ChemPubSoc Europe

DOI: 10.1002/ejoc.201701278

EurJOC European Journal of Organic Chemistry

Communication

Functionalized 1,2,4-Triazoles

Selective Generation of (1*H*-1,2,4-Triazol-1-yl)methyl Carbanion and Condensation with Carbonyl Compounds

Pierrik Lassalas,[a] Aurélie Claraz,[a] Gaël Tran,[a] Jean-Pierre Vors,[b] Tomoki Tsuchiya,[b] Pierre-Yves Coqueron,[b] and Janine Cossy*[a]

Abstract: 2-(1*H*-1,2,4-Triazol-1-yl)ethanols have received significant interest in agricultural and medicinal chemistry owing to their herbicidal and antifungal activities. To develop a versatile method to access these substituted triazoles, we explored the generation of the (1*H*-1,2,4-triazol-1-yl)methyl carbanion and its condensation with carbonyl compounds. By judicious choice of a suitable anion precursor (tributylstannyl group) or a stabilizing anion group (phenylsulfanyl or phenylsulfinyl group), a wide range of aldehydes and ketones reacted with the carbanions to give a large diversity of 2-(1*H*-1,2,4-triazol-1-yl)ethanols in good yields.

Introduction

1,2,4-Triazoles and their derivatives were described for the first time by Bladin et al. in 1885.[1] Owing to their antifungal and herbicidal activities, the interest in 1,2,4-triazoles has grown exponentially during these last decades.[2] For example, commercially available 3-amino-1,2,4-triazole exhibits potent herbicidal activity, cyproconazole and tebuconazole are agricultural fungicides, whereas fluconazole is an antifungal drug (Figure 1).

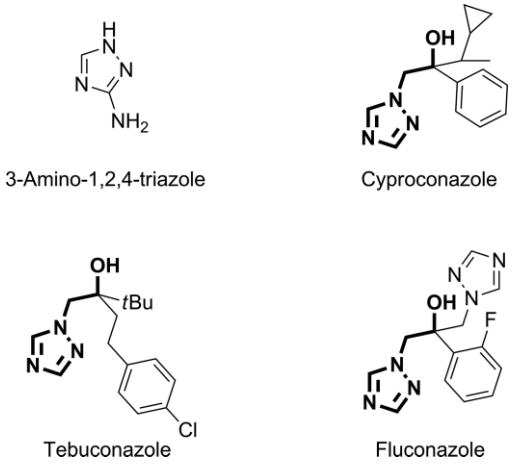
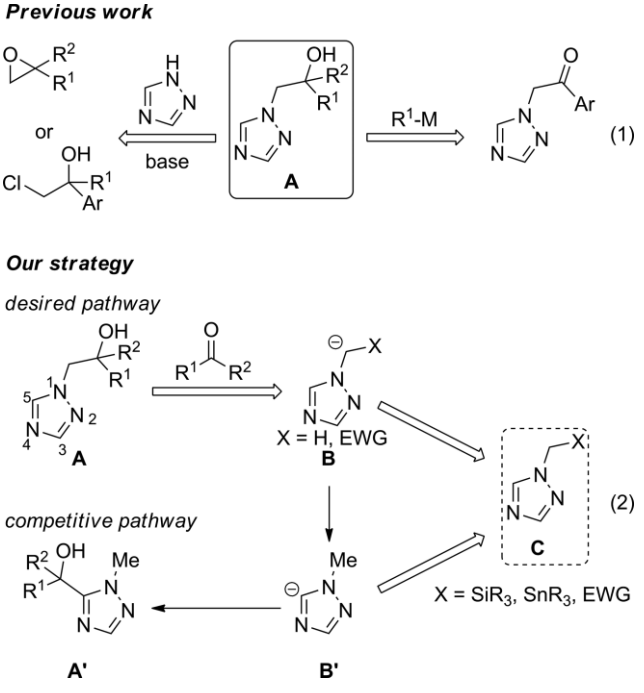


Figure 1. Biologically active 1,2,4-triazoles.

