JOC*Note*

Synthesis of 4-Aryl-1*H*-1,2,3-triazoles through TBAF-Catalyzed [3 + 2] Cycloaddition of 2-Aryl-1-nitroethenes with $TMSN_3$ under Solvent-Free Conditions

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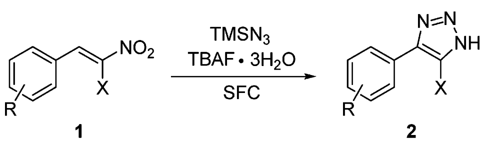

R = various substituents, X = CN, CO_2Et

TBAF-catalyzed [3 + 2] cycloaddition reactions of 2-aryl-1-cyano- or 2-aryl-1-carbethoxy-1-nitroethenes **1** with $TMSN_3$ under SFC allow the corresponding 4-aryl-5-cyano- or 4-aryl-5-carbethoxy-1*H*-1,2,3-triazoles **2** to be prepared under mild reaction conditions and with good to excellent yields (70–90%). The proposed protocol does not require dried glassware or inert atmosphere.

1*H*-1,2,3-Triazoles are heterocycles with a wide range of applications that are receiving a growing attention.[1] They are commercially employed as anticorrosive agents,[2] agrochemicals,[3] photostabilizer photographic materials,[4] and dyes.[4] In addition, they constitute the essential moiety of a number of drugs,[5] and they are also potent HIV-1 inhibitors,[6] anti-microbial agents,[7] as well as selective β_3-adrenergic receptor agonists.[8] They can also act as antiviral and anticonvulsant agents.[9]

1,2,3-Triazole synthesis has been intensively studied, and 1,2,3-triazoles are commonly prepared by the Huisgen 1,3-dipolar cycloaddition of azides with alkynes. The efficiency of this process is generally related to the presence of an electron-withdrawing group on the alkyne[10] and/or on the azide.[11,12] Recently, significant progress in the synthesis of these heterocycles has been achieved by Sharpless et al., who have defined a *Click chemistry* process in which a Cu(I)–acetylenic organometallic compound prepared in situ has been used as a 1,3-dipolarophile either in aqueous medium[13] or in organic solvent.[14]

Recently, Sharpless et al. have also reported the use of an alkylmagnesium bromide as 1,3-dipolarophile in dry THF for the synthesis of 1,5-disubstituted 1,2,3-triazoles under "Click conditions"[15] and demonstrated that acetylcholinesterase is an efficient catalyst for the reactions of azides with acetylenic compounds.[16]

Alternative synthetic routes for the preparation of 1,2,3-triazole moiety have been rarely pursued.[17] In particular, a very little attention has been devoted to [3+2] cycloaddition reactions of azides with electron-poor olefins and subsequent elimination reaction[18] (Scheme 1).

The scarce application of these substrates is probably due to the poor reactivity of the reactants, which require harsh reaction conditions generally leading to unsatisfac-

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[1] (a) Dehne, H. In *Methodenischen Chemie (Houben-Weyl)*; Shumann, E., Ed.; Thieme: Stuttgart, 1994; Vol/ E 8d, 305–405 and 406–478. (b) Tomé, A. C. *Sci. Synth.* **2004**, *13*, 415–601.

[2] Morgan, N. H. (CHOMERICS, Inc.) *Eur. Pat. Appl.* EP 437979 A2 19910724, 1991.

[3] Fan, W. In *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Eds.; Pergamon: Oxford, U.K., 1996; Vol. 4, pp 1–126.

[4] Willis, R. J.; Marlow, I. D. *Eur. Pat Appl.* 400842, 1990; *Chem. Abstr.* **1991**, *114*, 164247b.

[5] (a) Cai, D.; Journet, M.; Larsen, R. D. US Patent US 6051707, 2000.

[6] (a) Alvarez, R.; Velazquez, S.; San-Felix, A.; Aquaro, S.; De Clercq, E.; Perno, C.-F.; Karlsson, A.; Balzarini, J.; Camarasa, M. J. *J. Med. Chem.* **1994**, *37*, 4185–4194. (b) Velaquez, S.; Alvarez, R.; Perez, C.; Gago, F.; De Clercq, E.; Balzarini, J.; Camarasa, M.-J. *Antivir. Chem. Chemother.* **1998**, *9*, 481–489.

