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Microwave-Enhanced Ionothermal CuAAC for the Synthesis of Glycoclusters on a Calix[4]arene Platform

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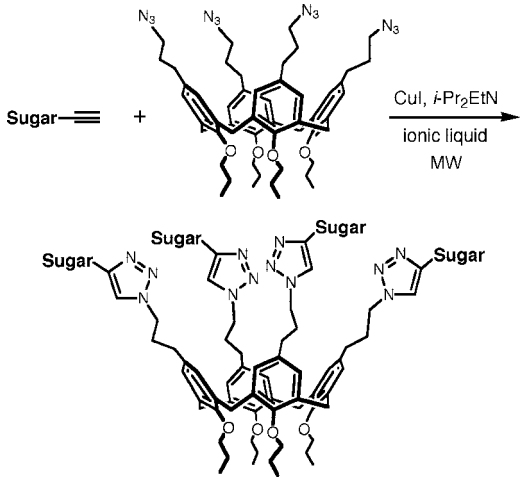

A tetra-azido calix[4]arene derivative was allowed to react with ethynyl tetra-*O*-benzyl-*C*-galactoside in the presence of CuI and *i*-Pr$_2$EtN in three different ionic liquids, that is, [C$_8$dabco][N(CN)$_2$], [C$_8$dabco][Br], and Ammoeng 110. Reactions were performed at 80 °C by thermal and MW dielectric heating. In all cases, multiple cycloadditions took place to give a triazole-linked tetra-*C*-galactosyl-calix[4]arene in up to 90% yield. The [C$_8$dabco][N(CN)$_2$] ionic liquid was also used to perform the multiclick reactions with propargyl *O*-lactoside and *S*-sialoside.

Among the many efforts that are made to modernize synthetic organic chemistry toward a sustainable development, the search for new reaction media that can effectively replace the traditional toxic and volatile organic solvents is driving intense research in academic and industrial laboratories. Synthesis in ionic liquids (ILs) has the potential to solve numerous pending problems, especially those regarding safety and environmental concerns. ILs are special molten salts with low melting points (<100 °C) and are typically constituted of organic cations (pyrrolidinium, pyridinium, tetralkylammonium, and tetralkylphosphonium ions) and inorganic anions. They may have high chemical and thermal stability, are good solvents for a wide range of organic and inorganic materials, and have vanishing low vapor pressure.[1] For these characteristics, ILs are considered as green solvents. Quite notably, their physicochemical properties can be modulated by different cation−anion combinations as well as suitable functionalization of the organic cation. In this way, task-specific ILs have been prepared[2] and conveniently applied in processes of industrial and ecological relevance such as the separation of CO_2 and SO_2 from gas streams,[3] the extraction of metal ions from aqueous solutions,[4] the hydrogenation of CO_2 to formic acid,[5] the efficient transformation of biomass-derived carbohydrates into 5-hydroxymethylfurfural, a versatile intermediate for liquid fuels production from renewable sources.[6] The recovery of unaltered ILs and recycling partly compensate their cost which, however, is in general quite reasonable. Together with the IL, also embedded organometallic catalysts are efficiently recycled as shown, for example, in recent Pd-catalyzed cross-coupling reactions using microflow systems.[7] Hence from a merely academic curiosity, ILs have reached over the past decade an important role in organic, inorganic, polymer, and biocatalytic synthesis.[8] Moreover, they have been proved to be good microwave absorbers[9] and therefore are well suited in reactions using microwave (MW) dielectric heating.[10] The advantages associated with the green solvent aspect of ILs and

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the green chemistry aspect of microwave irradiation have been very recently emphasized in highly improved methods for zeolite synthesis.[11,12] From a synthetic standpoint it appears quite convenient to validate the efficiency of organic processes in ILs, eventually under MW irradiation, because these studies can yield new and green synthesis methods. Following this reasoning, we recently reported[13] the first example of Cu(I)-catalyzed azide-alkyne cycloaddition (CuAAC)[14] (click reaction)[15] in ILs to give a triazole-linked *C*-disaccharide. Our work was stimulated by the tremendous impact exerted by the CuAAC in numerous areas of life and material sciences[16] and the belief that the execution of this formidable reaction in ILs will furnish the opportunity for new applications. Hence, we would like to report in this note a further demonstration of the viability of the CuAAC in ILs with the assistance of microwave irradiation. Also in this case we have selected a reaction in an area of our own research interest such as the multiple glycosylation of a calix[4]arene to give structurally defined glycoclusters.[17]

