This item is the archived peer-reviewed author-version of:

Chemoselective addition of isocyanides to N-tert-butanesulfinimines

Reference:

Janssen Guido V., Janssen Elwin, Vande Velde Christophe, Ehlers Andreas W., Slootweg J.Chris, Ruijter Eelco, Lammertsma Koop, Orru Romano V.A.- Chemoselective addition of isocyanides to N-tert-butanesulfinimines

Organic letters / American Chemical Society - ISSN 1523-7060 - 16:19(2014), p. 5116-5119

Full text (Publishers DOI): <http://dx.doi.org/doi:10.1021/ol502463s>

Handle: <http://hdl.handle.net/10067/1194610151162165141>

Chemoselective Addition of Isocyanides to *N*-*tert*-Butanesulfinimines

Guido V. Janssen[†], Elwin Janssen[†], Christophe M. L. Vande Velde[‡], Andreas W. Ehlers[†], J. Chris Slootweg[†], Eelco Ruijter[†], Koop Lammertsma,^{†*} and Romano V. A. Orru^{†*}

[†]Department of Chemistry and Pharmaceutical Sciences, Amsterdam Institute for Molecules, Medicines & Systems (AIMMS), VU University Amsterdam, De Boelelaan 1083, NL-1081 HV Amsterdam, The Netherlands

[‡]Faculty of Applied Engineering, Advanced Reactor Technology, University of Antwerp, Salesianenlaan 90, BE-2660 Hoboken, Belgium

Supporting Information Placeholder

ABSTRACT: The reaction of isocyanides with *N*-*tert*-butanesulfinimines shows remarkable chemoselectivity. β -sulfinylamino isocyanides are formed exclusively with aromatic sulfinimines, while α -sulfeneimino acetamides result when using aliphatic derivatives. A mechanism is suggested for the latter transformation, together with an explanation for the observed selectivity. Finally, a scope study is presented for this remarkably chemoselective reaction.

Isocyanides are common building blocks for the synthesis of nitrogen containing compounds.¹ Their ability to function both as a nucleophile and as an electrophile makes them of great importance in multicomponent reactions (MCRs)^{1b,2} that allow for the efficient synthesis of diverse sets of complex molecules.³

The typical reaction behavior of isocyanides **1** (Scheme 1A) involves nucleophilic attack of the isocyanide carbon to an electrophile, followed by trapping of the resulting nitrilium⁴ intermediate **2** by a nucleophile to form α -adducts **3**. This reactivity serves as the basis for many isocyanide-based MCRs (iMCRs) such as the classical Ugi and Passerini reactions.^{1b}

Scheme 1. A) Typical reactivity of isocyanides. B) Typical reactivity of α -acidic isocyanides.

Isocyanides with an electron-withdrawing group (EWG) at the α -position usually react differently.⁵ Upon deprotonation, the α -carbon can be functionalized with an electrophile, allowing for subsequent intramolecular nucleophilic attack to the isocyanide to give cyclic imines **6** (Scheme 1B).⁶ Thus, α -

acidic isocyanides can serve as building blocks in the synthesis of a range of interesting N-heterocycles such as imidazoles, imidazolines, oxazoles, oxazolines, dihydropyridones, pyrroles, and thiazoles.⁷

Recently, we exploited the reactivity depicted in Scheme 1B in iMCRs for the synthesis of 2-imidazolines by reacting imines with α -acidic isocyanides,⁸ and made optically pure 2-imidazolines **10** accessible in a highly efficient two-step procedure starting from sulfinimines **7** and 9-isocyanofluorene (**8a**, Scheme 2).⁹ The sulfinimines **7** in this procedure carry an aromatic group on the imine carbon atom. In the present study we show that pathway 1A (instead of 1B) is followed when the sulfinimine C-substituent is aliphatic instead. The obtained products are α -sulfeneimino acetamides (**12**, Scheme 3) which are useful aza-enolate building blocks upon deprotonation with LDA, but, so far, suffer from poor accessibility.¹⁰

Scheme 2. Synthesis of optically pure 2-imidazolines.

