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Synthesis of *C*-Carbamoyl-1,2,3-triazoles by Microwave-Induced 1,3-Dipolar Cycloaddition of Organic Azides to Acetylenic Amides

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Abstract: 1,3-Dipolar cycloaddition of organic azides **1**, **2**, or **3** to acetylenic amides **4** or **5** under solvent-free microwave irradiation produced the corresponding N-substituted *C*-carbamoyl-1,2,3-triazoles **7a**−**12a** in good to excellent yields. Under similar reaction conditions, 1,3-dipolar cycloaddition of diazide **6** and acetylenic amide **4** gave the azido-triazole **13a**.

1,3-Dipolar cycloaddition of azides to alkynes is a versatile route to 1,2,3-triazole,[1] and the progress in this area has been reviewed periodically.[2] Combinations of substituents on the azide[3,4] and the alkyne allow the preparation of diverse N-substituted 1,2,3-triazoles.[5] Substituents on the alkyne include importantly esters[6a−d] and also carboxyl, hydroxy, keto, aryl, haloalkyl, trimethylsilyl, phenylsulfonyl, or phosphonate groups.[4,6e−j] Classical 1,3-dipolar cycloadditions also include azides with metal acetylides,[7] alkynic Grignard reagents,[8] and phosphonium salts.[9]

Only rare examples of 1,3-dipolar cycloaddition of azides to acetylenic amides have been reported, and reaction times of 24 h to 1 week are reported.[6i,10] The low reactivity of acetylenic amides toward 1,3-dipolar cycloaddition with azides has remained a problem for direct access to biologically active 1,2,3-triazoles with an amide substituent; the preparation of these compounds has generally involved the use of easily available 1,2,3-triazole esters,[11] acids, or imines[12] as intermediates, followed by a functional group transformation to the amide.

Microwave heating has emerged as a powerful technique to promote a variety of chemical reactions.[13] Microwave reactions under solvent-free conditions are attractive in offering reduced pollution and low cost together with simplicity in processing and handling.[14] A recent report from Palacios et al. on microwave synthesis of 1,2,3-triazoles shows a substantial decrease in reaction times down to 5−30 min as compared to 30−40 h refluxing under thermal conditions for the 1,3-dipolar cycloaddition between phosphonate azides and acetylenic esters.[15] In continuation of an ongoing program in our laboratories to synthesize a variety of 1,2,3-triazoles under mild conditions, we now report the first examples of 1,3-dipolar cycloadditions of organic azides to acetylenic amides under solvent-free microwave irradiation.

Reactions of benzyl chloride, γ-phenylpropyl chloride, or α,α′-dichloro-*p*-xylene with sodium azide in ethanol/water (4:1) at reflux gave the corresponding azides **1**, **2**, or **6** in 85−97% yields.[16] *N*-Benzyl-2-propynamide (**4**) was obtained in 59% yield by the reaction of propiolic acid and benzylamine following the mixed anhydride method of Coppola et al.[17] 1-Piperidino-2-propyn-1-one (**5**) was similarly prepared from propiolic acid and piperidine in 68% yield.

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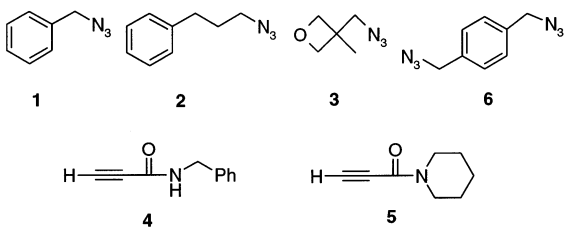
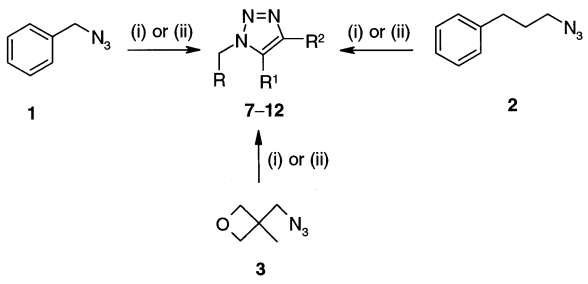


Microwave reactions were performed in sealed heavy-walled Pyrex tubes under controlled conditions in a safe and reproducible procedure. Single mode microwave irradiation was used at a fixed temperature, pressure, and irradiation power during the reaction time by an automatic power control.