As to the best of our knowledge there are no examples of calixarene functionalization in ILs, we studied in some details the model click reaction of ethynyl tetra-*O*-benzyl-*C*-galactoside **1a**[18] with the tetra-azidopropyl-calix[4]arene **2**[17e] (Scheme 1). This explorative study was finalized to identify the most efficient IL and at the same time address some crucial issues such as the solubility of the reagents, the extraction of the product, and IL recovery and reuse.

Hence, the reaction of the tetra-azide **2** with four equivalents of the alkyne **1a**, that is, one equivalent for each azido group of **2**, in the presence of catalytic CuI and excess *i*-Pr_2EtN (Hünig base) was performed in three different ILs **4**, **5**, and **6** at 80 °C (Table 1). These ILs were selected because they proved to be the most valuable among those employed in our recent work.[13]

Runs in each IL were carried out by thermal heating (oil bath) and MW dipolar heating[19] (Table 1). For the sake of comparison, the reaction of **1a** with **2** was also carried out by thermal heating in an apolar molecular solvent such as toluene (entry 1). After some experimentation the suitable reaction times were established to be 16 and 2 h under thermal and MW heating, respectively. The IL and reaction mixture were separated by extraction of the latter with diethyl ether or ethyl acetate. As judged from the yields of isolated (by column chromatography) triazole-linked[20] calix[4]arene tetra-galactoside **3a**, the most performing IL was *N*-octyl dabco-cation based dicyanamide ([C_8dabco][N(CN)$_2$], **4**) under MW heating for 2 h (entry 3). The recovered IL was reused in a subsequent run to give **3a** in

SCHEME 1

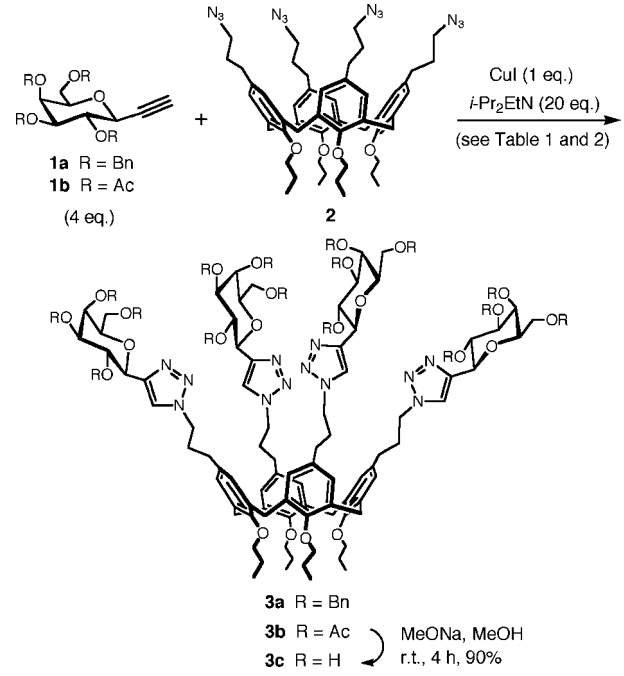
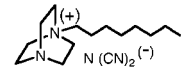
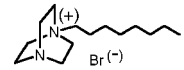
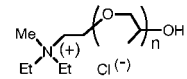


TABLE 1. Cycloaddition of *C*-Galactosyl Acetylene 1a and Tetra-Azido Calix[4]arene 2 in Toluene and Ionic Liquids (ILs) at 80 °C to Give the Glycoside Cluster 3a (see Scheme 1)

Entry	Solvent	Heating	Time (h)	Yield (%)[a]
1	toluene	thermal	16	70
2	 **4**	thermal	16	65
3	**4**	MW	2	90 (72)[b]
4	 **5**	thermal	16	73
5	**5**	MW	2	79
6	 **6**	thermal	16	55
7	**6**	MW	2	68

[a] Isolated yield after column chromatography on silica gel. [b] Using recycled IL.