[7] Genin, M. J.; Allwine, D. A.; Anderson, D. J.; Barbachyn, M. R.; Emmert, D. E.; Garmon, S. A.; Graber, D. R.; Grega, K. C.; Hester, J. B.; Hutchinson, D. K.; Morris, J.; Reischer, R. J.; Ford, C. W.; Zurenko, G. E.; Hamel, J. C.; Schaadt, R. D.; Stapert, D.; Yagi, B. H. *J. Med. Chem.* **2000**, *43*, 953–970.

[8] Brockunier, L. L.; Parmee, E. R.; Ok, H. O.; Candelore, M. R.; Cascieri, M. A.; Colwell, L. F.; Deng, L.; Feeney, W. P.; Forrest, M. J.; Hom, G. J.; MacIntyre, D. E.; Tota, L.; Wyvratt, M. J.; Fisher, M. H.; Weber, A. E. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 2111–2114.

[9] Palhagen, S.; Canger, R.; Henriksen, O.; van Parys, J. A.; Riviere, M. E.; Karolchyk, M. A. *Epilepsy Res.* **2001**, *43*, 115–124.

[10] (a) Sheehan, J. C.; Robinson, C. A. *J. Am. Chem. Soc.* **1951**, *73*, 1207–1210. (b) Wiley, R. H.; Hussung, K. F.; Moffat, J. *J. Org. Chem* **1956**, *21*, 190–192. (c) Kirmse, W.; Horner, L. *Liebigs Ann. Chem.* **1958**, *614*, 1–3. (d) Tanaka, Y.; Velen, S. R.; Miller, S. I. *Tetrahedron* **1973**, *29*, 3271–3283. (e) De Pasquale, R. J.; Padgett, C. D.; Rosser, R. W. *J. Org. Chem.* **1975**, *40*, 810–811. (f) Abu-Orabi, S. T.; Atfah, M. A.; Jibril, I.; Mari'i, F. M.; Fakhri, M.; Ali, A. A. *J. Heterocycl. Chem.* **1989**, *26*, 1461–1468. (f) Journet, M.; Cai, D.; Kowal, J. J.; Larsen, R. D. *Tetrahedron Lett.* **2001**, *42*, 9117–9118. (g) Katritzky, A.; Singh, S. K. *J. Org. Chem.* **2002**, *67*, 9077–9079. (h) Garanti, L.; Molteni, G. *Tetrahedron Lett.* **2003**, *44*, 1133–1135. (i) Haryu, K.; Vahermo, M.; Mutikainen, I.; Yli-Kauhauloma, J. *J. Comb. Chem.* **2003**, *5*, 826–833. (j) Helms, B.; Mynar, J.; Hawker, C. J.; Fréchet, J. M. *J. Am. Chem. Soc.* **2004**, *126*, 15020–15021.

[11] (a) Huisgen, R.; Knorr, R.; M oius, L.; Szeimies, G. *Chem. Ber.* **1965**, *98*, 4014–4021. (b) Huisgen, R.; Blaschke, H. *Chem. Ber.* **1965**, *98*, 2985–2997. (c) Woerner, F. P.; Reimlinger, H. *Chem. Ber.* **1970**, *103*, 1908–1917.

[12] (a) Gold, v. H. *Liebigs Ann. Chem.* **1965**, *688*, 205–216. (b) Winter, W.; Müller, E. *Chem. Ber.* **1974**, *107*, 715–716.

[13] (a) Tornøe, C. W.; Christensen, C.; Meldal, M. *J. Org. Chem.* **2002**, *67*, 3037–3064. (b) Rostovstev, V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2002**, *41*, 2596–2599. (c) Chan, T. R.; Hilgraf, R.; Sharpless, K. B.; Fokin, V. V. *Org. Lett.* **2004**, *6*, 2853–2855. (d) Feldman, A. K.; Colasson, B.; Fokin, V. V. *Org. Lett.* **2004**, *6*, 3897–3899. (e) Appukkuttan, P.; Dehaen, W.; Fokin, V. V.; Van der Eycken, E. *Org. Lett.* **2004**, *6*, 4223–4225. (f) Sivakumar, K.; Xie, F.; Cash, B. M.; Long, S.; Barnhill, H. N.; Wang, Q. *Org. Lett.* **2004**, *6*, 4603–4606. (g) Himo, F.; Lovell, T.; Hilgraf, R.; Rosostev, V. V.; Noodleman, L.; Sharpless, K. B.; Fokin, V. V. *J. Am. Chem. Soc.* **2005**, *127*, 210–216.