Optimization of the reaction conditions were carried out on the cycloaddition of benzyl azide (**1**) to *N*-benzyl-2-propynamide (**4**) under solvent-free conditions, and different combinations of temperature, time and irradiation power were studied in order to achieve the maximum chemical yield at the lowest reaction temperature. Thus, microwave irradiation of the mixture containing benzyl azide (**1**) and the acetylenic amide **4** at 55 °C for 30 min. resulted in complete conversion of the reactants into N-substituted 1,2,3-triazole **7** without the formation of side products or any noticeable decomposition. Monosubstituted alkynes yield regioisomers of different chromatographic and spectroscopic properties; a study by Häbich et al. involving NOE-experiments with both the regioisomers showed that the triazole-*H* of the more polar major isomer resonates downfield compared to that of the less polar minor isomer.[6i] Accordingly, thin layer chromatographic analysis and ^{1}H NMR spectrum of the crude reaction mixture showed the formation of **7** as a mixture of two regioisomers **7a** and **7b** with the more polar and sterically less congested regioisomer **7a** predominating in a 3:1 ratio. *N*,1-Dibenzyl-1*H*-1,2,3-triazole-4-carboxamide (**7a**) showed the triazole-*H* singlet at 8.67 ppm while that of the minor isomer *N*,1-dibenzyl-1*H*-1,2,3-triazole-5-carboxamide (**7b**) resonated at 8.25 ppm. The major regioisomer **7a** was separated from the mixture by fractional recrystallization to give the pure product in 65% yield. By contrast, thermal reaction of benzyl azide (**1**) and the acetylenic amide **4** failed to induce any cycloaddition at 55−60 °C and the starting materials were recovered unchanged even after 24 h. TLC monitoring of the thermal reaction at a higher temperature (∼110 °C) showed a slow reaction, but formation of the triazole was significant only after 12 h refluxing in toluene.

The above optimized microwave reaction conditions were applied to the synthesis of a variety of novel N-substituted 1,2,3-triazoles. Thus, reaction of benzyl azide (**1**) with acetylenic tertiary amide **5** gave the triazole **8** as a mixture of regioisomers **8a** and **8b** in a 3:1 ratio. Similar reactions of γ-phenylpropyl azide (**2**) with acetylenic amides **4** or **5** produced the regioisomeric mixtures of triazoles **9a** and **9b** or **10a** and **10b**, in a 3:1 ratio, respectively. Under similar reaction conditions, reaction of 3-(azidomethyl)-3-methyloxetane (**3**) with acetylenic amides **4** or **5** gave the triazoles **11a** and **12a** in 84 and 80% yields, respectively, along with the formation of minor isomers **11b** and **12b** in trace amounts as shown by the ^{1}H NMR spectrum of the crude reaction mixture. The major regioisomers **8a**, **9a**, **10a**, **11a**, and **12a** were separated and fully characterized by ^{1}H and ^{13}C NMR spectroscopy and elemental analysis or high-resolution mass spectrometry (Scheme 1).

SCHEME 1



	R	R^1	R^2	Y(%)[a]
7a	Ph	H	$CONHCH_2Ph$	65
7b	Ph	$CONHCH_2Ph$	H	--
8a	Ph	H	COpiperidinyl	63
8b	Ph	COpiperidinyl	H	--
9a	$Ph(CH_2)_2$	H	$CONHCH_2Ph$	62
9b	$Ph(CH_2)_2$	$CONHCH_2Ph$	H	--
10a	$Ph(CH_2)_2$	H	COpiperidinyl	65
10b	$Ph(CH_2)_2$	COpiperidinyl	H	--
11a	$C(CH_3)(CH_2OCH_2)$	H	$CONHCH_2Ph$	84
11b	$C(CH_3)(CH_2OCH_2)$	$CONHCH_2Ph$	H	--
12a	$C(CH_3)(CH_2OCH_2)$	H	COpiperidinyl	80
12b	$C(CH_3)(CH_2OCH_2)$	COpiperidinyl	H	--

[a] Isolated yield of major regioisomer

(i) acetylenic amide **4** (1 equiv), 55 °C, 120 W, 30 min.
(ii) acetylenic amide **5** (1 equiv), 85 °C, 170 W, 30 min.

