Azido Alcohols

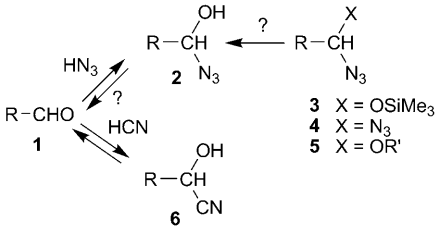
DOI: 10.1002/anie.201003246

Extremely Simple but Long Overlooked: Generation of α-Azido Alcohols by Hydroazidation of Aldehydes**

Klaus Banert, Christian Berndt, Samia Firdous, Manfred Hagedorn, Young-Hyuk Joo, Tobias Rüffer, and Heinrich Lang*

Dedicated to Professor Harald Günther on the occasion of his 75th birthday

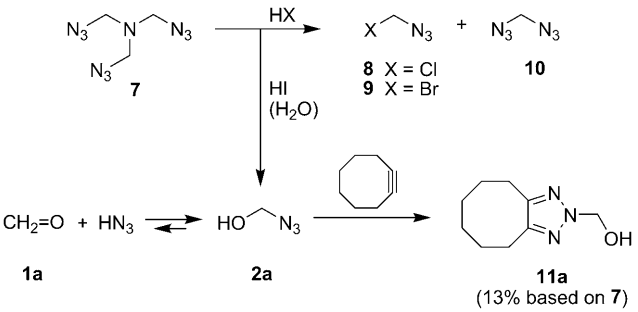
Cyanohydrins **6** are easily formed from aldehydes **1** and hydrogen cyanide and have proved to be highly useful substrates in synthesis (Scheme 1).[1] In contrast, the reaction



Scheme 1. α-Azido alcohols **2** postulated as short-lived intermediates.

of **1** with hydrazoic acid to prepare α-azido alcohols **2** is completely unknown. Attempts to generate **2** by methanolysis of silyl ethers **3** led only to **1**.[2] α-Azido alcohols of type **2** have been discussed as short-lived intermediates in the solvolysis of diazides **4**, which also yielded the final products **1**.[3] Protonation of **2** at N-α leads to an intermediate that is generally accepted to explain the mechanism of the Schmidt reaction.[4] Recently, in situ formation of azidomethanol (**2a**) was postulated in the reaction of formaldehyde and sodium azide in the presence of acetic acid. This reaction was completed by copper(I)-catalyzed cycloaddition at terminal alkynes to give 1,2,3-triazoles.[5] In all of these cases, there is no spectroscopic proof of intermediates **2**, whereas compounds of types **3**[2,6] and **4**[7,8] and also α-azido ethers **5**[8,9] can be prepared easily from precursors **1** or the corresponding acetals or enol ethers and then isolated and characterized. This led to the presumption that hydrazoic acid does not react with aldehydes readily.[9a]

Since we did not question this statement or at least did not doubt the elusiveness of α-azido alcohols **2**, we obtained evidence for these compounds incidentally. By treatment of triazide **7** with anhydrous hydrogen halide, we prepared azidochloromethane (**8**) and azidobromomethane (**9**) besides diazide **10** (Scheme 2).[10] The desired products are intermediates in the nucleophilic substitution of the corresponding dihalomethanes to generate **10** but could not be detected in these transformations.[10,11] Whereas **8** was isolated as an explosive colorless liquid, **9** was less stable and thus characterized only in solution.[10] When **7** was reacted with hydrogen iodide in chloroform under apparently not completely anhydrous conditions, we surprisingly got azidomethanol (**2a**), which we analyzed by NMR and IR spectroscopy (Table 1). Its structure was additionally confirmed by treatment with cyclooctyne[12] and isolation of the stable product **11a**, which resulted from 1,3-dipolar cycloaddition followed by rearrangement (see also Figure 1 for the molecular structure of **11a** based on X-ray diffraction analysis). Solutions of **2a** in chloroform showed only small proportions of the cleavage products **1a** and hydrazoic acid. Thus, it is logical that the equilibrium of **1a**/HN_3 and **2a** favors the α-azido alcohol, which is very easily available by simply mixing **1a** and hydrazoic acid in chloroform.[13]



Scheme 2. Synthesis of azidomethanol (**2a**).