Considering the biological activities of these compounds, we were interested in developing an easy method to access 2-(1*H*-1,2,4-triazol-1-yl)ethanols **A** (Scheme 1). The previously reported syntheses of **A** relied on the addition of 1,2,4-triazole to epoxides[3] or to 2-chloro-1-aryl ethanols[4] as well as the addition of organometallic reagents to aromatic β-keto triazoles[5] [Scheme 1, Equation (1)]. Nevertheless, these processes involved the preparation of a highly sensitive epoxide or were limited to aromatic substituents, which hamper the discovery of new potent biologically active 2-(1*H*-1,2,4-triazol-1-yl)ethanol derivatives. To implement a more general and versatile method for the preparation of **A**, we envisaged the specific generation of anion **B** from **C** [Scheme 1, Equation (2)]. However, as anion



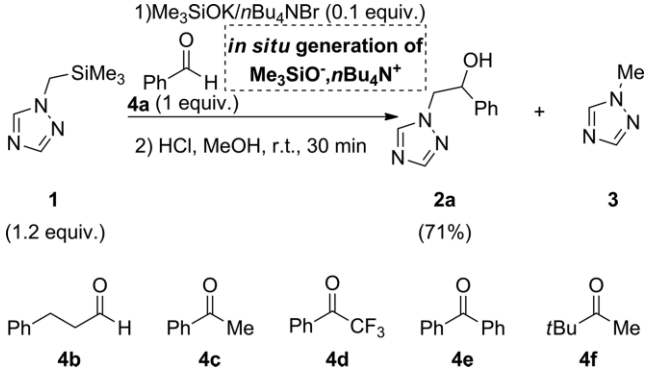
Scheme 1. Preparation of compounds **A**.

[a] *Laboratory of Organic Chemistry, Institute of Chemistry, Biology and Innovation (CBI), ESPCI Paris, CNRS (UMR8231), PSL Research University, 10 rue Vauquelin, 75231 Paris Cedex 05, France*
E-mail: janine.cossy@espci.fr
https://www.lco.espci.fr/Home
[b] *Bayer SAS, Small Molecule Research - Disease Control Chemistry, 14 Impasse Pierre Baizet, 69263 Lyon Cedex 09, France*
Supporting information and ORCID(s) from the author(s) for this article are available on the WWW under https://doi.org/10.1002/ejoc.201701278.

B′ can be generated under basic conditions, undesired compounds of type **A′** can be obtained. Herein, we report the selective reactivity of 1-methylene-1*H*-1,2,4-triazoles to access compounds **A**.

Results and Discussion

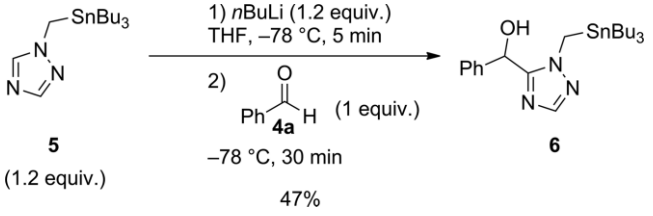
At first, the reactivity of 1-[(trimethylsilyl)methyl]-1*H*-1,2,4-triazole (**1**) was investigated. The fluoride-catalyzed reaction of **1** with carbonyl compounds was previously reported by using tetrabutylammonium fluoride (TBAF) or CsF.[6] However, only aromatic aldehydes gave satisfactory yields. A mixture of **A** and **A′** was obtained with aromatic ketones, and competitive formation of the silyl enol ether was observed with enolizable carbonyl compounds. Replacement of the fluoride by a stoichiometric amount of an alkoxide (e.g., *t*BuOK or Me_3SiOK) did not increase the scope of the reaction.[7] Recently, it was shown that the combination of Me_3SiOK/nBu_4NCl allowed the activation of organotrimethylsilanes through the generation of a carbanion equivalent that could react with carbonyl derivatives, and this system was shown to be autocatalytic.[8] Thus, compound **1**[9] was treated with 0.1 equivalents of Me_3SiOK/nBu_4NBr (in situ generation of Me_3SiO^-,nBu_4N^+) at room temperature in the presence of benzaldehyde (**4a**) (Scheme 2). Under these conditions, we were pleased to isolate the desired alcohol **2a** in good yield (71 %). Unfortunately, upon using nonaromatic aldehyde **4b**, aromatic ketones **4c**–**e**, and aliphatic ketone **4f**, only desilylated product **3** was formed and compounds **A** were not isolated.