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(19) Experiments run in a single-mode cavity dedicated reactor Biotage Initiator. Temperature measured externally on the outside vessel wall by an IR sensor.

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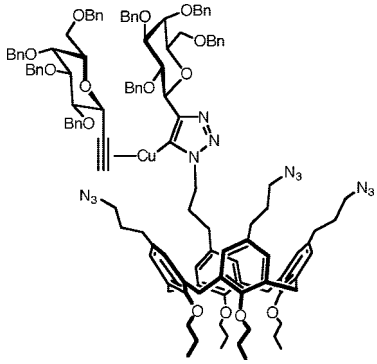

FIGURE 1. Proposed intermediate in the multiple CuAAC leading to the *C*-glycoside cluster **3a**.

high yield (Table 1, entry 3). The excellent yield (90%) of pure glycocluster **3a** compared with that (65%, entry 2) obtained by thermal heating after 16 h demonstrated that MW dipolar heating not only reduced the reaction time substantially but also increased the efficiency of the multiple click CuAACs.

Partially glycosylated calix[4]arene derivatives were not observed by NMR analysis of the crude reaction mixture formed in either thermal or MW heated experiments. On the other hand, trace amounts of unreacted tetra-azide **2** were isolated by chromatography. This is in agreement with the earlier observation of Rodionov, Fokin, and Finn on the click reaction of vicinal diazides wherein the first triazole formed served as accelerating element of the subsequent cycloaddition.[21] Accordingly, we suggest that the first click reaction on **2** leads to the formation of a copper(I) triazolide intermediate,[22] which binds the sugar alkyne to give a system of the form shown in Figure 1 with subsequent rapid intramolecular capture by an adjacent azido group.[23,24] The cone conformation of the calix[4]arene platform and the flexibility of the azidopropyl chain constitute suitable geometrical factors for the occurrence of the intramolecular click process. The same mechanism can be applied to the third and forth click reaction. Very likely the ILs stabilize the various Cu(I) complexes that are involved in the CuAAC.[21,25]

Another point that is worth commenting is that reactions of **1a** with **2** in ILs **4**, **5**, and **6** (Table 1, entries 2, 4, and 6) under thermal heating afforded the glycocluster **3a** in comparable yields to that registered in toluene (entry 1). This result supports the feasibility of the green multiple click CuAAC on a calix[4]arene substrate using readily available ILs even when the microwave apparatus is not available.

The optimized conditions (MW heating, 2 h) established for the cycloaddition of **1a** and **2** in $[C_8dabco][N(CN)_2]$ **4** were employed to perform the reaction of other sugar alkynes with the same tetra-azide **2**. The good yield (Table 2, entry 2) of the

TABLE 2. Cycloaddition of Tetra-Azido Calix[4]arene 2 and Sugar Alkynes in Toluene and IL 4 at 80 °C to Give the Corresponding Glycoside Clusters (see Scheme 1 and Figure 2)

entry	alkyne	solvent	heating	time (h)	cluster	yield (%)[a]
1	**1b**	toluene	thermal	16	**3b**	84
2	**1b**	**4**	MW	2	**3b**	72
3	**7**	toluene	thermal	16	**9**	77
4	**7**	**4**	MW	2	**9**	79
5	**8**	toluene	thermal	16	**10**	58
6	**8**	**4**	MW	2	**10**	32

[a] Isolated yield after column chromatography on silica gel.