This approach to α-azido alcohols **2** can be transferred to electron-poor aldehydes like **1v**,**cc**,**dd**,**ee** as well as to simple aliphatic or even aromatic aldehydes (Table 2). When 0.6 M solutions of hydrazoic acid and **1e** in chloroform were mixed in different ratios, the corresponding Job plot showed a

[*] Prof. Dr. K. Banert, C. Berndt, S. Firdous, Dr. M. Hagedorn, Dr. Y.-H. Joo
Chemnitz University of Technology, Organic Chemistry
Strasse der Nationen 62, 09111 Chemnitz (Germany)
Fax: (+49) 371-531-21229
E-mail: klaus.banert@chemie.tu-chemnitz.de
Homepage: http://www.tu-chemnitz.de/chemie/org/indexe.html
Dr. T. Rüffer, Prof. Dr. H. Lang
Chemnitz University of Technology, Inorganic Chemistry
Strasse der Nationen 62, 09111 Chemnitz (Germany)

[**] We gratefully acknowledge financial support from the Deutsche Forschungsgemeinschaft (Ba 903/12-1). S.F. thanks DAAD for a fellowship. We are grateful to Christoph Müller and Dr. Jens Wutke for experimental support.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201003246.

Table 1: Selected spectroscopic data of α-azido alcohols.[a]

2a	^{1}H NMR:	$\delta = 4.31$ (t, $^3J = 8.0$ Hz, OH), 4.59 ppm (d, $^3J = 8.0$ Hz)
	^{13}C NMR:	$\delta = 75.50$ ppm (t, $^1J_{CH} = 163.1$ Hz)
	IR ($CDCl_3$):	$\tilde{\nu} = 3453$ cm^{-1} (OH), 2137 (N_3)
2b	^{1}H NMR[b]:	$\delta = 1.44$ (d, $^3J = 5.6$ Hz, 3H, H2), 3.55 (d, br., $^3J = 6.0$ Hz, 1H, OH), 5.07 ppm (dq, $^3J = 6.0$ Hz, $^3J = 5.6$ Hz, 1H, H1)
	^{13}C NMR[b]:	$\delta = 21.89$ (q, C2), 82.65 ppm (d, C1)
2j	^{1}H NMR[c]:	$\delta = 2.88$ (dd, $^2J = 13.6$ Hz, $^3J = 5.6$ Hz, 1H, H2), 2.96 (dd, $^2J = 13.6$ Hz, $^3J = 5.2$ Hz, 1H, H2'), 3.38 (d, br., $^3J = 8.4$ Hz, 1H, OH), 5.11 (ddd, $^3J = 8.4$ Hz, $^3J = 5.6$ Hz, $^3J = 5.2$ Hz, 1H, H1), 7.20–7.40 ppm (m, 5H, Ph)
	^{13}C NMR[c]:	$\delta = 42.50$ (t, C2), 86.02 (d, C1), 127.17 (s, C_{ipso}), 128.55 (d, C_{ortho}), 129.72 (d, C_{meta}), 134.77 ppm (d, C_{para})

[a] ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ at 21 °C and 400 and 100 MHz, respectively; for additional data, see the Supporting Information. [b] Measured at −50 °C. [c] Measured at −55 °C.