We first reacted (*R*)-cyclohexylsulfinimine¹¹ **11a** with 9-isocyanofluorene (**8a**), using our previously reported procedure for the synthesis of **9** (2 equiv TMSOTf, 1.1 equiv DIPEA, THF, −78 °C, 3 hours),⁹ to obtain α -sulfeneimino acetamide **12a** in 34% isolated yield.¹² After optimization, using 1 equiv instead of 2 equiv of TMSOTf and no added base, the yield of **12a** was improved significantly to 95% (Scheme 3).

Scheme 3. Initial reaction (top) and the proposed mechanism (bottom) for the formation of 12a. Relative B3LYP/6-31G(d,p) energies (in kcal·mol^{−1}) for the conversion of (*R*)-11a and 8a to 12a.

The observed peak ($m/z = 407.2131$) in the ESI mass spectrum cannot distinguish between β -amino isocyanide **9a** and α -sulfeneimino acetamide **12a**, but the ¹H NMR spectrum showed a significant deshielding for the NH²-CH¹ protons (7.0 and 6.2 ppm vs. 5.1 and 3.8 ppm in **9**, Scheme 3). Together with the absence of the characteristic signal for isocyanides in the IR spectrum (ca. $\nu = 2100$ cm^{−1}), we conclude that α -sulfeneimino acetamide **12a** was formed instead of **9a**.

The formation of **12a** presumably starts by attack of the nucleophilic isocyanide carbon atom on the silylated sulfinimine **TMS-11a**, to give **13a**, and likely proceeds to intermediate **15a** via the cyclic transition state **14a**.¹³ Subsequently, a 1,3-H shift gives **16a**, which on hydrolysis yields α -sulfeneimino acetamide **12a**. DFT calculations¹⁴ at the B3LYP/6-31G(d,p) level of theory estimate an exothermic formation of intermediate **13a** ($\Delta E = -9.3$ kcal·mol^{−1}). While the formation of **15a** is only slightly favored ($\Delta\Delta E = -3.4$ kcal·mol^{−1}),¹³ the 1,3-H shift to the silylated α -sulfeneimino acetamide **16a** is highly exothermic ($\Delta\Delta E = -42.8$ kcal·mol^{−1}), and yields **12a** after hydrolysis acetamide.

Evidently, the chemoselectivity for the reaction of alkyl substituted sulfinylimines differs from those bearing an aromatic group. This concurs with a similar distinction reported for the addition of isocyanides to aliphatic and aromatic imines.¹⁵ Apparently, the difference in electrophilicity of the imine carbon governs the selectivity for the reactions with isocyanides. The extent of the conjugative stabilization of the sulfinimines plays a crucial role in this distinction. The more

conjugated (aryl substituted) system is less electrophilic compared to the less conjugated (alkyl substituted) sulfinimines.

Computations (B3LYP/6-31G(d,p))¹⁴ indeed show that in the addition of isocyanide **8a** to phenyl substituted sulfinimine **TMS-7a** (Scheme 4) results in a higher barrier ($\Delta E^\ddagger$ 13.1 kcal·mol^{−1} (**TS1**)) compared to that for the addition of **8a** to cyclohexyl substituted imine **TMS-11a** ($\Delta E^\ddagger$ 3.9 kcal·mol^{−1} (**TS2**)). The obtained full chemoselectivity can thus be explained from the energy difference between **TS1** and **TS2** ($\Delta E = 9.2$ kcal·mol^{−1}) that results in a ratio of >500:1 at the reaction temperature (−78 °C). Moreover, the formation of the initial adduct is exothermic by 9.3 kcal·mol^{−1} in case of cyclohexyl (**13b**), while that for **13a** is endothermic by 4.8 kcal·mol^{−1}. The fact that aromatic silylated sulfinimines (Scheme 2) do react with deprotonated **8a** with the α -carbon to give β -sulfinylamino isocyanides **9**,⁹ is rationalized by the higher nucleophilicity of the anionic carbon compared to that of the terminal isocyanide carbon atom.

Scheme 4. Barriers (B3LYP/6-31G(d,p)) in kcal·mol^{−1} for the nucleophilic addition of isocyanide 8a to silylated sulfinimines.