Scheme 2. Me_3SiOK/nBu_4NBr-catalyzed condensation of **1** with carbonyl derivatives **4**.

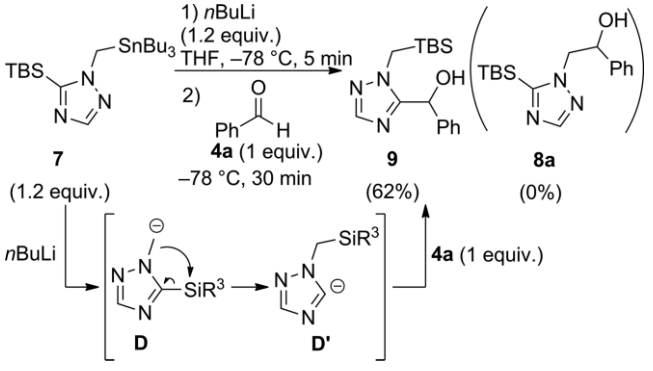
Owing to the limited reactivity of **1** towards carbonyl derivatives, the generation of carbanion **B** from 1-[(tributylstannyl)-methyl]-1*H*-1,2,4-triazole (**5**) by metal–metal exchange was examined. Triazole **5**[10] was treated with a stoichiometric amount of *n*BuLi at –78 °C in THF, and after 5 min, benzaldehyde (**4a**) was added. After 30 min at –78 °C, **2a** was not obtained, but alcohol **6** was isolated in 47 % yield (Scheme 3).

To circumvent this competitive deprotonation at C5, the C5 position of **5** was protected by a *tert*-butyldimethylsilyl (TBS) group. Surprisingly, if TBS-protected triazole **7**[11] was involved



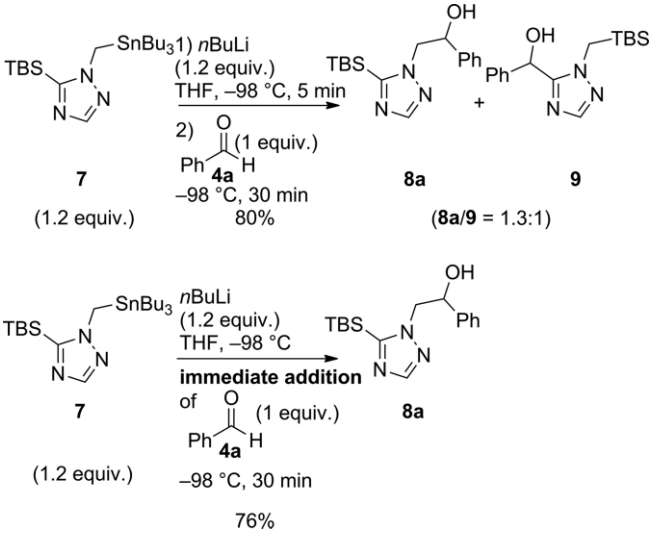
Scheme 3. Formation of **6** from **5**.

in the transmetalation process, the addition of benzaldehyde (**4a**) at –78 °C did not lead to alcohol **8a** but to **9** in 62 % yield. This unexpected product presumably arose from rapid 1,3-Brook rearrangement of transient lithiated species **D** (Scheme 4).[12]



Scheme 4. Formation of **9** from **7** through a 1,3-Brook rearrangement.

