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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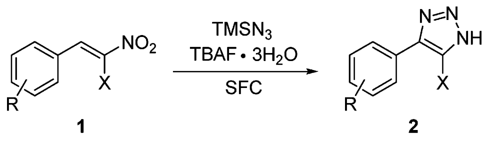

R = various substituents, X = CN, CO_2Et

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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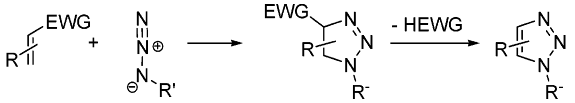
10.1021/jo0507845 CCC: $30.25

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

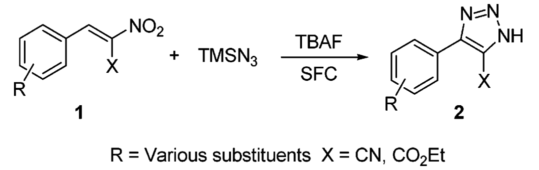
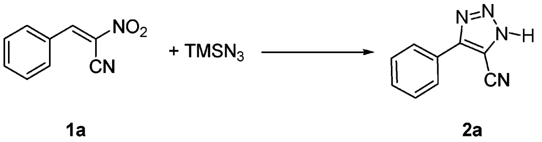


TABLE 1. Optimization of the Reaction of (*E*)-2-Phenyl-1-cyano-1-nitroethene (1a) with $TMSN_3$[a] at 30 °C



entry	catalyst[b]	medium	time (h)	conversion[c] (%)
1		SFC	24	
2	$TiCl_4$	SFC	24	
3	$TiCl_4$	DCE	24	
4	$TiCl_4 \cdot 2THF$	SFC	24	
5	$TiCl_4 \cdot 2THF$	DCE	24	
6	TBABr	SFC	15	98
7	$TBAF \cdot 3H_2O$	SFC	3	99
8	$TBAF \cdot 3H_2O$	THF	10	99
9	$TBAF \cdot 3H_2O$	DCE	11	91

[a] 2.0 equiv. [b] 0.1 equiv. [c] Reaction conversions determined by ^1H 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 $TiCl_4 \cdot 2THF$ 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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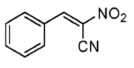
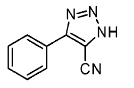
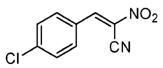
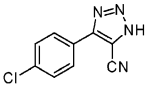
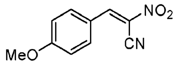
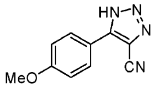
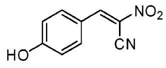
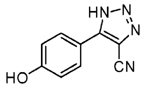
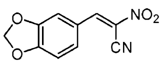
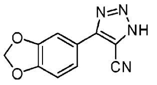
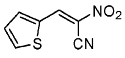
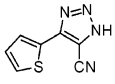
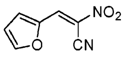
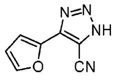
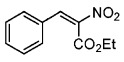
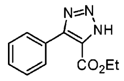
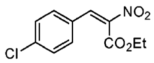
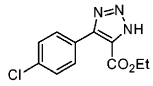
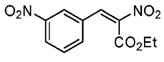
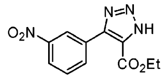
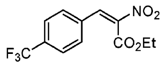
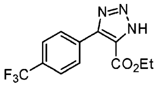
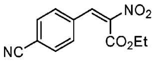
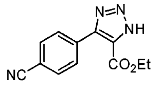
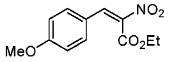
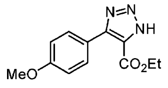
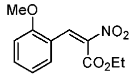
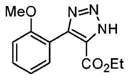
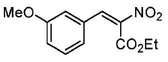
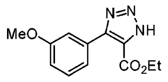
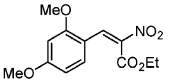
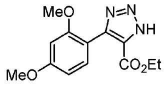
TABLE 2. Synthesis of 4-Aryl-5-cyano-1*H*-1,2,3-triazoles 2a−g under SFC at 30 °C[a]

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·3H_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); ^1H 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.