Thus, using microwave irradiation, we have developed a novel synthesis of N-substituted 1,2,3-triazoles under mild conditions by the cycloaddition of simple azides and acetylenic amides. Next, we explored the synthesis of unsymmetrical bis-triazoles starting from a bis-azide, 1,4-bis(azidomethyl)benzene (**6**), by the successive 1,3-dipolar cycloaddition reactions with different acetylenic amides. Microwave irradiation of 1 equiv of bis-azide **6** and 1 equiv of *N*-benzyl-2-propynamide (**4**) for 30 min. at 55 °C produced the azidotriazole **13a** as the major regioisomer in 56% yield. However, further reaction of **13a** with the second amide, 1-piperidino-2-propyn-1-one (**5**) failed to give the unsymmetrically substituted bis-triazole **14** under various reaction conditions (Scheme 2).

In summary, we have introduced a general method for the direct preparation of a variety of *C*-carbamoyl-1,2,3-triazoles under mild conditions using microwave activation.

Experimental Section

Melting points are uncorrected. All of the reactions under microwave irradiation were conducted in heavy-walled Pyrex tubes sealed with aluminum crimp caps fitted with a silicon septum. Microwave heating was carried out with a single mode cavity Discover microwave synthesizer (CEM Corp., NC), producing continuous irradiation at 2455 MHz. ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded in $CDCl_3$ (with TMS for ^{1}H and chloroform-*d* for ^{13}C as the internal reference) unless specified otherwise.

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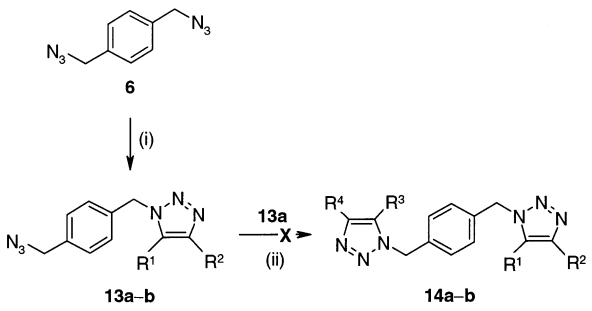
SCHEME 2



	R^1	R^2	R^3	R^4	Y(%)[a]
13a	H	$CONHCH_2Ph$	--	--	56
13b	$CONHCH_2Ph$	H	--	--	--
14a	H	$CONHCH_2Ph$	H	COpiperidinyl	--
14b	H	$CONHCH_2Ph$	COpiperidinyl	H	--

[a] Isolated yield of major regioisomer

(i) acetylenic amide **4** (1 equiv), 55 °C, 120 W, 30 min.
(ii) acetylenic amide **5** (1 equiv), 85 °C, 170 W, 30 min.

Benzyl azide (**1**),[18] γ-phenylpropyl azide (**2**),[19] and 1,4-bis-(azidomethyl)benzene (**6**)[20] were prepared following a general procedure.[16] 3-(Azidomethyl)-3-methyloxetane (**3**) was provided by Naval Air Weapons Station, China Lake, CA.