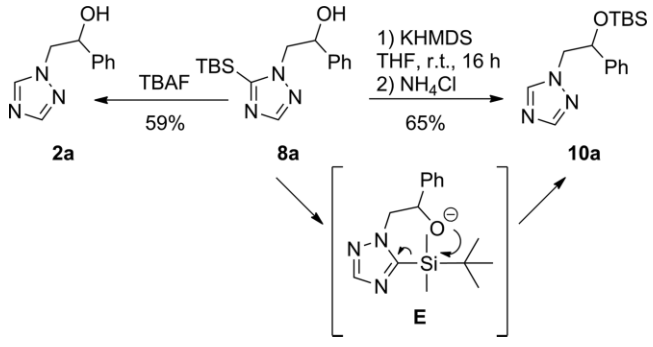
The Brook rearrangement was efficiently slowed down by decreasing the temperature to –98 °C, but an inseparable mixture of compounds **8a**/**9** in a 1.3:1 ratio was still obtained. Delightfully, this ratio was improved to 9.5:1 by the addition of benzaldehyde (**4a**) immediately after treatment of **7** with *n*BuLi. These conditions enabled the isolation of desired product **8a** in 76 % yield (Scheme 5).



Scheme 5. Improvement of the reaction conditions to synthesize **8a** from **7**.

Notably, the C5–Si bond of isolated alcohol **8a** could be cleaved by a 1,5-Brook rearrangement (intermediate **E**) by treat-

ment with potassium hexamethyldisilazane (KHMDS) (1 equiv.), and TBS-protected alcohol **10a** was obtained in 65 % yield (Scheme 6).[13] Alternatively, **2a** could be isolated in 59 % yield if **8a** was treated with TBAF.

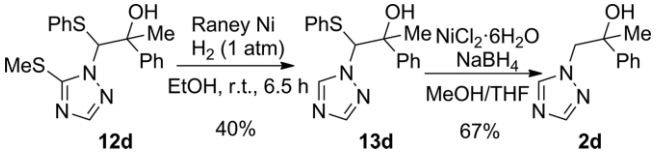


Scheme 6. Desilylation of C5 in **8a**.

Other aldehydes and ketones were involved in the condensation process. The results are summarized in Table 1. Aliphatic aldehyde **4b** was unreactive (Table 1, entry 2), but aromatic and heteroaromatic ketones led to **8** in moderate to good yields (45 to 62 %) (Table 1, entries 3–6). Noteworthy, enolizable ketones **4d** and **4f** were well tolerated. Nevertheless, if sterically hindered ketones **4g** and **4h** were used, corresponding triazoles **8** were not formed (Table 1, entries 7 and 8).

As carbanions can be stabilized by a phenylsulfanyl group,[14] we turned our attention to the generation of a phenylthio-stabilized carbanion by deprotonation of 1-phenylthio-1*H*-1,2,4-triazole[15] derivatives with *n*BuLi at –78 °C, and to avoid deprotonation at the C5 position,[16] the reactivity of **11**[17] was considered. A representative set of aldehydes and ketones were tested as electrophiles. The reaction proved to be quite general, and the results are depicted in Table 2. Notably, sterically hindered aromatic and aliphatic ketones **4g** and **4h** afforded the corresponding alcohols **12** in good yields (Table 2, entries 7 and 8). However, a limitation was observed with enolizable aliphatic aldehyde **4b** (Table 2, entry 2).

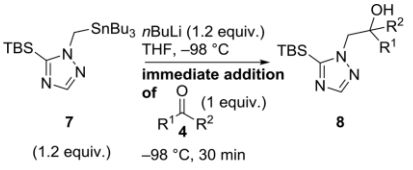
To transform **12** into compounds **A**, **12d** was used as a model substrate to realize the desulfurization. Treatment of **12d** with a large excess amount of Raney nickel in EtOH resulted in sulfide **13d** as the only isolable product (40 %). Triazole **2d** was eventually obtained in 67 % yield from **13d** after treatment with in situ generated Ni_2B (from $NiCl_2{\cdot}6H_2O/NaBH_4$)[18] (Scheme 7).[19]



Scheme 7. Desulfurization of **12d**.