[14] Kamijo, S.; Jin, T.; Huo, Z.; Yamamoto, Y. *J. Am. Chem. Soc.* **2003**, *125*, 7786–7787.

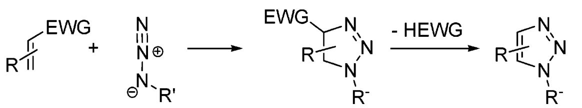
[15] Krasinki, A.; Fokin, V. V.; Sharpless, K. B. *Org. Lett.* **2004**, *6*, 1237–1240.

[16] Lewis, W. G.; Green, L. G.; Grynszpan, F.; Radié, Z.; Carlier, P. R.; Taylor, P.; Finn, M. G.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2002**, *41*, 1053–1057.

[17] (a) Dong, Z.; Hellmund, K. A.; Pyne, S. G. *Aust. J. Chem.* **1993**, *46*, 1431–1436. (b) Batanero, D. B.; Barba, F. *Heterocycles* **2004**, *65*, 1175–1180. (c) Raghavendra, M. S.; Lam, Y. *Tetrahedron Lett.* **2004**, *45*, 6129–6132.

10.1021/jo0507845 CCC: $30.25

SCHEME 1. [3 + 2] Cycloaddition/Elimination Strategy for the Synthesis of 1*H*-1,2,3-Triazoles from Electron-Poor Olefins



tory yields. To the best of our knowledge, an efficient catalyst for this process is still unavailable.

Considering that electron-poor olefins are widely accessible and despite current knowledge, we believe that this alternative approach to 1,2,3-triazoles has not showed its potential yet.

Our research is mainly focused on the definition of new, chemically efficient, easy-to-operate, and environmentally responsible synthetic procedures for the preparation of target molecules.[19,20] To reach this goal, we have been performing reactions in water[19] or under solvent-free conditions (SFC),[19] searching for new catalysts that would express their best efficiency in these alternative reaction media.[19,20]

Recently, we have reported an environmentally friendly protocol for the preparation of 1*H*-tetrazoles by a tetrabutylammonium fluoride (TBAF)-catalyzed cycloaddition of aryl- or alkylnitriles with trimethylsilyl azide (TMSN$_3$) under SFC.[19] Starting from these results and considering that we have been investigating the synthetic utility of α-cyano- and α-carbetoxy-α-nitroethenes **1**,[19b,c,h,20b] we have planned to use TBAF as a catalyst in the [3 + 2] cycloadditions of these electron-poor olefins with TMSN$_3$ under SFC (Scheme 2). Acceptors **1** can open a straightforward and environmentally friendly access route to a new class of triazoles such **2**.

To our knowledge, α-nitroethenes have never been used as acceptors in the reaction with an azide except for the preparation of 1*H*-1,2,3-triazoles **2** (X = H, R = H, *p*-Cl, *p*-Br) via reaction of the corresponding *β*-nitrostyrene **1** (X = R = H) with sodium azide in DMF.[18c] In these cases, yields were poor.

Initially, we have optimized the reaction conditions by studying the cycloaddition reaction of (*E*)-2-phenyl-1-cyano-1-nitroethene (**1a**) with TMSN$_3$ at 30 °C. The results are illustrated in Table 1.

SCHEME 2. Synthesis of 4-Aryl-Substituted 1*H*-1,2,3-Triazoles 2 Starting from Nitroethenes 1

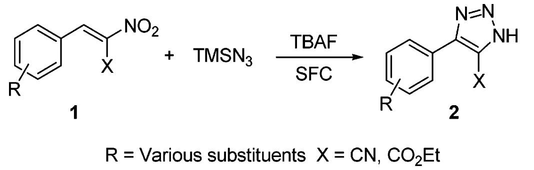
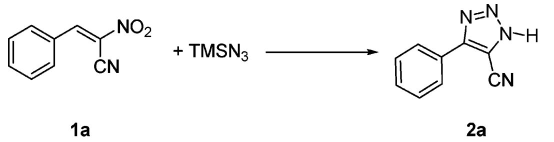


TABLE 1. Optimization of the Reaction of (*E*)-2-Phenyl-1-cyano-1-nitroethene (1a) with TMSN$_3$[a] at 30 °C



entry	catalyst[b]	medium	time (h)	conversion[c] (%)
1		SFC	24	
2	TiCl$_4$	SFC	24	
3	TiCl$_4$	DCE	24	
4	TiCl$_4$·2THF	SFC	24	
5	TiCl$_4$·2THF	DCE	24	
6	TBABr	SFC	15	98
7	TBAF·3H$_2$O	SFC	3	99
8	TBAF·3H$_2$O	THF	10	99
9	TBAF·3H$_2$O	DCE	11	91

[a] 2.0 equiv. [b] 0.1 equiv. [c] Reaction conversions determined by ^{1}H NMR analyses.