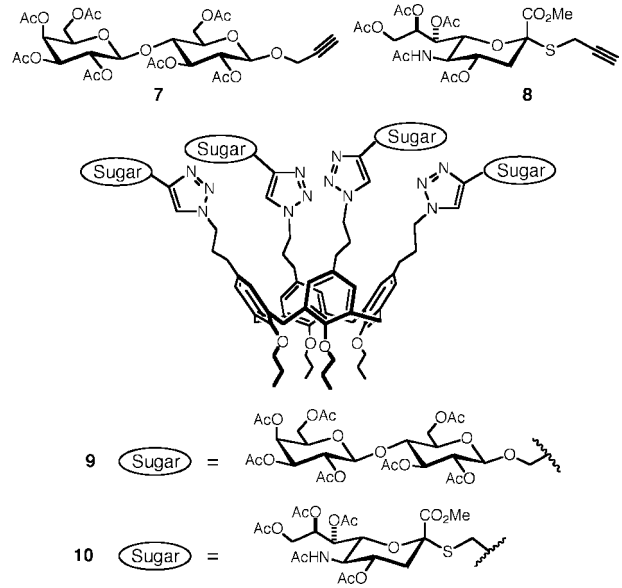

FIGURE 2. Propargyl glycosides **7** and **8** and *O*- and *S*-glycoside clusters **9** and **10** prepared by cycloaddition with **2**.

glycocluster **3b** formed from the reaction with the ethynyl tetra-*O*-acetyl-*C*-galactoside[18] **1b** (Scheme 1) demonstrated the compatibility of *O*-acetyl protecting groups with the ionotropic conditions. This allowed ready access by transesterification to the product **3c** displaying free hydroxy sugar fragments. Also the reaction of **2** with a peracetylated disaccharide such as the propargyl *O*-lactoside[26] **7** (Figure 2) occurred to a good extent to give the densely glycosylated calix[4]arene **9**[27] (Figure 2) in almost identical yield to that registered in the molecular solvent toluene (Table 2). Quite rewarding was also the successful cycloaddition of **2** with a complex multifunctionalized monosaccharide such as the propargyl *S*-sialoside[28] **8** (Figure 2). In this case, however, the yield of the isolated sialocluster **10**[17g] (Figure 2) from the reaction in the IL was much lower than that in toluene (Table 2). This was mainly due to the difficult separation of the product **10** from the ionic liquid by extraction with ethyl acetate as operated in the other reactions. The product was recovered by gel filtration on a column of Sephadex LH20 and purified by chromatography on a silica gel column.[29]

In conclusion, from this and our recent work,[13] it appears that CuAACs employing multifunctionalized biomolecules such as carbohydrates can be carried out in ionic liquids with similar efficiency as in organic solvents. ILs with their high polarity

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(22) For the isolation and X-ray structure determination of such intermediate from a model click reaction, see: (a) Nolte, C.; Mayer, P.; Straub, B. F. *Angew. Chem., Int. Ed.* **2007**, *46*, 2101–2103.

(23) The same mechanism cannot operate by using calix[4]arene alkynes. Accordingly we observed that a sluggish reaction takes place between an upper rim tetra-ethynyl-calix[4]arene and a *C*-glycosylmethyl azide (see ref 17e).

(24) A referee suggested that more than a single copper atom is involved in the reaction, i.e., dinuclear alkynyl copper(I) complexes, as reported in recent papers, see ref 21 and (a) Ahlquist, M.; Fokin, V. V. *Organometallics* **2007**, *26*, 4389–4391. (b) Straub, B. F. *Chem. Commun.* **2007**, 3868–3870.

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(26) Tietze, L. F.; Bothe, U. *Chem.−Eur. J.* **1998**, *4*, 1179–1183.

(27) The glycocluster **9** was transformed into the free hydroxy sugar derivative **9-OH** (see Supporting Information).

(28) Gan, Z.; Roy, R. *Can. J. Chem.* **2002**, *80*, 908–916.

(29) A tris-sialoside was isolated in 13% yield as previously observed when the reaction of **2** and **8** was carried out in DMF. See ref 17g.

constitute an ideal medium for performing reactions under MW irradiation, thus reducing substantially the reaction time that is needed by thermal heating while the yield of the product is the same if not higher.[30] Hence the click CuAAC in ILs is a complementary "green" method to that using water as a solvent.[15a] ILs, however, do not present the main drawback of water due to the limited aqueous solubility of most neutral organic substrates. Hence, the use of ILs as solvents in a wide range of CuAACs now becomes of interest.

