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

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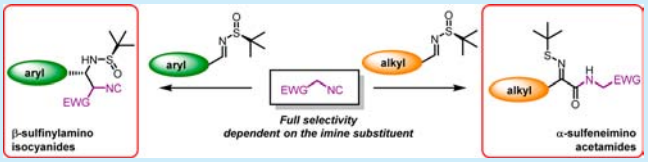
Supporting Information

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.

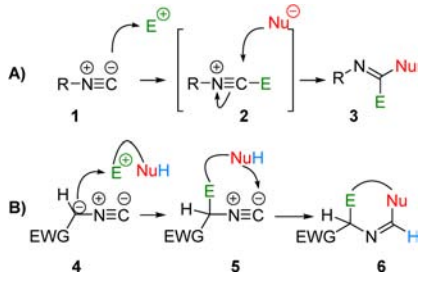


Isocyanides are common building blocks for the synthesis of nitrogen containing compounds.[1] Their ability to function both as a nucleophile and as an electrophile makes them of great importance in multicomponent reactions (MCRs)[1b,2] that allow for the efficient synthesis of diverse sets of complex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

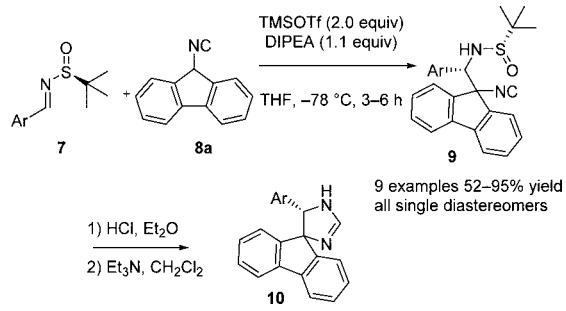
The typical reaction behavior of isocyanides **1** (Scheme 1A) involves nucleophilic attack of the isocyanide carbon to an electrophile, followed by trapping of the resulting nitrilium[4] intermediate **2** by a nucleophile to form *α*-adducts **3**. This reactivity serves as the basis for many isocyanide-based MCRs (iMCRs) such as the classical Ugi and Passerini reactions.[1b]

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]

Scheme 1. (A) Typical Reactivity of Isocyanides; (B) Typical Reactivity of *α*-Acidic Isocyanides



Scheme 2. Synthesis of Optically Pure 2-Imidazolines



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]

We first reacted (*R*)-cyclohexylsulfinimine[11] **11a** with 9-isocyanofluorene (**8a**), using our previously reported procedure for the synthesis of **9** (2 equiv of TMSOTf, 1.1 equiv of DIPEA, THF, −78 °C, 3 h),[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).

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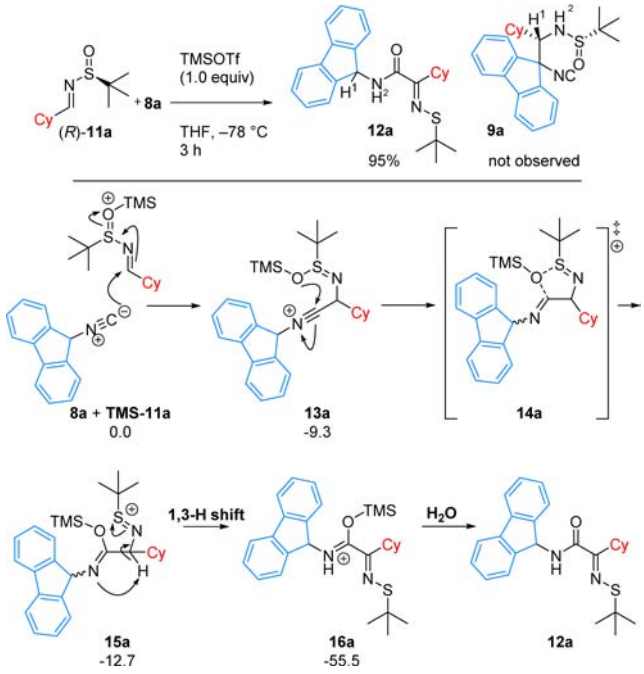
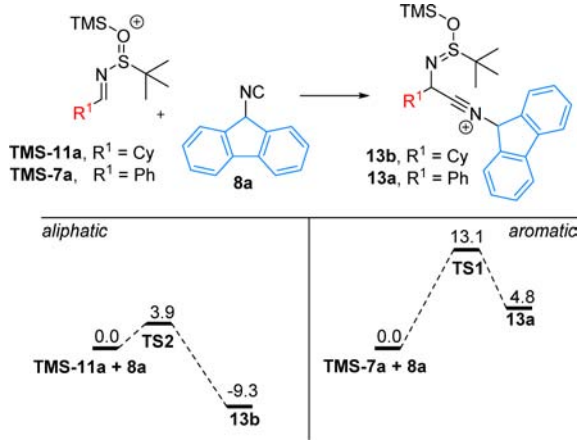
Scheme 3. Initial Reaction (top) and the Proposed Mechanism (bottom) for the Formation of 12a[a]