Under SFC and in the absence of any additive, nitroethene **1a** did not react with TMSN$_3$ (2.0 equiv) even after 24 h (Table 1, entry 1). Similarly, TiCl$_4$, chosen as a representative and commonly used Lewis acid catalyst in many organic processes, and its THF complex TiCl$_4$·2THF were not able to promote the cycloaddition of **1a** with TMSN$_3$ both under SFC and in dichloroethane (DCE) (Table 1, entries 2–5).

By using 0.1 equiv of tetrabutylammonium bromide (TBABr) as catalyst under SFC at 30 °C, triazole **2a** was obtained as the sole reaction product after 15 h (Table 1, entry 6). Under these reaction conditions HNO$_2$-elimination and tautomeric rearrangement always followed the cycloaddition process.

A better result was achieved by using 0.1 equiv of TBAF. In the presence of this salt, the reaction of **1a** with TMSN$_3$ was complete in only 3 h at 30 °C (Table 1, entry 7). By using THF or DCE as reaction medium longer times (10 and 11 h, respectively) were observed (Table 1, entries 8 and 9). The excellent catalytic activity of TBAF under SFC was then used for the preparation of a variety of triazoles (**2a**–**g**). The results are illustrated in Table 2.

In the presence of 0.1 equiv of TBAF, nitroethenes **1a**–**e** reacted at 30 °C with TMSN$_3$ (2.0 equiv) under SFC and in very short times and gave triazoles **2a**–**e** in excellent yields (75–90%) (Table 2, entries 1–5), independently from the substituent at the phenyl ring. When 2-thienyl or 2-furfuryl was the aryl substituent (**1f**, **1g**), reaction rates and isolated yields of the corresponding **2f** and **2g** were still satisfactory (Table 2, entries 6 and 7).

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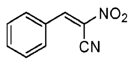
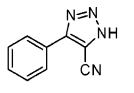
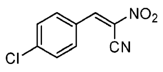
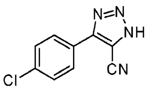
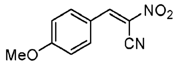
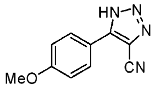
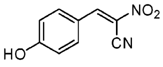
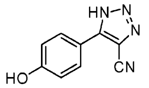
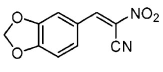
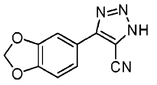
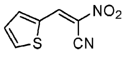
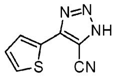
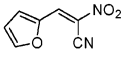
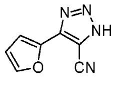
(18) (a) Maiorana, S.; Pocar, D.; Dalla Croce, P. *Tetrahedron Lett.* **1966**, *7*, 6043–6045. (b) Meek, J. S.; Fowler, J. *J. Org. Chem.* **1968**, *33*, 985–991. (c) Zefirov, M. S.; Chapovskaya, N. K.; Kolesnikov, V. V. *Chem. Commun.* **1971**, 1001–1002. (d) Beck, G.; Günther, D. *Chem. Ber.* **1973**, 2758–2766. (e) Shin, C. G.; Yonezawa, Y.; Yoshimura, J. *Tetrahedron Lett.* **1974**, *15*, 7–10. (f) Chakrasali, R. T.; Ila, H.; Junjappa, H. *Synthesis* **1988**, 453–455. (g) Chakrasali, R. T.; Ila, H.; Junjappa, H. *Synthesis* **1988**, 851–854.