Experimental Section

5,11,17,23-Tetrakis{3-[4-(2,3,4,6-tetra-*O*-benzyl-*β*-D-galacto-pyranosyl)-1H-1,2,3-triazol-1-yl]propyl}-25,26,27,28-tetrapropoxy-calix[4]arene (3a). A mixture of ethynyl *C*-galactoside **1a** (110 mg, 0.20 mmol), calix[4]arene tetra-azide **2** (46 mg, 0.05 mmol), freshly distilled *N,N*-diisopropylethylamine (175 μL, 1.00 mmol), CuI (9.5 mg, 0.05 mmol), and anhydrous toluene (2 mL) was sonicated in an ultrasound cleaning bath for 1 min, then stirred in the dark at 80 °C for 16 h, cooled to room temperature, diluted with AcOEt (50 mL), washed with 1 M phosphate buffer at pH 7 (2 × 10 mL), dried (Na_2SO_4), and concentrated. The residue was eluted from a column of silica gel with cyclohexane-AcOEt (from 3:1 to 2:1) to give **3a** (109 mg, 70%) as a syrup.

When the cycloaddition was carried out in ionic liquids (0.50 g) heating at 80 °C in an oil bath for 16 h or in a microwave oven for 2 h, the crude reaction mixture was extracted with 4 × 6 mL of AcOEt (in the case of IL **5** and, after dilution with 1 mL of H_2O, IL **4**) or Et_2O (in the case of IL **6**). The combined organic phases were concentrated and eluted from a column of silica gel to give pure **3a** (see Table 1); $[\alpha]_D = -9.5$ (*c* 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39−7.21 (m, 64H, Ar, 4 H-5 Tr.), 7.16−7.10 (m, 12H, Ar), 7.04−6.98 (m, 8H, Ar), 6.39 and 6.37 (2d, 8H, J = 1.5 Hz, Ar calix.), 4.97 and 4.64 (2d, 8H, J = 11.5 Hz, 4 PhCH_2), 4.75 and 4.71 (2d, 8H, J = 11.7 Hz, 4 PhCH_2), 4.69 and 4.35 (2d, 8H, J = 10.7 Hz, 4 PhCH_2), 4.48 (d, 4H, $J_{1,2}$ = 9.7 Hz, 4 H-1), 4.42 and 4.36 (2d, 8H, J = 11.6 Hz, 4 PhCH_2), 4.36 and 3.01 (2d, 8H, J = 13.1 Hz, 4 ArCH_2Ar), 4.24 (dd, 4H, $J_{2,3}$ = 9.6 Hz, 4 H-2), 4.09−3.99 (m, 8H, 4 ArCH$_2$CH$_2$CH_2), 4.04 (dd, 4H, $J_{3,4}$ = 2.5, $J_{4,5}$ = 0.6 Hz, 4 H-4), 3.80 (t, 8H, J = 7.5 Hz, 4 $CH_3CH_2CH_2O$), 3.70 (dd, 4H, 4 H-3), 3.69 (ddd, 4H, $J_{5,6a}$ = 7.1, $J_{5,6b}$ = 6.0 Hz, 4 H-5), 3.58 (dd, 4H, $J_{6a,6b}$ = 9.0 Hz, 4 H-6a), 3.54 (dd, 4H, 4 H-6b), 2.23−2.18 (m, 8H, 4 ArCH_2CH$_2$CH$_2$), 1.96−1.82 (m, 16H, 4 ArCH$_2$CH_2CH$_2$, 4 $CH_3CH_2CH_2O$), 0.98 (t, 12H, J = 7.5 Hz, 4 $CH_3CH_2CH_2O$). ^{13}C NMR (75 MHz, $CDCl_3$): δ 154.9 (C Ar), 145.8 (C-4 Tr.), 138.8 (C Ar), 138.4 (C Ar), 138.2 (C Ar), 137.8 (C Ar), 134.7 (C Ar), 133.3 (C Ar), 128.4−127.5 (CH Ar), 122.5 (C-5 Tr.), 84.4 (C-5), 78.3 (C-2), 77.3 (C-3), 76.7 ($CH_3CH_2CH_2O$), 74.9 (PhCH_2), 74.6 (PhCH_2), 73.9 (C-1, C-4), 73.4 (PhCH_2), 72.4 (PhCH_2), 68.6 (C-6), 49.4 (ArCH$_2$CH$_2$$CH_2$), 31.9 (ArCH$_2$$CH_2CH_2$, ArCH$_2CH_2CH_2$), 30.9 (ArC$H_2$Ar), 23.1 ($CH_3CH_2CH_2O$), 10.3 ($CH_3CH_2CH_2O$); ESI MS (3119.94): 1560.0 (M+2)/2. Anal. Calcd for $C_{196}H_{212}N_{12}O_{24}$: C, 75.45; H, 6.85; N, 5.39. Found: C, 75.11; H, 6.64; N, 5.19.

