JOURNAL OF combinatorial CHEMISTRY

Article

Combining Biginelli Multicomponent and Click Chemistry: Generation of 6-(1,2,3-Triazol-1-yl)-Dihydropyrimidone Libraries

Bogdan Khanetskyy, Doris Dallinger, and C. Oliver Kappe

J. Comb. Chem., **2004**, 6 (6), 884-892• DOI: 10.1021/cc0498938 • Publication Date (Web): 06 October 2004

More About This Article

Additional resources and features associated with this article are available within the HTML version:

- Supporting Information
- Links to the 8 articles that cite this article, as of the time of this article download
- Access to high resolution figures
- Links to articles and content related to this article
- Copyright permission to reproduce figures and/or text from this article

View the Full Text HTML

Journal of Combinatorial Chemistry is published by the American Chemical Society.
1155 Sixteenth Street N.W., Washington, DC 20036

Combining Biginelli Multicomponent and Click Chemistry: Generation of 6-(1,2,3-Triazol-1-yl)-Dihydropyrimidone Libraries

Bogdan Khanetskyy, Doris Dallinger, and C. Oliver Kappe*

Institute of Chemistry, Karl-Franzens-University Graz, Heinrichstrasse 28, A-8010 Graz, Austria

Received June 24, 2004

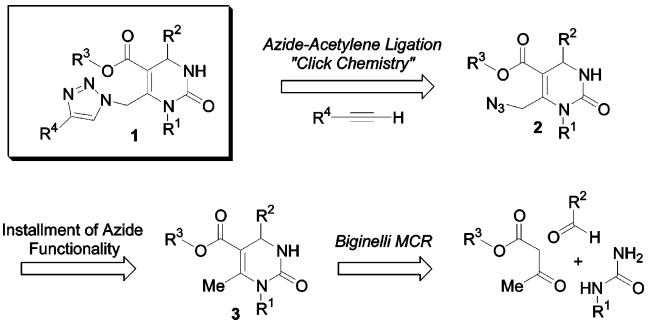
Efficient solution-phase protocols for the high-throughput synthesis of 6-(1,2,3-triazol-1-yl)-dihydropyrimidones are reported. The multistep sequence involves the initial bromination of dihydropyrimidones precursors (DHPMs, Biginelli compounds) at the C6-methyl position, using a recyclable polymer-supported brominating agent under rapid flow-through conditions (residence time of 1 min). The 6-bromomethyldihydropyrimidone intermediates were subsequently subjected to a microwave-assisted azidation step (25 min), providing the key 6-azidomethyldihydropyrimidone precursors. In the final step of the sequence, the azides were treated with terminal acetylenes under Cu(I) catalysis (azide-acetylene ligation, "click chemistry") to provide the target 6-(1,2,3-triazol-1-yl)-dihydropyrimidones in a regiospecific fashion (1,4-triazoles) in moderate overall yield utilizing controlled microwave irradiation (20 min). In total, a library of 27 compounds was prepared with 4 points of diversity.

1. Introduction

The laborious process of lead discovery and lead optimization has recently been aided by combinatorial chemistry for the rapid generation of test compounds for screening. Because of the large number of compounds that are involved, combinatorial chemistry is even more dependent than traditional synthetic chemistry on the reliability of the individual transformations that are utilized in the process. Click chemistry is a new approach to synthesis that facilitates this process, making use of a few near-perfect chemical transformations for the synthesis and assembly of chemical scaffolds with potential biological activity.[1,2] Its applications are increasingly found in many aspects of drug discovery, ranging from lead finding through combinatorial chemistry and target-templated in situ chemistry, to proteomics and DNA research, using bioconjugate reactions.[3]