(19) As representative papers, see: (a) Fringuelli, F.; Pizzo, F.; Vaccaro, L. *Synthesis* **2000**, 646–650. (b) Amantini, D.; Fringuelli, F.; Piermatti, O.; Pizzo, F.; Vaccaro, L. *Green Chem.* **2001**, *3*, 229–232. (c) Fringuelli, F.; Matteucci, M.; Piermatti, O.; Pizzo, F.; Burla, M. C. *J. Org. Chem.* **2001**, *66*, 4661–4666. (d) Fringuelli, F.; Pizzo, F.; Tortoioli, S.; Vaccaro, L. *Adv. Synth. Catal.* **2002**, *344*, 379–384. (e) Fioroni, G.; Fringuelli, F.; Pizzo, F.; Vaccaro, L. *Green Chem.* **2003**, *5*, 425–428. (f) Fringuelli, F.; Pizzo, F.; Rucci, M.; Vaccaro, L. *J. Org. Chem.* **2003**, *68*, 7041–7045. (g) Fringuelli, F.; Pizzo, F.; Tortoioli, S.; Vaccaro, L. *J. Org. Chem.* **2003**, *68*, 8248–8251. (h) Amantini, D.; Fringuelli, F.; Piermatti, O.; Pizzo, F.; Vaccaro, L. *J. Org. Chem.* **2003**, *68*, 9263–9268. (i) Fringuelli, F.; Pizzo, F.; Vaccaro, L. *J. Org. Chem.* **2004**, *69*, 2315–2321.

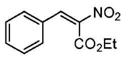
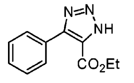
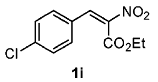
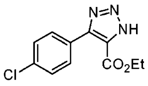
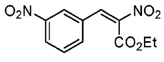
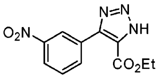
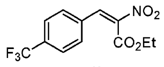
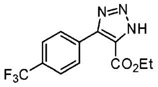
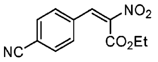
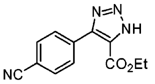
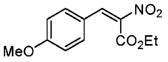
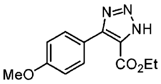
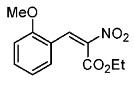
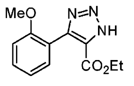
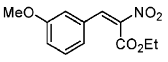
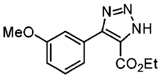
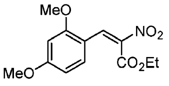
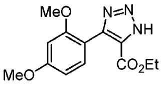
(20) (a) Amantini, D.; Fringuelli, F.; Pizzo, F.; Vaccaro, L. *J. Org. Chem.* **2001**, *66*, 6734–6737. (b) Amantini, D.; Fringuelli, F.; Pizzo, F. *J. Org. Chem.* **2002**, *67*, 7238–7243. (c) Fringuelli, F.; Pizzo, F.; Tortoioli, S.; Vaccaro, L. *Tetrahedron Lett* **2003**, *44*, 6785–6787. (d) Amantini, D.; Beleggia, R.; Fringuelli, F.; Pizzo, F.; Vaccaro, L. *J. Org. Chem.* **2004**, *69*, 2896–2898. (e) Fringuelli, F.; Pizzo, F.; Tortoioli, S.; Vaccaro, L. *J. Org. Chem.* **2004**, *69*, 7745–7747. (f) Fringuelli, F.; Pizzo, F.; Tortoioli, S.; Vaccaro, L. *J. Org. Chem.* **2004**, *69*, 8780–8785.

TABLE 2. Synthesis of 4-Aryl-5-cyano-1*H*-1,2,3-triazoles 2a−g under SFC at 30 °C[a]

Entry	Substrate	Time (h)	Triazoles	Yield (%)[b]
1	 **1a**	3	 **2a**	85
2	 **1b**	0.15	 **2b**	90
3	 **1c**	3	 **2c**	75
4	 **1d**	3	 **2c**	70
5	 **1e**	1	 **2e**	85
6	 **1f**	2	 **2f**	75
7	 **1g**	3	 **2g**	75

[a] 0.1 equiv of $TBAF\cdot3H_2O$ and 2.0 equiv of $TMSN_3$. [b] Yield of isolated product.

TABLE 3. Synthesis of 4-Aryl-5-carbethoxy-1*H*-1,2,3-triazoles 2h−p under SFC[a]

Entry	Substrate[21]	T (°C)	Time (h)	Triazoles	Yield (%)[b]
1	 **1h**	50	7	 **2h**	80
2	 **1i**	50	4	 **2i**	85
3	 **1j**	50	7	 **2j**	85
4	 **1k**	50	5	 **2k**	75
5	 **1l**	50	6	 **2l**	70
6	 **1m**	80	8	 **2m**	70
7	 **1n**	80	8	 **2n**	75
8	 **1o**	80	9	 **2o**	70
9	 **1p**	80	12	 **2p**	70

[a] 4 equiv of $TMSN_3$ and 0.1 equiv of TBAF. [b] Yield of isolated product.