To explore the scope of the reaction at the isocyanide carbon atom, we examined the reactivity of a range of aliphatic sulfinimines in the reaction with several isocyanides (Tables 1 and 2).¹⁷ Linear (Me, *n*-hexyl) and branched (*i*-Pr) alkyl substituted imines reacted with 9-isocyanofluorene to the corresponding α -sulfeneimino acetamides in reasonable yields (52–60%, entries 1–3). In contrast, the yield for the benzyl derivative **12e** was poor (12% + decomposition products), possibly due to tautomerization of the silylated sulfinimine to the corresponding enamide leading to side reactions (entry 4). The *t*-butyl derivative **11f** showed no reactivity even after 8 hours, which may be attributed to steric congestion (entry 5).

The reaction also demonstrates a relatively broad scope in isocyanides, as several α -acidic isocyanides react smoothly (Table 2). For example, *p*-nitrobenzyl isocyanide (**8b**) reacts with imine **11b** to afford **12g** in 65% yield (entry 1). Also tosylmethyl isocyanide (TosMIC) **9b** reacts with imines **11b** and **11a** to afford the desired products **12h** and **12j** in 55% and 65% yield, respectively (entries 2–3). For compounds **12g** and **12h** we were able to determine the crystal structure, which confirm the α -sulfeneimino acetamide framework (Figure 1).¹⁸

Table 1. Variation of aliphatic sulfinimines.^a

entry	imine ¹⁷	isocyanide	product (yield(%)) ^b
-------	---------------------	------------	---------------------------------

^a Conditions: TMSOTf (1.0 equiv), THF, -78°C , 3 h. ^b Isolated yields.

Figure 1. Molecular structures of compound 12g (left) and 12h (right). Hydrogen atoms are omitted for clarity and the displacement ellipsoids are drawn at 50% probability level.

Subsequently, we employed methyl α -phenyl isocyanoacetate (**8d**), which also reacts smoothly with methyl and isopropyl functionalized imines **11b** and **11d** to give **12j** and **12k** in 71% and 60% yield, respectively (entries 4–5).

From the proposed mechanism (Scheme 3), the α -acidity of the isocyanide reactant does not seem to be a controlling factor for the reaction. This implies that the reaction is not limited to α -acidic isocyanides. However, electron-rich aliphatic isocyanides **8e** and **8f** were completely unreactive and only the starting materials were isolated (entries 6 and 7). A similar lack of reactivity was observed for benzyl isocyanide (**8g**) (entry 8). On the other hand, isocyanide **8h** bearing an additional phenyl group reacted smoothly to give the desired product **12o** in 85% yield (entry 9). The inductively electron-withdrawing effect of a β -heteroatom is apparently insufficient, since only starting materials were isolated in the reaction of morpholinoethyl isocyanide (**8i**, entry 10). In contrast, the aromatic isocyanide **8j** is reactive under the conditions and affords **12q** in 59% yield (entry 10). Similarly, electron-rich aromatic isocyanide **8k** reacted with imine (*R*)-**11b** and afforded product **12r** in 34% yield. However, it must be noted that the nucleophilicity of electron rich isocyanides is still lower than aliphatic ones.¹⁹ For the reaction, the isocyanide reactant needs apparently to be

slightly electron-deficient to enable the formation of sulfenimines.

Table 2. Variation of isocyanides.^a

entry	imine	isocyanide	product (yield(%) ^b)
1	(<i>R</i>)- 11b	8b	12g (65)
2	(<i>R</i>)- 11b	8c	12h (55)
3	(<i>R</i>)- 11a	8c	12i (65)
4	(<i>R</i>)- 11b	8d	12j (71)
5	(<i>R</i>)- 11d	8d	12k (60)
6	(<i>R</i>)- 11b	8e	12l (0)
7	(<i>R</i>)- 11b	8f	12m (0)
8	(<i>R</i>)- 11b	8g	12n (0)
9	(<i>R</i>)- 11b	8h	12o (85)
10	(<i>R</i>)- 11b	8i	12p (0)
11	(<i>R</i>)- 11b	8j	12q (59)
12	(<i>R</i>)- 11b	8k	12r (34)

^a Conditions: TMSOTf (1.0 equiv), THF, -78°C , 3 h. ^b Isolated yields.