To increase the stability of the anion and to avoid protection of the triazole at C5, sulfoxide **14**[20] was evaluated as a carbanion precursor. After treatment of **14** with LiHMDS at –78 °C for 20 min, carbonyl derivatives **4** were added to the reaction media. Owing to the presence of three stereogenic centers in **15**, a complex mixture of diastereomers was obtained. If this mixture was too complex for structural determination, the reduction of crude sulfoxide **15** to sulfide **13** was directly realized by using $Zn/TiCl_4$.[21] The results are reported in Table 3. The condensation of **14** with a wide range of aromatic and aliphatic aldehydes (Table 3, entries 1 and 2) and aromatic and enolizable ketones (Table 3, entries 4–7 and 9) was possible. Nevertheless, no reaction occurred with highly sterically hindered aromatic ketones **4c** and **4g** (Table 3, entries 3 and 8).

Table 1. Reactivity of **7** with different carbonyl derivatives **4**.



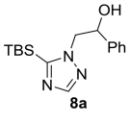
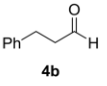
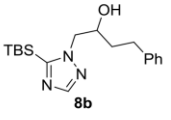
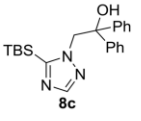
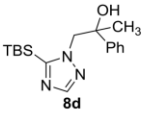
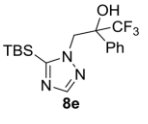
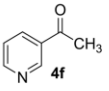
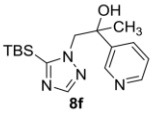
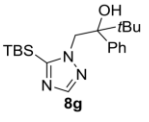
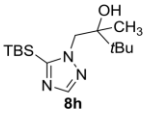
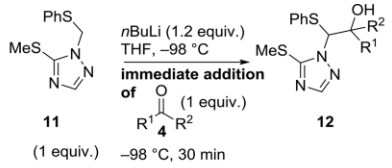
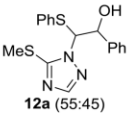
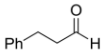
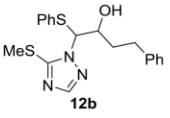
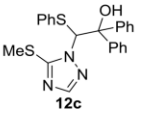
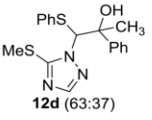
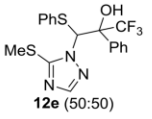
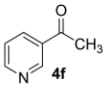
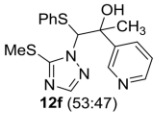
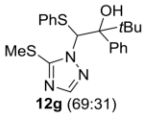
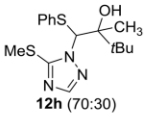
Entry	4	8	Yield
1	 **4a**	 **8a**	76%
2	 **4b**	 **8b**	-
3	 **4c**	 **8c**	45%
4	 **4d**	 **8d**	62%
5	 **4e**	 **8e**	62%
6	 **4f**	 **8f**	60%
7	 **4g**	 **8g**	-
8	 **4h**	 **8h**	-

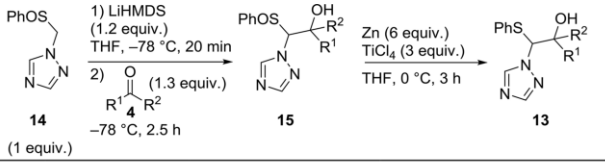
Table 2. Reactivity of **11** with different carbonyl derivatives **4**.

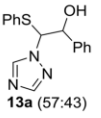
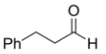
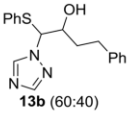
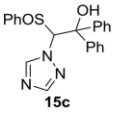
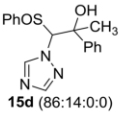
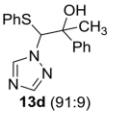
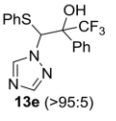
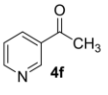
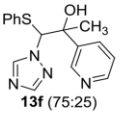
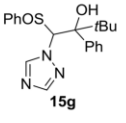
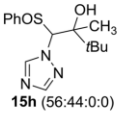


Entry	4	12 (dr)[a]	Yield
1	 **4a**	 **12a** (55:45)	54%
2	 **4b**	 **12b**	-
3	 **4c**	 **12c**	49%
4	 **4d**	 **12d** (63:37)	82%
5	 **4e**	 **12e** (50:50)	78%
6	 **4f**	 **12f** (53:47)	80%
7	 **4g**	 **12g** (69:31)	90%
8	 **4h**	 **12h** (70:30)	90%

[a] The diastereomeric ratios were determined by analysis of the crude material by ^{1}H NMR spectroscopy.

