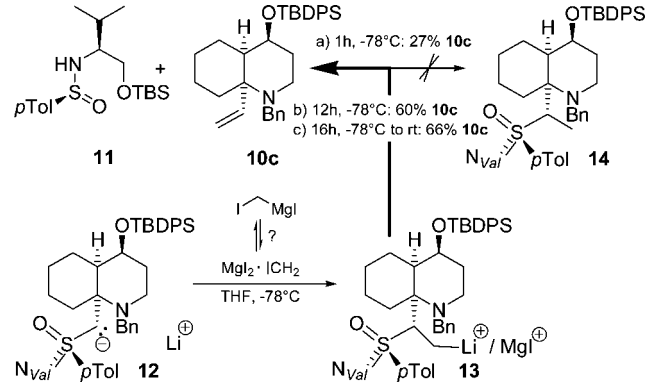
cooled capillary. Finally, the reaction mixture was stirred overnight at which point it reached room temperature (method a) in Table 1). To our delight, both the 2-azabicyclo-[3.3.0]octanes ($n = 0$) as well as the 2-azabicyclo[4.4.0]decanes ($n = 1$) delivered the expected angular vinyl substituted products **10i** in reasonable to good yields, depending on the *N*-protecting group.

These results clearly demonstrate again the enhanced electrophilicity of α-metalated alkyl halogenides as compared to the halogenides themselves as was demonstrated experimentally[14b] and predicted by theory.[12]

Mechanistically, it seems reasonable that the α-deprotonated sulfoximine **12** reacts first with either iodomethylmagnesium iodide or the magnesium iodide complexed methylene[12b] to yield carbanionic species **13** which in turn *β*-eliminates to the desired olefin **10c** and sulfinamide **11** (Scheme 4). By comparison with an independently synthesized sample, it was shown that this amide was generated with complete retention of the sulfur configuration.

The whole process is somewhat related to olefinating desulfurizations of sultones[15a] and sulfones.[15b] An interesting difference is that in our case the carbanionic intermediate **13** cannot be trapped to the α-methylated sulfoximine **14** by protonation. Instead, quenching the reaction after 1 or 16 h at −78 °C delivered only the olefin **10c** in 27% or 60% yield, respectively. Therefore, we conclude that with our systems the carbenoid uptake is rate limiting and the subsequent elimination is a fast process which in turn is in accordance with our finding that the deprotonated α-position is almost inert toward electrophilic substitution (s. above).

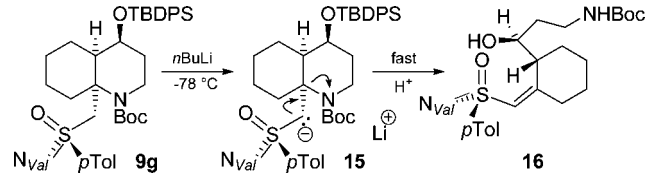
Scheme 4. Mechanistic Considerations[a]



[a] The α-methylated product **14** was never observed.

As can be seen from Table 1, *N*-protection by an electron-releasing substitutent is a necessary precondition for the reaction to work with the catalytically cleavable allyl or benzyl groups being particularly useful. Indeed, the *N*-Boc-protected azabicycle **9g** was not desulfurized under standard reaction conditions (Table 1, entry 10), but delivered the ring opened product **16** in 60% yield (already 47% after only 1 min. reaction time, Scheme 5).

Scheme 5. Retro-Michael Addition with EWG-Protected Derivatives



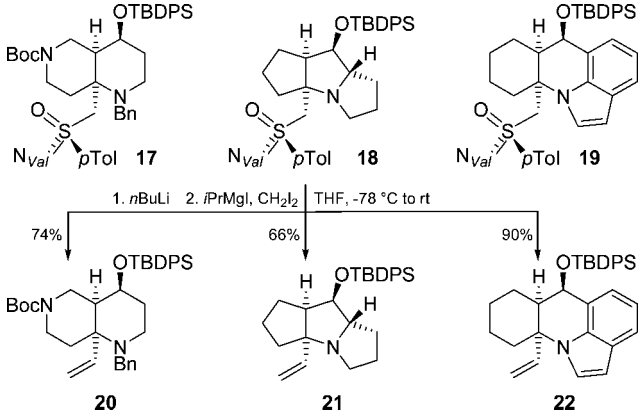
In order to facilitate the experimental procedure we next tried to develop a one-pot variant of the reaction. Toward this end, we first tried to combine the deprotonation with carbenoid formation.