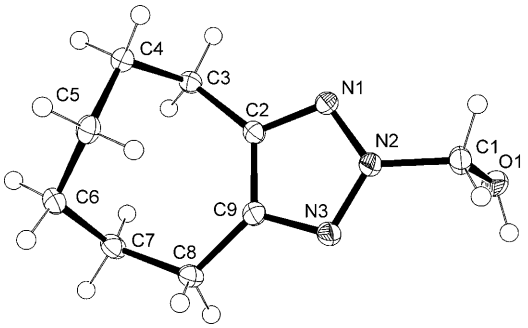
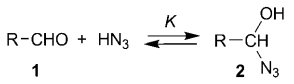
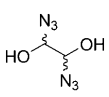


Figure 1. Molecular structure of **11a** determined by single-crystal X-ray diffraction analysis.

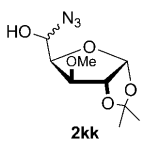
Table 2: Definition of substituent R in aldehydes **1** and α-azido alcohols **2**.



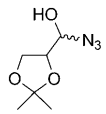
a H	**m** $CH_2CH_2C(Me)=CH_2$	**y** $(CH_2)_3Br$
b Me	**n** $CH_2CH=C=CH_2$	**z** $(CH_2)_3OTs$
c Et	**o** $CH_2CH_2C\equiv CH$	**aa** $CH_2CH_2CMe_2N_3$
d Pr	**p** $(CH_2)_3C\equiv CH$	**bb** $CH_2CH_2CMe_2Br$
e *i*Pr	**q** CH_2Cl	**cc** CO_2Et
f *t*Bu	**r** CH_2Br	**dd** $CO_2CH_2CH=CH_2$
g *c*Bu	**s** CH_2N_3	**ee** $CO_2CH_2C\equiv CH$
h *c*Pent	**t** $CH_2P^+Ph_3\,Cl^-$	**ff** Ph
i *c*Hex	**u** $CH(OMe)_2$	**gg** C_6H_4-2-NO_2
j Bn	**v** CCl_3	**hh** C_6H_4-4-NO_2
k $CHPh_2$	**w** $CH_2CH_2N_3$	**ii** C_6H_3-2,4-$(NO_2)_2$
l CH_2CH_2Ph	**x** $(CH_2)_3N_3$	



2jj



2kk



2ll

maximum proportion of **2e** in the case of equimolar starting materials. Thus, a 1:1 adduct of type **2** forms, which was also supported unequivocally by ^{1}H NMR data (see the Supporting Information). Specifically, the vicinal coupling resulting from OH and CH groups and the presence of diastereotopic protons or other diastereotopic groups (see, for example, **2e**,**g**,**h**,**i**,**k**,**u**) as a consequence of the stereogenic center of **2** exclude diazides **4** and trimers of **1** (1,3,5-trioxanes). Also ^{13}C NMR data can be used to distinguish between **2**, **4**, and 1,3,5-trioxanes (Table 1). The latter were generated very slowly from some of the aldehydes like **1b**,**c**,**d**, whereas diazides **4** were detected as side products when **1b** or **1c** were treated with hydrazoic acid in water or when **1l** was subjected to hydrazoic acid and *p*-toluenesulfonic acid. Hydrazoic acid did not add to nonactivated C–C double or triple bonds (see the cases **m**,**n**,**o**,**p**,**dd**, and **ee**), and we did not observe either cleavage of esters or acetals, or nucleophilic substitution of halides. Thus, **1q** and **1r** led to equilibria with **2q** and **2r**, respectively, but not to diazide **2s**, which was generated from **1s**. In contrast to aldehydes **1g**,**h**,**i**, cyclopropanecarbaldehyde did not react observably with hydrazoic acid. We assume that the three-membered ring stabilizes the partial positive charge at the carbonyl carbon atom, reduces the electrophilicity, and increases the thermodynamic stability of the aldehyde. Similar arguments can be utilized to explain the low proportion of **2ff** in equilibrium with **1ff** and hydrazoic acid.