Table 3. Reactivity of **14** with different carbonyl derivatives **4**.

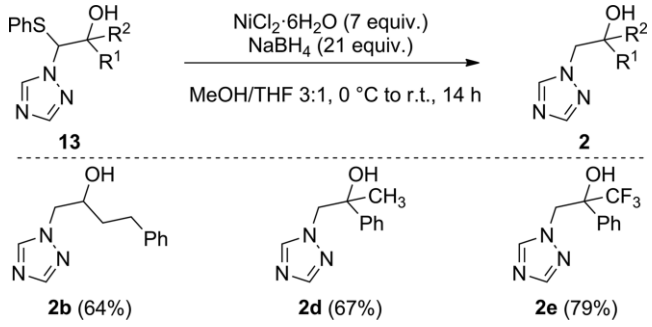


Entry	4	15 (dr)[a]	16 (dr)[a]	Yield
1	 **4a**	*not isolated*	 **13a** (57:43)	74%
2	 **4b**	*not isolated*	 **13b** (60:40)	75%
3	 **4c**	 **15c**	-	-
4	 **4d**	 **15d** (86:14:0:0)	-	95%
5	 **4d**	*not isolated*	 **13d** (91:9)	92%
6	 **4e**	*not isolated*	 **13e** (>95:5)	91%
7	 **4f**	*not isolated*	 **13f** (75:25)	90%
8	 **4g**	 **15g**	-	-
9	 **4h**	 **15h** (56:44:0:0)	-	85%

[a] The diastereomeric ratios were determined by analysis of the crude material by ^{1}H NMR spectroscopy.

Noteworthy, **15d** could be isolated in 95 % yield, and direct treatment of nonpurified **15d** with Zn/$TiCl_4$ afforded **13d** in 92 % yield over two steps from **14**, which proved that the reduction was nearly quantitative (Table 3, entries 4 and 5).

Compounds **13b**, **13d**, and **13e** were transformed in good yields into compounds **2b**, **2d**, and **2e**, respectively, by treatment with $NiCl_2$·$6H_2O$/$NaBH_4$ as described previously. The results of this reductive cleavage of the C–S bond are summarized in Scheme 8.



Scheme 8. Desulfurization of **13**.

Conclusions

In conclusion, we showed that 2-(1*H*-1,2,4-triazol-1-yl)ethanol derivatives **A** could be obtained selectively by generation of the (1*H*-1,2,4-triazol-1-yl)methyl carbanion. Among the precursors, 1-[(trimethylsilyl)methyl]-, 1-[(tributylstannyl)methyl]-, 1-[(phenylsulfanyl)methyl], 1-[(phenylsulfinyl)methyl]-1*H*-1,2,4-triazoles, and 1-[(phenylsulfinyl)methyl]-1*H*-1,2,4-triazoles were the best to access a large diversity of 2-(1*H*-1,2,4-triazol-1-yl)ethanols **2** in good yields. We believe that, in the future, such a method will find useful applications in the synthesis of new biologically active compounds.

Experimental Section

General Procedure for Table 1: To a stirred solution of 5-(*tert*-butyldimethylsilyl)-1-[(tributylstannyl)methyl]-1*H*-1,2,4-triazole (**7**) (1.17 equiv.) in THF at –98 °C was added dropwise *n*BuLi (1.18 equiv.). Instantly, the solution turned yellow. Immediately at the end of the addition, a solution of electrophile **4** (1 equiv.) in THF was added dropwise at –98 °C, and the resulting solution was stirred for 30 min at the same temperature. A saturated aqueous solution of NH_4Cl was added at –98 °C, and the mixture was warmed up to room temperature. The aqueous phase was extracted with EtOAc (3 ×). The combined organic layer was dried with Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel) to afford **8**.