Reactions that qualify as click chemistry are modular, wide in scope, give very high yields, generate only inoffensive byproducts that can be removed by nonchromatographic methods, and are stereospecific.[1−3] In addition, these transformations must consistently give high yields with various starting materials, be easy to carry out, insensitive to oxygen and water and use only readily available reagents.[1−3] The Huisgen 1,3-dipolar cycloaddition of alkynes and azides[4] is, by far, the most well-known example of click chemistry, leading to 1,2,3-triazoles, which are an important class of biologically active *N*-heterocycles.[5] The recently discovered significant rate acceleration of the terminal acetylene-azide coupling event under Cu(I) catalysis yielding 1,4-substituted 1,2,3-triazoles in a regiospecific fashion[6,7] has prompted renewed interest into this [3+2] cycloaddition process.[8]

Scheme 1. Retrosynthetic Strategy for the Generation of Triazolyl-Decorated Dihydropyrimidone Libraries **1**, Combining Biginelli Multicomponent Condensations with Click Chemistry



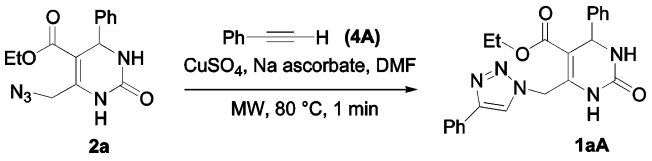
In the context of our research in the area of multicomponent reactions (MCRs) of the Biginelli type,[9] we became interested in combining click chemistry (azide−acetylene cycloadditions) with MCR strategies. MCRs themselves are increasingly important in organic and medicinal chemistry, because they offer significant advantages over conventional linear-type syntheses.[10] The Biginelli three-component condensation protocol is particularly attractive,[9] because the resulting privileged dihydropyrimidone (DHPM) scaffold **3** (Scheme 1) displays a wide range of biological activities which has led to the development of a number of lead compounds based on that structural core.[11]

Here, we report an efficient synthesis of libraries represented by structure **1** by performing rapid, high-yielding microwave-assisted azide-acetylene ligations. For this purpose, readily available 6-azidomethyl-functionalized DHPMs **2** were prepared as key intermediates utilizing high-throughput MCR protocols and reacted with a set of terminal acetylenes under Cu(I) catalysis. This leads to an attractive linkage of two important *N*-heterocyclic pharmacophores with four points of diversity (R^1-R^4) that can easily be

* Author to whom correspondence should be addressed. Phone: +43-316-3805352. Fax: +43-316-3809840. E-mail address: oliver.kappe@uni-graz.at.

10.1021/cc0498938 CCC: $27.50
Published on Web 10/06/2004

Scheme 2

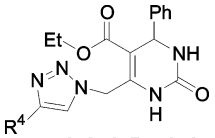


addressed by selecting the appropriate building blocks (Scheme 1).