Using weighed samples of **1** and titrated solutions of hydrazoic acid in $CDCl_3$ and with the help of ^{1}H NMR spectra, we determined the equilibrium constant K for some of the reactions depicted in Table 2. Small values of K were found in case of aromatic substrates **1ff**,**gg**,**hh**,**ii**, whereas electron-poor aldehydes such as **1q, 1v**, and **1cc** led to higher values of K (Table 3). Thus, the K values of **2** behave similarly to those of the corresponding aldehyde hydrates,[14] but there is no strict correlation. Aldehydes with branching at the α position like **1e** gave slightly lower values than the linear isomers such as **1d**. Such a steric effect may also account for the K value resulting from **1v**, which is only a little higher than that of **1q**, although the trichloromethyl group is a stronger acceptor. An intramolecular hydrogen bond in **2gg** can explain the greater K value of **1gg** relative to that of isomeric **1hh**. At lower temperatures (−25 °C versus 20 °C), we

Table 3: Equilibrium constants K for $\mathbf{1} + HN_3 \rightleftarrows \mathbf{2}$.[a]

1/2	K [L mol^{-1}]	T [°C]	1/2	K [L mol^{-1}]	T [°C]
a	10.1 ± 1.1	20.0	**n**	0.92 ± 0.06	20.3
b	0.93 ± 0.12	21.2	**q**	12.5 ± 1.3	20.3
c	0.59 ± 0.03	21.2	**t**	0.76 ± 0.06	19.5
d	0.42 ± 0.10	20.8	**v**	13.5 ± 1.1	21.4
e	0.27 ± 0.05	21.0	**cc**	ca. 620	20.0
g	0.42 ± 0.02	19.8	**ff**	0.0028 ± 0.0002	22.0
h	0.30 ± 0.01	20.3	**gg**	0.0205 ± 0.0002	20.2
i	0.33 ± 0.02	21.0	**hh**	0.0163 ± 0.0009	20.4
j	0.59 ± 0.07	21.1	**hh**	0.0487 ± 0.0009	−25.0
j[b]	1.89 ± 0.02	21.3	**ii**	0.1176 ± 0.0004	20.2
j	5.87 ± 0.08	−25.0	**kk**	12.8 ± 1.0	20.5
k	0.40 ± 0.09	21.0	**kk**	ca. 340	−25.0

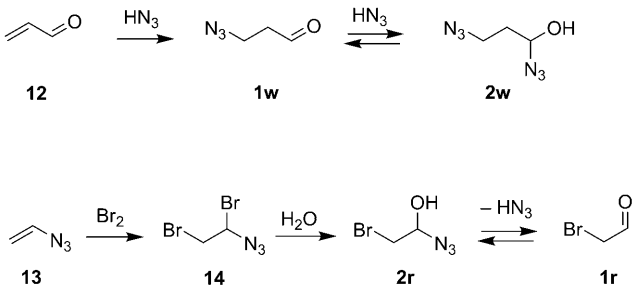
[a] Determined in $CDCl_3$ by ^{1}H NMR spectroscopy. Substituents R of compounds **1** and **2** are defined in Table 2. [b] Determined in [D_6]DMSO.

observed significantly higher K values (see **1j**, **1hh**, and **1kk**). More polar solvents like DMSO led also to greater proportions of the α-azido alcohols **2**.

Glyoxal (**1jj**) reacted with two equivalents of hydrazoic acid to afford a mixture of *meso*- and *rac*-**2jj** (ca. 1:1). For this transformation, a K value of $(85.9 \pm 2.2)\ L^2 mol^{-2}$ ($CDCl_3$, 19.8 °C) was calculated. Treatment of hydrazoic acid with chiral carbohydrates bearing an aldehyde unit also furnished two anomers. For example, **2kk** was formed as 2.5:1 mixture of α-azido alcohols, whereas nearly equal proportions of anomers **2ll** (ca. 4:3) resulted from aldehyde **1ll**. Because equilibria are fast at room temperature, these diastereomeric products should be generated under thermodynamic control.