[a]Relative B3LYP/6-31g(d,p) energies (in kcal·mol^{-1}) are give for the conversion of (*R*)-**11a** and **8a** to **12a**.

Scheme 4. Barriers (B3LYP/6-31G(d,p)) (in kcal·mol^{-1}) for the Nucleophilic Addition of Isocyanide 8a to Silylated Sulfinimines



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 ^{1}H NMR spectrum showed a significant deshielding for the NH^2–CH^1 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. ν = 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** (Scheme 3).[13] Subsequently, a 1,3-H shift gives **16a**, which on hydrolysis

Table 1. Variation of Aliphatic Sulfinimines[a]

entry	imine[17]	isocyanide	product (yield(%)[b])
1	(*R*)-**11b**	**8a**	**12b** (60)
2	(*R*)-**11c**	**8a**	**12c** (52)
3	(*R*)-**11d**	**8a**	**12d** (52)
4	(*R*)-**11e**	**8a**	**12e** (12)
5	(*R*)-**11f**	**8a**	**12f** (0)

[a]Conditions: TMSOTf (1.0 equiv), THC, −78 °C, 3 h. [b]Isolated yields.

yields α-sulfeneimino acetamide **12a**. DFT calculations[14] at the B3LYP/6-31G(d,p) level of theory estimate an exothermic formation of intermediate **13a** (ΔE = −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 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** (ΔE = 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 the 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-

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Table 2. Variation of Isocyanides[a]

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

[a]Conditions: TMSOTf (1.0 equiv), THF, −78 °C, 3 h. [b]Isolated yields.

sulfinylamino isocyanides **9**[9] is rationalized by the higher nucleophilicity of the anionic carbon compared to that of the terminal isocyanide carbon atom.

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 afford 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),

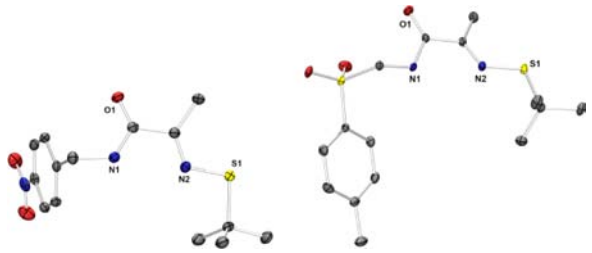

Figure 1. Molecular structures of compounds **12g** (left) and **12h** (right). Hydrogen atoms are omitted for clarity, and the displacement ellipsoids are drawn at the 50% probability level.

possibly due to tautomerization of the silylated sulfinimine to the corresponding enamide leading to side reactions (entry 4). The *tert*-butyl derivative **11f** showed no reactivity even after 8 h, 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-sulfenimino acetamide framework (Figure 1).[18]

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). Apparently, the isocyanide needs to be electron-deficient to enable product formation. 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. These results are in line with the general reactivity trend, as even electron-rich aromatic isocyanides can be considered less nucleophilic than aliphatic isocyanides.[19]

In conclusion, we have developed an efficient reaction for the synthesis of α-sulfeneimino acetamides starting from electron-deficient isocyanides 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 ^{1}H and ^{13}C NMR spectra

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for all new compounds, and X-ray crystallographic data for **12g** and **12h**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(12) There is a full switch in mechanism because the corresponding *β*-sulfinylamino isocyanide was not observed in the crude ^{1}H 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.

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(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.

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(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. These 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.

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