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TBAF-Catalyzed Synthesis of 5-Substituted 1*H*-Tetrazoles under Solventless Conditions

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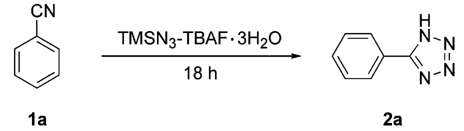
Abstract: Tetrabutylammonium fluoride (TBAF) is an efficient catalyst in the [3 + 2] cycloaddition reaction of organic nitriles **1** with trimethylsilyl azide ($TMSN_3$) in solventless conditions. The corresponding 5-substituted 1*H*-tetrazoles **2** were obtained under mild conditions and in 80−97% yields.

Tetrazoles are a class of heterocycles with a wide range of applications that is receiving considerable attention.[1] This functionality has been frequently used as a metabolically stable surrogate for a carboxylic acid group,[2] and tetrazoles have shown valuable properties as precursors of a variety of nitrogen-containing heterocycles[3] and have found use in various material sciences, including photography, information recording systems, and explosives.[4]

5-Substituted 1*H*-tetrazoles **2** are usually obtained by the addition of azide ion to organic nitriles **1**, and many methods are reported in the literature.[5] Unfortunately, each of those protocols suffers from some disadvantages: the use of both toxic metals and expensive reagents, drastic reaction conditions, water sensitivity, and the presence of dangerous hydrazoic acid.

TABLE 1. TBAF-Catalyzed Reaction of Benzonitrile (1a) with $TMSN_3$ under Solventless Conditions



entry	$TMSN_3$ (equiv)	TBAF (equiv)	*T* (°C)	C^a (%)
1	1.0		85	
2	1.0	0.1	85	35
3	1.5	0.1	85	40
4	1.5	0.1	120	78
5	1.5	0.3	85	89
6	1.5	0.5	85	>99

[a] Determined by ^1H NMR analysis.

Recently, Sharpless and co-workers have reported an innovative and safe procedure for the preparation of **2** starting from the corresponding nitriles **1**, by using NaN_3 and stoichiometric amounts of Zn(II) salts in water.[6] This procedure has shown a good level of generality but in the case of sterically hindered aromatic or alkyl inactivated nitriles high temperatures (140−170 °C) are usually required.

Our research group devoted particular attention to the development of environmentally friendly and efficient protocols by using water as the reaction medium[7] or by working under solventless conditions.[8]

To improve the ecocompatibility of organic processes we are also focusing our attention on the development of nonmetallic catalysts, and recently, we reported that by using $TMSN_3$ in the presence of catalytic tetrabutylammonium bromide (TBABr) a variety of alcohols and phenols are readily converted into the corresponding OTMS derivatives in high yields and selectivities under solventless conditions.[8a] Our aim is to extend this research to other important organic transformations such as addition and cycloaddition reactions.

We inquired into the use of $TMSN_3$ as azide source in the conversion of nitriles **1** to **2** by using the anionic activation of silicon−nitrogen bond strategy.[9] $TMSN_3$ has been already used in such transformations in the presence of either an equimolar amount of a strong Lewis acid such as $AlMe_3$[5b] or by using a catalytic amount of toxic dialkyltin oxide.[5c]

We hypothesized that fluoride anion could be an efficacious basic activator for the cycloaddition of $TMSN_3$ to organic nitriles and tetrabutylammonium fluoride (TBAF) a good candidate as fluoride ion source. To establish the feasibility of our approach, the conversion

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(1) Butler, R. N. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Eds.; Pergamon: Oxford, U.K., 1996; Vol. 4.

(2) Singh, H.; Chawla, A. S.; Kapoor, V. K.; Paul, D.; Malhotra, R. K. *Prog. Med. Chem.* **1980**, *17*, 151−183.

(3) Huisgen, R.; Sauer, J.; Sturm, H. J.; Markgraf, J. H. *Chem. Ber.* **1960**, *93*, 2106−2124. (b) Moderhack, D. *J. Prakt. Chem./Chem.-Ztg.* **1988**, *340*, 687−709.

(4) Ostrovskii, V. A.; Pevzner, M. S.; Kofmna, T. P.; Shcherbinin, M. B.; Tselinskii, I. V. *Targets Heterocycl. Syst.* **1999**, *3*, 467−526. (b) Koldobskii, G. I.; Ostrovskii, V. A. *Usp. Khim.* **1994**, *63*, 847−865.

(5) Duncia, J. V.; Pierce, M. E.; Santella, J. B., III. *J. Org. Chem.* **1991**, *56*, 2395−2400. (b) Huff, B. E.; Staszak, M. A. *Tetrahedron Lett.* **1993**, *34*, 8011−8014. (c) Wittenberger, S. J.; Donner, B. G. *J. Org. Chem.* **1993**, *58*, 4139−4141. (d) Koguro, K.; Oga, T.; Mitsui, S.; Orita, R. *Synthesis* **1998**, 910−914. (e) Curran, D. P.; Hadida, S.; Kim, S.-Y. *Tetrahedron* **1999**, *55*, 8997−9006.