In conclusion, we have developed an efficient reaction for the synthesis of α -sulfeneimino acetamides starting from electron-deficient and aliphatic *N*-*tert*-butanesulfinimines *via* a cascade pathway. The resulting α -sulfeneimino acetamides were isolated in good to excellent yields using a range of electron-poor isocyanides as well as several aliphatic *N*-*tert*-butanesulfinimines.

ASSOCIATED CONTENT

Supporting Information

Detailed experimental procedures, computational details, characterization data and copies of ^1H and ^{13}C NMR spectra for all new compounds as well as X-ray crystallographic data for **12g** and **12h**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

AUTHOR INFORMATION

Corresponding Authors

* E-mail: k.lammertsma@vu.nl

* E-mail: r.v.a.orrui@vu.nl

Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENT

The Dutch National Research School Combination – Catalysis (NRSC-C) is gratefully acknowledged for financial support. Matthias Zeller (Youngstown State University) is kindly acknowledged for collecting the dataset for **12g**. The X-ray diffractometer was funded by NSF Grant 0087210, Ohio Board of Regents Grant CAP-491, and by Youngstown State University. Kristof Van Hecke (Universiteit Gent) is kindly acknowledged for providing instrument time for measuring the X-ray data for **12h**. The X-ray diffractometer was funded by the Hercules Foundation (project AUGÉ/11/029 "3D-SPACE: 3D Structural Platform Aiming for Chemical Excellence").