The use of TBAF under SFC was then extended to the reactions of 2-aryl-1-carbethoxy-1-nitroethenes **1h**−**p** with $TMSN_3$ (Table 3). These 1,3-dipolarophiles although less reactive than benzylydenes **1a**−**g**, reacted with $TMSN_3$ (4.0 equiv) in the presence of 0.1 equiv of TBAF, under acceptable mild conditions (50−80 °C). Also in this case the nature of the substituent and its position in the aromatic ring little influenced the reactivity of the substrate. In all cases, [3 + 2] cycloadditions were complete in a reasonable time (4−12 h) and triazoles **2h**−**p** were isolated in good yields (70−85%).

All the reactions were performed by mixing under vigorous stirring the heterogeneous mixture of a benzylydene **1**[21] with $TMSN_3$ (2.0 or 4.0 equiv) in the presence of 0.1 equiv of TBAF,[22] at the temperature and for the time reported in Tables 2 and 3. The reaction of **1a** was also performed on a 100 mmol scale without encountering any additional problems, and triazole **2a** was isolated in 87% yield. Triazoles **2** have been isolated in pure form after silica gel column chromatography of the crude reaction mixtures. All the prepared triazoles have been fully characterized, and the corresponding charts, except for **2h** whose spectroscopic data have already been reported,[10i] are included in Supporting Information.

In conclusion, TBAF is the first organic catalyst able to efficiently catalyze the cycloaddtion reaction of an electron-poor olefin with $TMSN_3$ making this approach to 1*H*-1,2,3-triazoles a valid and viable alternative to classic Huisgen 1,3-dipolar cycloaddition of azides with alkynes. Following an easy procedure that does not require dried glassware and inert atmposphere, a wide variety of 4-aryl-1*H*-1,2,3-triazoles **2** have been prepared under mild and environmentally friendly conditions.

Experimental Section

Representative Experimental Procedure. General experimental details can be found in the Supporting Information. *CAUTION*: Azides can be very explosive compounds and should be handled with great care. During our study, we used $TMSN_3$

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(21) *Z*)-α-Cyanonitroethenes **1a**−**g** were prepared as the pure (*Z*) stereoisomer by the reported procedure.[19b] In the case of α-carbethoxynitroethenes **1h**−**p** by following the reported procedure, *E*/*Z* mixtures were sometimes obtained and used.[22]

(22) Lehnert, W. *Tetrahedron* **1972**, *28*, 663−666.

and we encountered no problems.[23] In a screw-capped vial equipped with a magnetic stirrer, TBAF·$3H_2O$ (0.064 g, 0.2 mmol), (E)-1-cyano-2-pheny-l-nitroethene (**1a**) (0. 348 g, 2.0 mmol), and $TMSN_3$ (0.460 g, 4.0 mmol) were consecutively added, and the resulting mixture was left under vigorous stirring at 30 °C for 3 h. The crude reaction mixture was charged on a silica gel column chromatography (petroleum ether/ethyl acetate 8/2 (gradient); silica/sample 15:1). Pure 4-phenyl-1*H*-1,2,3-triazole-5-carbonitrile (**2a**) was isolated as a white solid in 85% yield (0.289 g). The product was recrystallizated from ethyl acetate: white crystals; mp = 185−186 °C; R_f = 0.20 (Etp/AcOEt/AcOH/80/17/3); IR (KBr, cm^{-1}): 687 (s), 775 (s), 687 (s), 775 (s), 1273 (s), 1497 (m), 2241 (m), 2809 (m), 2845 (m), 2906 (m), 3076 (m), 3104 (m); ^{1}H NMR (400 MHz, CD_3OD) δ: 7.40−7.70 (m, 2H, 7.90−7.96 (m, 2H); ^{13}C NMR ((400 MHz, CD_3OD) δ: 114.0, 117.9, 127.0, 127.7, 130.3, 132.2, 148.4. Anal. Calcd for $C_9H_6N_4$: C, 52.55; H, 5.14; N, 30.64. Found: C, 52.59; H, 5.32; N, 30.80.

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Supporting Information Available: Detailed experimental procedures and spectral data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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[23] For a discussion on the hazards associated with azides, see: *Prudent Practice for Handling Hazardous Chemicals in Laboratories*; National Academic Press: Washington, DC, 1983; pp 87−88. For human toxicity, see: *The Merck Index*, 12th ed.; Merck & Co.: Rahway, NJ, 1996; pp 4818 and 8726.