General Procedure for Table 2: To a stirred solution of 5-(methylsulfanyl)-1-[(phenylsulfanyl)methyl]-1*H*-1,2,4-triazole (**11**) (1 equiv.) in THF at –78 °C was added dropwise *n*BuLi (1.1 equiv.), and the resulting bright yellow solution was stirred for 5 min. Electrophile **4** (1.2 equiv.) was added dropwise at –78 °C, and the resulting solution was stirred for 1 h. A saturated aqueous solution of NH_4Cl was added at –78 °C, and the mixture was warmed up to room temperature. The aqueous phase was extracted with EtOAc (3 ×). The combined organic layer was washed with brine, dried with Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel) to afford **12**.

General Procedure for Table 3: To a stirred solution of 1-[(phenylsulfinyl)methyl]-1*H*-1,2,4-triazole (**14**) (1 equiv.) in THF at –78 °C was added dropwise LiHMDS (1.25 equiv.). After stirring for 20 min, electrophile **4** (1.3 equiv.) was added dropwise at –78 °C, and the resulting solution was stirred for 2.5 h. A saturated aqueous solution of NH_4Cl was added at –78 °C, and the mixture was warmed up to room temperature. The aqueous phase was extracted with EtOAc (3 ×). The combined organic layer was washed with brine, dried with Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel) to afford **15**.

Synthesis of 13 from Crude Residue 15: To a stirred suspension of Zn in THF at 5 °C was added dropwise $TiCl_4$, and the resulting mixture was stirred for 30 min at 5–10 °C. Crude residue **15** was added, and the resulting solution was stirred at 10–15 °C for 3 h. After complete consumption of the starting material (monitored by TLC), H_2O was added, and the aqueous phase was extracted with Et_2O (3 ×). The combined organic layer was washed with a saturated aqueous solution of $NaHCO_3$ and brine, dried with Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel) to afford **13**.

Acknowledgments

Bayer-CropScience is acknowledged for financial support.