2. Results and Discussion

2.1. Cu(I)-Catalyzed Azide-Acetylene Cycloadditions in the Biginelli Series. Model Studies. To test the viability of the desired click chemistry approach, linking DHPM scaffolds of the Biginelli type with a 1,2,3-triazole moiety, we selected the [3+2] cycloaddition of the known[12] 6-azidomethyl-dihydropyrimidone **2a** with phenylacetylene (**4A**) as a model reaction (Scheme 2). Although alternative attachment points of an azide functionality on the DHPM scaffold can be envisaged, the ease and flexibility with which an azide group can be installed at the C6 position of the DHPM core (see below) made this the most obvious choice. As a starting point for optimizing the reaction, we have chosen the originally reported[7] $CuSO_4$/sodium ascorbate conditions, where the required Cu(I) catalyst species is generated in situ. Utilizing 2 mol % of the catalyst and aqueous *tert*-butyl alcohol as a solvent, full conversion to the desired product **1aA** could be obtained within 5 h at room temperature. Consistent with previous observations,[6−8] the reaction is apparently insensitive to the other functionalities present on the DHPM core, such as the ester and amide/urea groups, and the product is obtained as a single (anti-, 1,4-substituted)[6,7] regioisomer. Although the reaction proceeded to full conversion, according to thin-layer chromatography (TLC) and high-performance liquid chromatography (HPLC) monitoring, isolation of the product quantitatively from the *tert*-butyl alcohol/water mixture was difficult. Therefore, we screened other reaction conditions such as the use of water[1,2] or organic solvents (dimethyl formamide (DMF), *N*-methyl-2-pyrrolidone (NMP)) as reaction media, in addition to the use of copper metal as a catalyst source in a variety of solvents.[1,2] For our particular application of click chemistry, the use of DMF as a solvent, using the traditional $CuSO_4$/sodium ascorbate catalyst precursor consistently provided the highest yields. After completion of the cycloaddition process (as monitored by TLC and HPLC), the triazole product can be precipitated in high yield (73%) and purity (>98% by HPLC at 215 nm and ^{1}H NMR) by addition to ice/water. For the test reaction displayed in Scheme 2, full conversion at room temperature required 1 h. By performing the same reaction, utilizing controlled microwave heating at 80 °C,[13,14] complete conversion was achieved within 1 min (isolated yield of 73%). Although stability tests with DHPM **2a** demonstrated this azide to be stable under microwave irradiation (in 1,2-dichlorobenzene) up to 150 °C for 30 min, optimum results for the click chemistry presented in Scheme 2, in terms of yield and purity of isolated product, were obtained in the 80−100 °C temperature region. In this context, we have also briefly examined the [3+2] azide-acetylene cycloaddition **2a** + **4A** → **1aA** under strictly thermal conditions (DMF, MW, 150 °C) in the absence of the Cu(I) catalyst. As expected,[6,7,15] mixtures of both isomeric cycloadducts (anti and syn triazoles) were obtained, and several hours of irradiation were required to achieve full conversion (see Experimental Section for details).

Table 1. Yields of Triazolyl-dihydropyrimidones **1aA**, **1aB**, ..., **1aJ** (see Scheme 1) Prepared by Microwave-Assisted Cycloaddition of Equimolar Amounts of Azide **1a** with Terminal Acetylenes **4A**−**J** ($R^4C{\equiv}CH$)[a]



1aA, 1aB....1aJ

product	R^4	yield (%)
1aA	phenyl	73
1aB	3-(Me)-phenyl	82
1aC	3-(Cl)-phenyl	87
1aD	2-(CF_3)-phenyl	63
1aE	3,5-($F)_2$-phenyl	66
1aF	pyridin-3-yl	76
1aG	$PhOCH_2$	77
1aH	$PhCH_2OCH_2$	77
1aI	$HOCH_2$	76
1aJ[b]	Me_3Si	68

[a] Reaction conditions: MW, DMF, $CuSO_4$/Na Ascorbate, 90 °C, 10 min. Yields are isolated yields of pure compounds (>98% by HPLC). All compounds have been fully characterized by ^{1}H NMR, mass spectroscopy (MS), and elemental analysis. For details, see the Experimental Section. [b] The reaction was performed at room temperature for 4 h in *tert*-butyl alcohol/H_2O 1:1, using 3 equiv of trimethylsilylacetylene.

Having optimized conditions for the Cu(I)-catalyzed azide-acetylene ligation in hand, we next explored the scope of the cycloaddition process, using a diverse set of 10 terminal acetylenes (**4A**−**J**) as cycloaddition partners (Table 1). All 10 aryl, heteroaryl, and alkylacetylenes **4** used did undergo the anticipated click chemistry with azide **2a** and furnished the desired triazoles **1aA**, **1aB**, ..., **1aJ** in good isolated yields (63−87%). Generally, 10 min of microwave irradiation at 90 °C was sufficient to allow full conversion for all acetylenes. The triazole products were isolated via the addition of ice water and were fully characterized. Only in the case of trimethylsilylacetylene (**4J**) did it prove advantageous to perform the reaction at room temperature in aqueous *tert*-butyl alcohol as the solvent, to achieve a higher isolated product yield. We note that some of the triazolyl-dihydropyrimidone products are slightly water soluble, contributing to the less than quantitative isolated yields upon aqueous workup. However, because of the simplicity of the workup procedure (avoiding chromatography or evaporation of solvent), no efforts were made to improve the yield by isolation of additional quantities of product from the aqueous solution.