(6) Demko, Z. P.; Sharpless, K. B. *J. Org. Chem.* **2001**, *66*, 7945−7950. (b) Demko, Z. P.; Sharpless, K. B. *Org. Lett.* **2002**, *4*, 2525−2527. (c) Himo, F.; Demko, Z. P.; Noodleman, L.; Sharpless, K. B. *J. Am. Chem. Soc.* **2002**, *124*, 12210−12216. (d) Himo, F.; Demko, Z. P.; Noodleman, L.; Sharpless, K. B. *J. Am. Chem. Soc.* **2003**, *125*, 9983−9987.

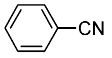
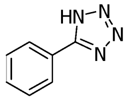
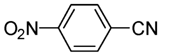
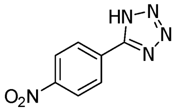
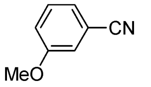
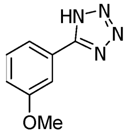
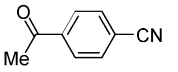
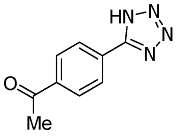
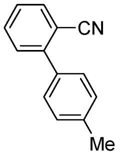
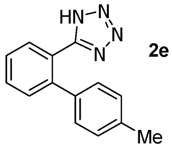
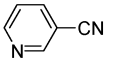
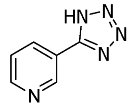
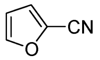
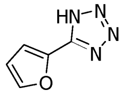
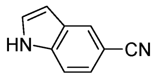
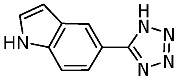
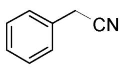
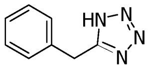
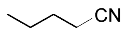
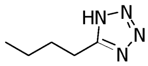
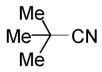
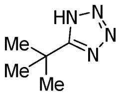
(7) For more recent papers, see: (a) Fringuelli, F.; Pizzo, F.; Vaccaro L. *Synthesis* **2000**, 646−650. (b) Amantini, D.; Fringuelli, F.; Piermatti, O.; Pizzo, F.; Vaccaro, L. *Green Chem.* **2001**, *3*, 229−232. (c) Fringuelli, F.; Matteucci, M.; Piermatti, O.; Pizzo, F.; Burla M. C. *J. Org. Chem.* **2001**, *66*, 4661−4666. (d) Fioroni, G.; Fringuelli, F.; Pizzo, F.; Vaccaro, L. *Green Chem.* **2003**, *5*, 425−428. (e) Fringuelli, F.; Pizzo, F.; Rucci, M.; Vaccaro, L. *J. Org. Chem.* **2003**, *68*, 7041−7045. (f) Fringuelli, F.; Pizzo, F.; Tortoioli, S.; Vaccaro, L. *J. Org. Chem.* **2003**, *68*, 8248−8251. (g) Fringuelli, F.; Piermatti, O.; Pizzo, F. *Synthesis* **2003**, 2331−2334. (h) Amantini, D.; Fringuelli, F.; Piermatti, O.; Pizzo, F.; Vaccaro, L. *J. Org. Chem.* **2003**, *68*, 9263−9268.

(8) 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.

(9) Corriu, R. J. P.; Perz, R.; Reye, C. *Tetrahedron* **1983**, *39*, 999−1009.

10.1021/jo0499468 CCC: $27.50

TABLE 2. Synthesis of 5-Substituted 1*H*-Tetrazoles 2 by Using TMSN$_3$ (1.5 equiv)−TBAF (0.5 equiv) under Solventless Conditions

Entry	Substrate	T (°C)	Time (h)	Product	Yield (%)[a]
1	 **1a**	85	18	 **2a**	86
2	 **1b**	85	3	 **2b**	95
3	 **1c**	85	6	 **2c**	88
4	 **1d**	85	7	 **2d**	94
5	 **1e**	120	36	 **2e**	97[b]
6	 **1f**	50	9	 **2f**	85
7	 **1g**	85	1	 **2g**	95
8	 **1h**	120	18	 **2h**	82
9	 **1i**	120	24	 **2i**	93
10	 **1j**	120	24	 **2j**	80
11	 **1k**	120	48	 **2k**	82

[a] Yield of isolated product. [b] 2 equiv of TMSN$_3$ was used.

of benzonitrile (**1a**) into the corresponding 5-phenyl-1*H*-tetrazole (**2a**) under solventless conditions was explored (Table 1).