General Procedure for Triazole Formation under Solvent-Free Microwave Irradiation. A dried heavy-walled Pyrex tube containing a small stir bar was charged with acetylenic amide **4** or **5** (1.2 mmol) and organic azide **1**, **2**, **3**, or **6** (1.2 mmol). The tube containing the reaction mixture was sealed with an aluminum crimp cap fitted with a silicon septum and then it was exposed to microwave irradiation (120−170 W) for 30 min at a temperature of 55 or 85 °C. The buildup of pressure in the closed reaction vessel was carefully monitored and was found to be typically in the range 4−10 psi. After the irradiation, the reaction tube was cooled with high-pressure air through an inbuilt system in the instrument until the temperature had fallen below 40 °C (ca. 2 min). The crude reaction mixture was analyzed by ^{1}H NMR spectroscopy to determine the ratio of regioisomeric triazoles formed. The reaction mixture was recrystallized to separate the major regioisomers **7a**−**13a** as the pure products.

***N*,1-Dibenzyl-1*H*-1,2,3-triazole-4-carboxamide (7a):** white needles (from chloroform); mp 211−213 °C; yield 65%; ^{1}H NMR (DMSO-d_6) δ 4.44 (d, J = 6.0 Hz, 2H), 5.66 (s, 2H), 7.22−7.37 (m, 10H), 8.67 (s, 1H), 9.11 (m, 1H); ^{13}C NMR (DMSO-d_6) δ 41.9, 53.1, 126.6, 126.7, 127.3, 128.0, 128.2, 128.3, 128.8 135.7, 139.6, 143.0, 159.6. Anal. Calcd for $C_{17}H_{16}N_4O$: C, 69.85; H, 5.52; N, 19.16. Found: C, 70.10; H, 5.90; N, 19.32.

[1-(3-Phenylpropyl)-1*H*-1,2,3-triazol-4-yl](piperidino)-methanone (10a): colorless needles (from diethyl ether/hexanes); mp 63 °C; yield 65%; ^{1}H NMR δ 1.60−1.80 (m, 6H); 2.28 (quintet, J = 7.3 Hz, 2H), 2.67 (t, J = 7.4 Hz, 2H), 3.71 (br s, 2H), 4.16 (br s, 2H), 4.37 (t, J = 7.0 Hz, 2H), 7.17−7.33 (m, 5H), 8.03 (s, 1H); ^{13}C NMR δ 24.6, 25.7, 26.7, 31.4, 32.3, 43.8, 47.8, 49.5, 126.4, 127.8, 128.4, 128.6, 139.8, 144.7, 159.8. Anal. Calcd for $C_{17}H_{22}N_4O$: C, 68.43; H, 7.43; N, 18.78. Found: C, 68.57; H, 7.81; N, 19.02.

1-[(3-Methyl-3-oxetanyl)methyl]-1*H*-1,2,3-triazol-4-yl(piperidino)methanone (12a): white plates (from chloroform/diethyl ether); mp 113−115 °C; yield 80%; ^{1}H NMR δ 1.28 (s, 3H), 1.69 (m, 6H), 3.71 (m, 2H), 4.17 (m, 2H), 4.46 (d, J = 6.3 Hz, 2H), 4.63 (s, 2H), 4.69 (d, J = 6.4 Hz, 2H), 8.06 (s, 1H); ^{13}C NMR δ 21.3, 24.6, 25.7, 26.7, 40.2, 43.8, 47.7, 56.9, 79.9, 128.8, 144.7, 159.4. Anal. Calcd for $C_{13}H_{20}N_4O_2$: C, 59.07; H, 7.63; N, 21.20. Found C, 59.01; H, 7.86; N, 20.97.

1-[4-(Azidomethyl)benzyl]-*N*-benzyl-1*H*-1,2,3-triazole-4-carboxamide (13a): white powder (from chloroform); mp 198−200 °C; yield 56%; ^{1}H NMR (DMSO-d_6) δ 4.44 (s, 4H), 5.67 (s, 2H), 7.20−7.40 (m, 9H), 8.68 (s, 1H), 9.11 (br s, 1H). Anal. Calcd for $C_{18}H_{17}N_7O$: C, 62.24; H, 4.93. Found C, 62.14; H, 5.07.

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Supporting Information Available: General procedure for the preparation of compounds **4** and **5**, characterization data for compounds **4**, **5**, **8a**, **9a**, and **11a**, and ^{1}H and ^{13}C NMR spectra of compounds **9a** and **11a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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