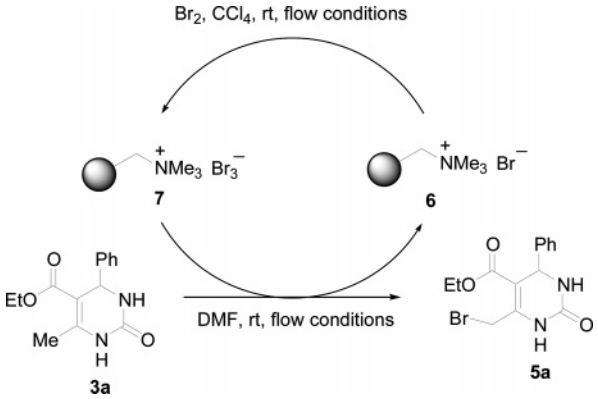
2.2. Synthesis of 6-(Triazol-1-yl)-Dihydropyrimidone Libraries. 2.2.1. Bromination of Dihydropyrimidones under Flow Conditions. To transform the click chemistry protocols elaborated previously to an integrated method suitable for the efficient generation of triazolyldihydropyrimidone libraries of type **1**, it was necessary to first develop

procedures for the rapid generation of 6-azidomethyldihydropyrimidones **2**. The published synthesis[12] of azide **2a** required initial bromination of the parent Biginelli DHPM **3a** with elemental bromine in chloroform at room temperature (12 h),[16] followed by displacement of the bromine with sodium azide in HMPT at 35 °C (48 h).[12] Both reported procedures clearly required adaptation to a high-throughput format. There are several reports in the literature describing the bromination of DHPMs **3** with elemental bromine.[16,17] All of these procedures require careful, dropwise addition of bromine at subambient temperatures to the DHPM to avoid overbromination to the corresponding *gem*-dibromo derivative.[16] In our own hands, we found that a slow, dropwise addition (within 1 h) of a bromine/chloroform solution (1.0 equiv) at 2−4 °C (ice-bath) to a suspension of DHPM **3a** in chloroform, according to the procedure reported by Zigeuner et al.,[16] provided (after stirring in an ice bath for an additional 3 h) the bromomethyl intermediate **5a** in 90% yield (HPLC conversion), with 7% of the *gem*-dibromo analogue being formed and 3% of starting material remaining (isolated yield of 75%). Performing the same reaction at room temperature led to a significant reduction in selectivity (11% dibromo derivative, 4% starting material). Disappointingly, screening a variety of solvents (i.e., methylene chloride, 1,2-dichloroethane, DMF) or switching to *N*-bromosuccinimide as the brominating reagent did not lead to an improvement of selectivity in the bromination.

In an attempt to obtain a better control of the selectivity in this crucial bromination step, we also explored the use of a polymer-supported brominating reagent. Polymer-assisted solution phase (PASP) synthesis, where reagents, catalysts, or scavengers are attached to an insoluble polymer support has attracted a considerable amount of attention in recent years.[18] The advantages associated with PASP synthesis have been well-documented and include simplified workup (filtration), standard solution-phase kinetics, easy analysis of reactions using conventional techniques, and the opportunity for the implementation of flow-through processes using cartridge (or column)-based reactors.[19]