Keywords: Heterocycles · Carbanions · Deprotonation · Ketones · Aldehydes

[1] a) J. A. Bladin, *Ber. Dtsch. Chem. Ges.* **1885**, *18*, 1544–1551; b) K. T. Potts, *Chem. Rev.* **1961**, *61*, 87–127.
[2] a) S. C. Holm, B. F. Straub, *Org. Prep. Proced. Int.* **2011**, *43*, 319–347; b) N. Longley, C. Muzoora, K. Taseera, J. Mwesigye, J. Rwebembera, A. Chakera, E. Wall, I. Andia, S. Jaffar, T. S. Harrison, *Clin. Infect. Dis.* **2008**, *47*, 1556–1561; c) J. K. Joung, E. I. Ramm, C. O. Pabo, *Proc. Natl. Acad. Sci. USA* **2000**, *97*, 7382–7387.
[3] Selected examples: a) W. Grammenos; I. R. Craig, N. Boudet, B. Mueller, J. Dietz, E. M. W. Lauterwasser, J. K. Lohmann, T. Grote, E. Haden, A. Escribano Cuesta (BASF SE), WO 2014082881, **2014**; b) J. Renner, J. Dietz, A. Glaettli, T. Grote, W. Grammenos, B. Mueller, J. K. Lohmann, S. Ulmschneider, M. Vrettou-Schultes (BASF SE), WO2010146112, **2010**; c) A. Tasaka, N. Tamura, Y. Matsushita, T. Kitazaki, R. Hayashi, K. Okonogi, K. Itoh, *Chem. Pharm. Bull.* **1995**, *43*, 432–440; d) T. Konosu, Y. Tajima, N. Takeda, T. Miyaoka, M. Kasahara, H. Yasuda, S. Oida, *Chem. Pharm. Bull.* **1990**, *38*, 2476–2486; e) A. K. Saksena, A. B. Cooper, H. Guzik, V. M. Girijavallabhan, A. K. Ganguly (Schering Corp.), WO 8805048, **1988**; f) M. Ogata, H. Matsumoto, K. Takahashi, S. Shimizu, S. Kida, A. Murabayashi, M. Shiro, K. Tawara, *J. Med. Chem.* **1987**, *30*, 1054–1068.
[4] Selected examples: a) M. Jautelat, J. Scherkenbeck, K. Stroech, S. Dutzmann, H. W. Dehne, G. Haenssler, K. H. Kuck (Bayer A.-G), EP 470466 A2, **1992**; b) P. A. Worthington (Imperial Chemical Industries PLC), EP 44605 A1, **1982**.
[5] Selected examples: a) H. Itoh, H. Kajino, T. Tsukiyama, J. Tobitsuka, H. Ohta, Y. Takahi, M. Tsuda, H. Takeshiba, *Bioorg. Med. Chem.* **2002**, *10*, 4029–4034; b) H. Eto, Y. Kaneko, T. Sakamoto, *Chem. Pharm. Bull.* **2000**, *48*, 982–990; c) J. F. Chollet, B. Mauze, L. Miginiac, *J. Organomet. Chem.* **1989**, *368*, 1–18.
[6] a) S. Shimizu, M. Ogata, *J. Org. Chem.* **1987**, *52*, 2314–2315; b) S. Shimizu, M. Ogata, *J. Org. Chem.* **1986**, *51*, 3897–3900. With the reported conditions, enolizable ketones produced compounds of type **A** in poor yields.
[7] S. Shimizu, M. Ogata, *Synth. Commun.* **1989**, *19*, 2219–2227.
[8] M. Das, D. F. O'Shea, *J. Org. Chem.* **2014**, *79*, 5595–5607.
[9] Compound **1** was prepared from 1,2,4-triazole and chloromethyltrimethylsilane according to a reported procedure[6] (see the Supporting Information for more details).
[10] See the Supporting Information for the synthesis of **5**.
[11] See the Supporting Information for the synthesis of **7**.
[12] A. G. Brook, *Acc. Chem. Res.* **1974**, *7*, 77–84.
[13] a) M. M. Kabat, J. Wicha, *Tetrahedron Lett.* **1991**, *32*, 1073–1076; b) A. B. Smith, M. Xian, W.-S. Kim, D.-S. Kim, *J. Am. Chem. Soc.* **2006**, *128*, 12368–12369.
[14] a) F. G. Bordwell, X. M. Zhang, *Acc. Chem. Res.* **1993**, *26*, 510–517; b) F. G. Bordwell, M. Van der Puy, N. R. Vanier, *J. Org. Chem.* **1976**, *41*, 1885–1886.
[15] M. K. Bernard, *Tetrahedron* **2000**, *56*, 7273–7284.

[16] S. Shimizu, M. Ogata, *Tetrahedron* **1989**, *45*, 637–642.
[17] See the Supporting Information for the synthesis of **11**.
[18] a) T. G. Back, D. L. Baron, K. Yang, *J. Org. Chem.* **1993**, *58*, 2407–2413; b) M. R. Euerby, R. D. Waigh, *Synth. Commun.* **1986**, *16*, 779–784.
[19] Notably, the direct desulfurization of **12d** with in situ generated Ni_2B did not proceed cleanly.
[20] Compound **14** was prepared in two steps from 1,2,4-triazole. After treatment of 1,2,4-triazole with chloromethyl phenyl sulfide in the presence of NaH, the resulting sulfide derivative was oxidized to sulfoxide **14** with $NaIO_4$ (see the Supporting Information for more details).
[21] a) M. Pohmakotr, S. Sithikanchanakul, *Synth. Commun.* **1989**, *19*, 3011–3020; b) J. Drabowicz, M. Mikolajczyk, *Synthesis* **1978**, *1978*, 138–139.

Received: September 12, 2017