At −50 to −65 °C, the equilibrations of **1**/HN_3 and **2** were retarded. Thus, hydrazoic acid along with the solvent and even the aldehydes **1a**–**f**,**q**,**v** could be removed in vacuum because the corresponding adducts **2** were less volatile. The residues were dissolved in precooled solvents to give solutions of pure or highly enriched α-azido alcohols **2**. Some of these products (**2a**–**d**) could be observed as solids or viscous liquids at low temperature. The best yields of **2** were achieved when the equilibrium was established at reduced temperature, for example at −25 °C in the refrigerator, before the volatile compounds were removed in vacuum at even lower temperatures.

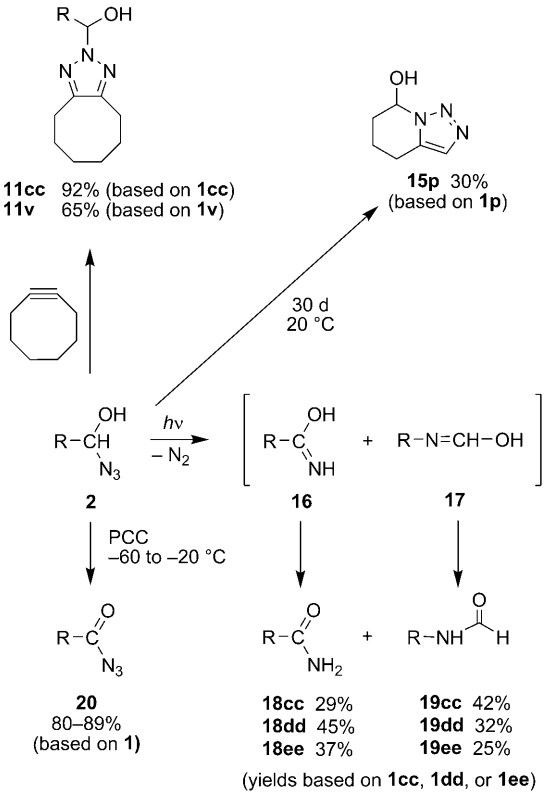
When the α-azido alcohol was liberated from hydrazoic acid at room temperature, the rapid equilibration caused complete cleavage of **2**. In such a case, only the aldehyde remained, and the formation of **2** from **1** and hydrazoic acid could be overlooked easily.[15] Treatment of acrolein (**12**) with an excess of hydrazoic acid was reported several times to afford the azide **1w**, but the generation of diazide **2w** was not noticed,[16,17] although it can be registered quite simply by NMR methods (Scheme 3). In 1910, vinyl azide (**13**) in water



Scheme 3. Generation of α-azido alcohols from starting materials **12** and **13**.

was subjected to bromine to prepare dibromide **14**. Owing to the explosive course of the reaction, however, **14** could not be characterized and **1r** was the only product identified.[18] Quite recently, it has been shown that **14** can be synthesized conveniently and quantitatively, when **13** is exposed to bromine in organic solvents at low temperature.[19] We treated **14** with wet dimethyl sulfoxide to get α-azido alcohol **2r** in equilibrium with **1r**/HN_3, which could also be reached by mixing **1r** and hydrazoic acid.

Like **2a**, the azide **2cc** furnished a stable 2*H*-1,2,3-triazole of type **11** upon reaction with cyclooctyne (Scheme 4). In contrast to **11cc**, product **11v** is unstable and tends to cleave into **1v** and 4,5,6,7,8,9-hexahydrocycloocta-1,2,3-triazole. A



Scheme 4. Reactions of α-azido alcohols **2**. The substituents R are defined in Table 2.