REFERENCES

- (1) (a) Ugi, I.; Werner, B.; Dömling, A. *Molecules* **2003**, *8*, 53. (b) *Isocyanide Chemistry: Applications in Synthesis and Material Science*; Nenajdenko, V. G., Ed.; John Wiley & Sons, Inc., **2012**.
- (2) (a) Dömling, A. *Curr. Opin. Chem. Biol.* **2000**, *4*, 318. (b) Dömling, A. *Curr. Opin. Chem. Biol.* **2002**, *6*, 306. (c) Akritopoulou-Zanze, I. *Curr. Opin. Chem. Biol.* **2008**, *12*, 324. (d) Biggs-Houck, J. E.; Younai, A.; Shaw, J. T. *Curr. Opin. Chem. Biol.* **2010**, *14*, 371. (e) De Graaff, C.; Ruijter, E.; Orru, R. V. A. *Chem. Soc. Rev.* **2012**, *41*, 3969. (f) Van Berkel, S. S.; Bögels, B. G. M.; Wijdeven, M. A.; Westermann, B.; Rutjes, F. P. J. T. *Eur. J. Org. Chem.* **2012**, *2012*, 3543.
- (3) (a) Vlaar, T.; Ruijter, E.; Maes, B. U. W.; Orru, R. V. A. *Angew. Chem. Int. Ed.* **2013**, *52*, 7084. (b) Koopmanschap, G.; Ruijter, E.; Orru, R. V. *Beilstein J. Org. Chem.* **2014**, *10*, 544.
- (4) (a) S. Kanemasa, *Sci. Synth.* **2004**, *19*, 53; (b) van Dijk, T.; Burck, S.; Rong, M. K.; Rosenthal, A. J.; Nieger, M.; Slootweg, J. C.; Lammertsma, K. *Angew. Chem. Int. Ed.* **2014**, *53*, 9068.
- (5) Gulevich, A. V.; Zhdanko, A. G.; Orru, R. V. A.; Nenajdenko, V. G. *Chem. Rev.* **2010**, *110*, 5235.
- (6) El Kaim, L.; Grimaud, L. *Tetrahedron* **2009**, *65*, 2153.
- (7) (a) Elders, N.; Ruijter, E.; Nenajdenko, V. G.; Orru, R. V. A. *Top. Heterocycl. Chem.* **2010**, *23*, 129. (b) Lygin, A. V.; de Meijere, A. *Angew. Chem. Int. Ed.* **2010**, *49*, 9094.
- (8) (a) Bon, R. S.; Hong, C.; Bouma, M. J.; Schmitz, R. F.; de Kanter, F. J. J.; Lutz, M.; Spek, A. L.; Orru, R. V. A. *Org. Lett.* **2003**, *5*, 3759. (b) Bon, R. S.; van Vliet, B.; Sprenkels, N. E.; Schmitz, R. F.; de Kanter, F. J. J.; Stevens, C. V.; Swart, M.; Bickelhaupt, F. M.; Groen, M. B.; Orru, R. V. A. *J. Org. Chem.* **2005**, *70*, 3542. (c) Paravidino, M.; Bon, R. S.; Scheffelaar, R.; Vugts, D. J.; Znabet, A.; Schmitz, R. F.; de Kanter, F. J. J.; Lutz, M.; Spek, A. L.; Groen, M. B.; Orru, R. V. A. *Org. Lett.* **2006**, *8*, 5369. (d) Elders, N.; Schmitz, R. F.; de Kanter, F. J. J.; Ruijter, E.; Groen, M. B.; Orru, R. V. A. *J. Org. Chem.* **2007**, *72*, 6135. (e) Elders, N.; Ruijter, E.; de Kanter, F. J. J.; Groen, M. B.; Orru, R. V. A. *Chem. Eur. J.* **2008**, *14*, 4961.
- (9) Janssen, G. V.; Vicente-García, E.; Vogel, W.; Slootweg, J. C.; Ruijter, E.; Lammertsma, K.; Orru, R. V. A. *Eur. J. Org. Chem.* **2014**, *2014*, 3762.
- (10) (a) Claus, P. K. In *Sulfenic Acids and Derivatives*; Patai, S., Ed.; John Wiley & Sons, Ltd.: New York, 1990; pp. 723. (b) Davis, F. A. *J. Org. Chem.* **2006**, *71*, 8993.
- (11) Optically pure *N*-tert-butanesulfinimines **11** (*ee* > 99%) were conveniently prepared from commercially available starting materials using a microwave assisted procedure: Collados, J. F.; Toledano, E.; Guijarro, D.; Yus, M. *J. Org. Chem.* **2012**, *77*, 5744.
- (12) There is a full switch in mechanism because the corresponding β -sulfinylamine isocyanide was not observed in the crude ^1H -NMR spectrum.
- (13) A similar mechanism is reported for the reaction of isocyanides with *in situ* generated *N*-acyl iminium ions, affording 5-aminooxazoles. Soeta, T.; Tamura, K.; Ukaji, Y. *Tetrahedron* **2014**, *70*, 3005.
- (14) Gaussian 09, Revision A.02, Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Mennucci, B.; Petersson, G. A.; Nakatsuji, H.; Caricato, M.; Li, X.; Hratchian, H. P.; Izmaylov, A. F.; Bloino, J.; Zheng, G.; Sonnenberg, J. L.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Montgomery, J. A., Jr.; Peralta, J. E.; Ogliaro, F.; Bearpark, M.; Heyd, J. J.; Brothers, E.; Kudin, K. N.; Staroverov, V. N.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Rega, N.; Millam, M. J.; Klene, M.; Knox, J. E.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Zakrzewski, V. G.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Dapprich, S.; Daniels, A. D.; Farkas, Ö.; Foresman, J. B.; Ortiz, J. V.; Cioslowski, J.; Fox, D. J. Gaussian, Inc., Wallingford CT, 2009.
- (15) Although we were not able to find the transition state computationally, all optimizations for **14** resulted in **15** as the local minimum. Therefore, we propose **14** as the most likely transition state for this step.
- (16) (a) Grassot, J.-M.; Masson, G.; Zhu, J. *Angew. Chem. Int. Ed.* **2008**, *47*, 947. (b) Scheffelaar, R.; Paravidino, M.; Mulwijk, D.; Lutz, M.; Spek, A. L.; de Kanter, F. J. J.; Orru, R. V. A.; Ruijter, E. *Org. Lett.* **2009**, *11*, 125.
- (17) Although it is not strictly required to use optically pure sulfinimines, they were used in this scope study because we had the (*R*)-sulfinamine available.
- (18) CCDC 1019912 (**12g**) and CCDC 1019913 (**12h**) both contain the supplementary crystallographic data for this paper. This data can be obtained free of charge from The Cambridge Crystallographic Data Centre via http://www.ccdc.cam.ac.uk/data_request/cif. For the experimental details of the X-ray crystal structure determination, see the Supporting Information.
- (19) Tumanov, V. V.; Tishkov, A. A.; Mayr, H. *Angew. Chem. Int. Ed.* **2007**, *46*, 3563–3566.