In a first experiment at −78 °C, we added 11 equiv of isopropylmagnesium iodide to sulfoximine **9c** to deprotonate the α-position. After that, 10 equiv of CH_2I_2 were added to generate the carbenoid which was expected to react with the carbanion. Unfortunately, after aqueous workup, the starting material was recovered quantitatively which was also found after replacement of the Grignard reagent by the same amount of *n*-BuLi. A deuteration experiment showed that the former was not basic enough to deprotonate the sulfoximine, thus explaining the failure of the first variant. The lack of success for the *n*-BuLi based variant remains unclear. This disappointing outcome of the reaction is somewhat surprising; the more so as a slight variation in the reaction conditions was met with at least partial success. When 1 equiv of *n*-BuLi was employed to deprotonate the sulfoximine, 10 equiv each of the Grignard and CH_2I_2 were added

to generate the carbenoid, and this was allowed to react with the carbanion, 14% of the olefin was isolated after all. Two conclusions may be drawn from these results. First, the metalated sulfoximine obviously competes for the CH_2I_2 whereby starting material is regenerated by protonation. Second, iodomethylmagnesium iodide appears to react differently with the carbanion as compared to lithiomethyl iodide. Obviously, only the former undergoes electrophilic substitution. Therefore, the deprotonation step and the carbenoid generation have to be separated, entailing the above-described two-vessel procedure to be the superior one.

Based on the successful desulfurization of the azabicyclo[4.4.0]decanes and azabicyclo[3.3.0]octanes depicted in Table 1, we next explored the constitutional scope of the reaction. Beside the decahydro[1,6]naphthyridin derivative **17**,[10] the tricyclic and quadricyclic sulfoximines **18** and **19** were of particular interest (Scheme 6).

Scheme 6. Constitutional Scope



These latter two compounds were resistant toward any other desulfurization method tried so far (LN, SmI_2, sodium amalgam). To our delight, the new functionalizing desulfurization worked very well in all these cases, delivering the highly functionalized polycyclic ring systems **20**−**22**. In connection with our efforts to develop peptide mimetics based on the asymmetric synthesis of azapolycyclic compounds from 2-alkenyl sulfoximines,[7a] this olefinating desulfurization represents a major breakthrough.

It not only permits the removal of the auxiliary, it adds value to the systems by the installation of a vinyl group suited for numerous further functionalizations. Moreover, as already mentioned, the sulfonimidoyl moiety is transformed to sulfinamide **11** with complete retention of the sulfur configuration, thus allowing the recyclisation of the auxiliary.[4,16]

In summary, we have developed a new functionalizing desulfurization for sulfoximines in the course of which a sulfonimidoylmethyl moiety is replaced by a vinyl group. The method relies on the electrophilic substitution of lithiated sulfoximines by the carbenoid generated from diiodomethane and isopropylmagnesium iodide followed by β-elimination. The reaction works even with sterically highly congested systems such as the ones described in this paper (neopentyl position).

Future work will be devoted to the synthesis of peptide mimetics following the strategy outlined in a previous publication.[7a] Moreover, the structural proximity of the 2-azabicyclo[4.4.0]derivatives **10** to the cyclindricine alkaloids[17] offers opportunities to explore synthetic routes to these biologically active compounds. Finally, the pyrrolo[3,2,1-*ij*]quinoline fragment embedded in the quadricycle **22** recommends this compound and derivatives thereof as potential 5-HT_{2c} receptor agonists[18] or indole analogues of flavonols.[19]

Acknowledgment. We gratefully acknowledge Solvay Pharmaceuticals (Hannover, Germany) for generous support.

Supporting Information Available: Experimental details and NMR spectra of compounds **10a**−**f**, **16**, and **20**−**22** and experimental data for the preparation of the starting *N*,*O*-protected sulfoximines **9a**−**g** as well as **17**−**19**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL8015995

(16) Reggelin, M.; Weinberger, H. *Tetrahedron Lett.* **1992**, *33*, 6959–6962. Reggelin, M.; Welcker, R. *Tetrahedron Lett.* **1995**, *36*, 5885–5886.
(17) Li, C.; Blackman, A. J. *Aust. J. Chem.* **1995**, *48*, 955–965. Li, C.; Blackman, A. J. *Aust. J. Chem.* **1994**, *47*, 1355–1361. Blackman, A. J.; Li, C.; Hockless, D. C. R.; Skelton, B. W.; White, A. H. *Tetrahedron* **1993**, *49*, 8645–8656.
(18) Isaac, M.; Slassi, A.; O'Brien, A.; Edwards, L.; MacLean, N.; Bueschkens, D.; Lee, D. K. H.; McCallum, K.; De Lannoy, I.; Demchyshyn, L.; Kamboj, R. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 919–921.
(19) Black, D. S.; Kumar, N.; Mitchell, P. S. R. *J. Org. Chem.* **2002**, *67*, 2464–2473.