slow intramolecular 1,3-dipolar cycloaddition transformed **2p** into the heterocycle **15p**. On irradiation with a mercury high-pressure lamp, α-azido alcohols lost dinitrogen to give amides **18** and **19** most probably via intermediates **16** and **17**, respectively. The two types of products, for example **18cc**,**dd**,**ee** and **19cc**,**dd**,**ee**, could be easily separated by chromatography. Thus, the results of the photolysis of **2** are different from those of the known[2] thermolysis of **3**, which takes place exclusively with a proton shift to generate the corresponding *N*-(trimethylsilyl)carboxamides. Oxidation of α-azido alcohols **2** with pyridinium chlorochromate (PCC) in chloroform led under very mild conditions to acyl azides **20b**,**c**,**j**,**k**,**q**,**cc**,**ff**,**gg**,**ii** (80–89% yield based on **1**) without inducing Curtius rearrangement. The starting material **2jj** afforded the known[20] oxalic acid diazide at −50 °C (82% yield of isolated product based on HN_3), and **2d** was oxidized by PCC at the same temperature to provide butyryl azide (97% yield based on ^1H NMR data). In control experiments under the latter conditions, it was shown that a mixture of butyric acid, hydrazoic acid, and PCC did not generate butyryl azide. On the other hand, **1d** and PCC alone (without HN_3) did not produce butyric acid at such low temperatures. Thus, our method for the preparation of acyl azides from

aldehydes via intermediates **2** can be a useful alternative to known[21] procedures.

Although we have investigated only a few reactions of α-azido alcohols up to now, we assume that these compounds will enrich the multifarious chemistry of organic azides.[22]

Received: May 28, 2010
Revised: August 30, 2010
Published online: November 25, 2010

Keywords: alcohols · aldehydes · azides · equilibrium reactions · nucleophilic addition

[1] a) J.-M. Brunel, I. P. Holmes, *Angew. Chem.* **2004**, *116*, 2810–2837; *Angew. Chem. Int. Ed.* **2004**, *43*, 2752–2778; b) M. North, *Tetrahedron: Asymmetry* **2003**, *14*, 147–176; c) R. J. H. Gregory, *Chem. Rev.* **1999**, *99*, 3649–3682.

[2] L. Birkofer, W. Kaiser, *Justus Liebigs Ann. Chem.* **1975**, 266–274.

[3] a) J. P. Richard, T. L. Amyes, V. Jagannadham, Y.-G. Lee, D. J. Rice, *J. Am. Chem. Soc.* **1995**, *117*, 5198–5205; b) J. P. Richard, T. L. Amyes, Y.-G. Lee, V. Jagannadham, *J. Am. Chem. Soc.* **1994**, *116*, 10833–10834; c) T. L. Amyes, J. P. Richard, *J. Am. Chem. Soc.* **1991**, *113*, 1867–1869.

[4] a) T. Katori, S. Itoh, M. Sato, H. Yamataka, *J. Am. Chem. Soc.* **2010**, *132*, 3413–3422; b) S. Grecian, J. Aubé in *Organic Azides: Syntheses and Applications* (Eds.: S. Bräse, K. Banert), Wiley, Chichester, **2010**, pp. 191–237.

[5] J. Kalisiak, K. B. Sharpless, V. V. Fokin, *Org. Lett.* **2008**, *10*, 3171–3174.

[6] a) K. Nishiyama, T. Yamaguchi, *Synthesis* **1988**, 106–108; b) D. A. Evans, L. K. Truesdale, *Tetrahedron Lett.* **1973**, *14*, 4929–4932; c) L. Birkofer, F. Müller, W. Kaiser, *Tetrahedron Lett.* **1967**, *8*, 2781–2783.

[7] a) H. Suzuki, C. Nakaya, *Synthesis* **1992**, 641–642; b) K. Nishiyama, M. Oba, A. Watanabe, *Tetrahedron* **1987**, *43*, 693–700.

[8] H. Yanai, T. Taguchi, *Tetrahedron Lett.* **2005**, *46*, 8639–8643.