In the absence of catalyst at 85 °C, no reaction occurred after 18 h (entry 1). By adding 0.1 equiv of TBAF trihydrate in the presence of 1 equiv of TMSN$_3$, 1*H*-tetrazole **2a** was formed (35% conversion, entry 2). No silylated compounds were detected under these reaction conditions showing that the use of TBAF was 2-fold advantageous for (a) the activation of the azide nucleophile and (b) the deprotection of *N*-silylated products.[10] At 85 °C, employing 1.5 equiv of TMSN$_3$ resulted in a negligible increase in reaction conversion to a 40% value (entry 3), while an increase in the reaction temperature to 120 °C resulted in 78% conversion (entry 4). A greater catalyst loading was thus necessary. By using 0.3 equiv of the ammonium salt an 89% conversion was reached

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[10] When alkyltin or alkylsilicon azide reagents are used, a subsequent deprotection step is normally required.[5a−c,e]

(entry 5), while with 0.5 equiv of TBAF a complete conversion was obtained after 18 h at 85 °C (entry 6). Other fluoride salts such as CsF and KF were shown to be less effective than TBAF (32 and 36% conversion, respectively); furthermore, carrying out the [3 + 2] reaction of **1a** in organic solvent resulted in lower conversions (toluene 91%, THF 82%, respectively). Having established that our approach was suitable for the preparation of **2a**, we decided to investigate the reaction scope and limitations by using the best conditions outlined in Table 1 on a variety of organic nitriles **1** (Table 2).

The catalytic system proved to be highly efficient in the case of aryl nitriles; thus, compounds **1a**−**d** reacted at 85 °C to give after a few hours the corresponding 5-aryl-1*H*-tetrazoles **2a**−**d** in high yields (entries 1−4).

Interestingly, 4-acetylbenzonitrile (**1d**) gave only 1*H*-tetrazole **2d** (entry 4) with the carbonyl functionality untouched.[11] The reaction of sterically demanding biphenyl nitrile **1e** is a very interesting case because the corresponding 1*H*-tetrazole **2e** is a subunit that has become ubiquitous in some of the most potent angiotensin II antagonists disclosed to date (e.g., Losartan and Irbesartan).[12] In addition, it is also reported that ortho-substituted aromatic nitriles are a class of substrates particularly difficult to convert into the corresponding 1*H*-tetrazoles, and very high temperatures (≥140 °C) and long reaction times (≥2 d) are usually necessary for good yields to be obtained.[6a] By using our protocol, the tetrazole **2e** was quantitatively isolated after 36 h at 120 °C (entry 5). Nicotinonitrile **1f** was a very reactive substrate affording the relative tetrazole **2f** in 85% yield after 9 h at 50 °C (entry 6). Excellent results were also obtained with acid-sensitive electron-rich heteroaromatic nitriles **1g**,**h**. 2-Cyanofuran **1g** smoothly gave **2g** in 95% yield after only 1 h at 85 °C (entry 7). 5-Cyanoindole **1h** gave complete conversion after 18 h at 120 °C, and the desired 5-tetrazolylindole **2h** was isolated in 82% yield (entry 8).

The [3 + 2] process was also extended to alkyl nitriles **1i**−**k**. At 120 °C, under standard reaction conditions, the corresponding 1*H*-tetrazoles **2i**−**k** were produced in 24−48 h and isolated in excellent yields (entries 9−11). All the reactions proceeded under homogeneous conditions except in the case of **1f** (entry 6) where the reaction mixture was heterogeneous.

In summary, TBAF was found to be an efficient catalyst in the synthesis of 5-substituted 1*H*-tetrazoles **2** by using $TMSN_3$ under solventless conditions. The general procedure herein described can be applied to both aryl and alkyl organic nitriles leading in each case to the preparation of **2** in excellent yields.[13] The chemical efficiency, the low cost of reagents, the water tolerance, and the absence of metal salts make this process particularly attractive. Furthermore, employing anionic catalysis in effecting 5-substituted 1*H*-tetrazoles **2** preparation could represent an advantage, especially when dealing with acid-labile compounds. We are currently examining the extension of this methodology to other azide acceptors.

Acknowledgment. The Università degli studi di Perugia and the Ministero dell'Istruzione dell'Università e della Ricerca (MIUR) are thanked for financial support COFIN 2002; COFINLAB 2001 (CEMIN); FIRB 2001: "Progettazione, preparazione e valutazione giologica e farmacologica di nouve molecole organiche quali potenziali farmaci innovativi".

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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[11] Ketones are reported to react with $TMSN_3$ under both NaN_3/15-crown-5 and metal halide catalyzed conditions: Nishiyama, K.; Yamaguchi, T. *Synthesis* **1988**, 106−108.

[12] Le Bourdonnec, B.; Meulon, E.; Yous, S.; Goossens, J.-F.; Houssin, R.; Hénichart, J.-P. *J. Med. Chem.* **2000**, *43*, 2685−2697 and references therein.

[13] **Representative Experimental Procedure.** To a screw-capped vial equipped with a magnetic stirrer were added $TBAF \cdot 3H_2O$ (0.315 g, 1.0 mmol), benzonitrile (**1a**) (0.206 g, 2.0 mmol) and $TMSN_3$ (0.345 g, 3.0 mmol), and the resulting mixture was heated under vigorous stirring at 85 °C for 18 h. The crude reaction mixture was transferred into a separatory funnel with 20 mL of ethyl acetate, and TBAF was removed by washing the organic phase with a 1 M HCl aqueous solution (3 × 5 mL). The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure to furnish pure 5-phenyl-1-*H*-tetrazole (**2a**) as a white solid in 86% yield (0.251 g).