5,11,17,23-Tetrakis{3-[4-(2,3,4,6-tetra-*O*-acetyl-*β*-D-galacto-pyranosyl)-1H-1,2,3-triazol-1-yl]propyl}-25,26,27,28-tetrapropoxy-calix[4]arene (3b). The cycloadditions between *C*-galactoside **1b** (71 mg, 0.20 mmol) and tetra-azide **2** (46 mg, 0.05 mmol) in toluene and IL **4** were performed as described for the preparation of **3a** to give, after column chromatography on silica gel (5:1 AcOEt-cyclohexane), **3b** as an amorphous solid in 84 and 72% yield, respectively; $[\alpha]_D = -6.4$ (*c* 0.3, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.66 (s, 4H, 4 H-5 Tr.), 6.46 (s, 8H, Ar), 5.54 (dd, 4H, $J_{3,4}$ = 3.4, $J_{4,5}$ = 0.5 Hz, 4 H-4), 5.46 (dd, 4H, $J_{1,2}$ = 10.0, $J_{2,3}$ = 10.2 Hz, 4 H-2), 5.22 (dd, 4H, 4 H-3), 4.80 (d, 4H, 4 H-1), 4.42 and 3.08 (2d, 8H, J = 13.0 Hz, 4 ArCH_2Ar), 4.27−4.21 (m, 8H, 4 ArCH$_2$CH$_2$CH_2), 4.18−4.12 (m, 12H, 4 H-5, 8 H-6), 3.87−3.81 (m, 8H, 4 $CH_3CH_2CH_2O$), 2.33 (t, 8H, J = 7.3 Hz, 4 ArCH_2CH$_2$CH$_2$), 2.20, 2.05, 2.02, and 1.92 (4s, 48H, 16 Ac), 2.06−1.89 (m, 16H, 4 ArCH$_2$CH_2CH$_2$, 4 $CH_3CH_2CH_2O$), 1.00 (t, 12H, J = 7.5 Hz, 4 $CH_3CH_2CH_2O$). ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.4, 170.2, 170.1, and 169.7 (CO), 155.1 (C Ar), 144.3 (C-4 Tr.), 134.9 (C Ar), 133.1 (C Ar), 128.0 (CH Ar), 122.2 (C-5 Tr.), 76.8 ($CH_3CH_2CH_2O$), 74.7 (C-5), 73.8 (C-1), 71.9 (C-3), 68.7 (C-2), 67.6 (C-4), 61.5 (C-6), 49.8 (ArCH$_2$CH$_2$$CH_2$), 31.9 (ArCH$_2$$CH_2CH_2$, ArCH$_2CH_2CH_2$), 31.0 (ArC$H_2$Ar), 23.2 ($CH_3CH_2CH_2O$), 20.7 and 20.6 ($CH_3CO$), 10.3 ($CH_3CH_2CH_2O$); ESI MS (2350.54): 1176.2 (M+2)/2. Anal. Calcd for $C_{116}H_{148}N_{12}O_{40}$: C, 59.27; H, 6.35; N, 7.15. Found: C, 59.01; H, 6.21; N, 6.93.

Supporting Information Available: Experimental procedures and physical data of **3c**, **9**, and **9-OH**. Copies of the ^{1}H and ^{13}C NMR spectra of **3a-c**, **9**, and **9-OH**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(30) We found that the cycloaddition in IL **4** at 80 °C between a *C*-glucosyl acetylene and a 6-azido-glucoside described in our previous work (ref 13) required 16 h under thermal heating and only 2 h using MW dielectric heating.