[9] a) A. Hassner, R. Fibiger, A. S. Amarasekara, *J. Org. Chem.* **1988**, *53*, 22–27; b) S. Kirchmeyer, A. Mertens, G. A. Olah, *Synthesis* **1983**, 500–502; c) A. Hassner, R. Fibiger, D. Andisik, *J. Org. Chem.* **1984**, *49*, 4237–4244; d) E. P. Kyba, A. M. John, *Tetrahedron Lett.* **1977**, *18*, 2737–2740; e) M. Omura, K. Iwanami, T. Oriyama, *Chem. Lett.* **2007**, *36*, 532–533.

[10] K. Banert, Y.-H. Joo, T. Rüffer, B. Walfort, H. Lang, *Tetrahedron Lett.* **2010**, *51*, 2880–2882.

[11] a) A. Hassner, M. Stern, *Angew. Chem.* **1986**, *98*, 479–480; *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 478–479; b) A. Hassner, M. Stern, H. E. Gottlieb, *J. Org. Chem.* **1990**, *55*, 2304–2306.

[12] L. F. Tietze, T. Eicher, *Reaktionen und Synthesen im Organisch-Chemischen Praktikum und Forschungslaboratorium*, 2nd ed., Thieme, Stuttgart, **1991**, p. 40.

[13] **Caution!** For potential hazards in handling hydrazoic acid and organic azides, see: T. Keicher, S. Löbbecke in *Organic Azides: Syntheses and Applications* (Eds.: S. Bräse, K. Banert), Wiley, Chichester, **2010**, pp. 3–27.

[14] J. P. Guthrie, *J. Am. Chem. Soc.* **2000**, *122*, 5529–5538.

[15] Thus, compounds **2** have different properties than the silylated analogues **3**, which can be distilled under reduced pressure (see Ref. [2]).

[16] a) J. H. Boyer, *J. Am. Chem. Soc.* **1951**, *73*, 5248–5252; b) A. J. Davies, A. S. R. Donald, R. E. Marks, *J. Chem. Soc. C* **1967**, 2109–2112; c) J. Szmuszkovicz, M. P. Kane, L. G. Laurian, C. G. Chidester, T. A. Scahill, *J. Org. Chem.* **1981**, *46*, 3562–3564.

[17] Transformations similar to the reaction **12**→**1w**: a) C. Gauthier, Y. Ramondenc, G. Plé, *Tetrahedron* **2001**, *57*, 7513–7517; b) S.-G. Kim, T.-H. Park, *Synth. Commun.* **2007**, *37*, 1027–1035.

[18] M. O. Forster, S. H. Newman, *J. Chem. Soc.* **1910**, *97*, 2570–2579.

[19] K. Banert in *Organic Azides: Syntheses and Applications* (Eds.: S. Bräse, K. Banert), Wiley, Chichester, **2010**, pp. 115–166.

[20] H. Roesky, O. Glemser, *Chem. Ber.* **1964**, *97*, 1710–1712.

[21] a) N. D. Arote, K. G. Akamanchi, *Tetrahedron Lett.* **2007**, *48*, 5661–5664; b) L. Marinescu, J. Thinggaard, I. B. Thomsen, M. Bols, *J. Org. Chem.* **2003**, *68*, 9453–9455; c) D. S. Bose, A. V. N. Reddy, *Tetrahedron Lett.* **2003**, *44*, 3543–3545; d) D.-J. Chen, Z.-C. Chen, *Tetrahedron Lett.* **2000**, *41*, 7361–7363; e) J. G. Lee, K. H. Kwak, *Tetrahedron Lett.* **1992**, *33*, 3165–3166; f) P. S. Reddy, P. Yadagiri, S. Lumin, D.-S. Shin, J. R. Falck, *Synth. Commun.* **1988**, *18*, 545–551.

[22] *Organic Azides: Syntheses and Applications* (Eds.: S. Bräse, K. Banert), Wiley, Chichester, **2010**.