In the case of brominations, several reports have been published in the literature that involve macroporous Amberlyst A-26 polystyrene resin in the perbromide form (**7**) as a solid-supported brominating agent.[20,21] For our purposes, a suitable perbrominated resin **7** was readily prepared by treatment of commercially available Amberlyst A-26, Br^--form (3.5 mequiv Br/g) (**6**) with excess elemental bromine in carbon tetrachloride (CCl_4) following literature procedures, providing orange, odorless beads (see Experimental Section for details).[20] Our initial experiments utilizing perbromide resin **7** for the bromination of DHPM **3a**, using chloroform or 1,2-dichloroethane as a solvent, did not show any improvement in selectivity. Furthermore, the reaction was somewhat slower than using elemental bromine in the solution phase. By switching to anhydrous DMF as the solvent, however, we were able to achieve rapid brominations at room temperature, leading after 10 min to the same product distribution that was achieved in the solution-phase experiment described previously (4 h, 4 °C) using chloroform as a solvent (**3a**/**5a**/dibromo analogue ratio of 3:90:7). A 2−3-fold excess of the resin was used; therefore, the reaction required careful monitoring and control. A prolonged exposure of the reaction mixture (>30 min) to the brominating resin led to significant amounts of the *gem*-dibromo analogue being formed. To have more control over the bromination event, we envisioned the use of a flow-through reactor setup where a solution of DHPM **3a** is passed through a cartridge filled with the polymer-supported brominating reagent **7**. We reasoned that, in this way, overbromination may be minimized by continuous removal of the desired mono-brominated DHPM **5a** (Scheme 3) from the active brominating reagent. Indeed, by passing a solution of DHPM **3a** (1 mmol) in 5 mL of DMF through a small cartridge filled with brominating polymer (inner diameter (i.d.) of 9 mm, ca. 1 g of resin **7**), highly selective monobrominations were achieved. Typically, with a residence time of only ∼1 min, 96% conversion (HPLC) to the desired bromo DHPM **5a** was achieved, with only 3% of the *gem*-dibromo analogue being formed and 1% unreacted starting material remaining. These bromination results were highly reproducible, and by regenerating the brominating reagent with elemental bromine under flow conditions (**6** → **7**, Scheme 3), the same reactor was reused 8 times without any deterioration in the bromination results. This proved particularly valuable for the final synthesis of triazolyldihydropyrimidone libraries where a collection of DHPM derivatives needed to be brominated in a high-throughput format (see below). The need for regeneration of the brominating flow reactor was readily noticeable from the decolorization of the orange polymer beads. To remove the formed hydrobromic acid from the reaction mixture which would prevent an efficient azidation in the subsequent reaction step (see below), a second flow cartridge filled with basic alumina was added to the processing sequence.

Scheme 3



2.2.2. Azidation of Bromo Dihydropyrimidones under Microwave Conditions. The published conditions[12] for the conversion of bromo-DHPM **5a** to the azido-DHPM **2a** require a 48-h treatment of bromide **5a** with sodium azide (1.5 equiv) in hexamethylphosphoric triamide (HMPT) at 35 °C. These conditions proved to be reproducible, but we note that (i) the reaction cannot be monitored by HPLC or TLC, because the retention times of both the bromo and the azido compounds are virtually identical, requiring reaction monitoring via Fourier transform infrared (FT-IR) spectroscopy ($\nu(N_3) = 2110\ cm^{-1}$) or ^1H NMR spectroscopy; and

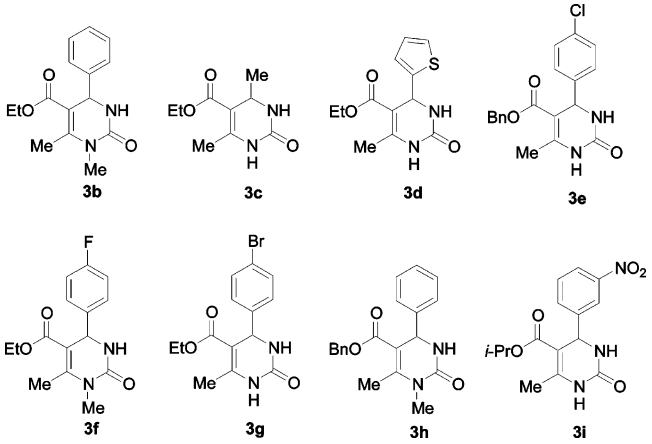
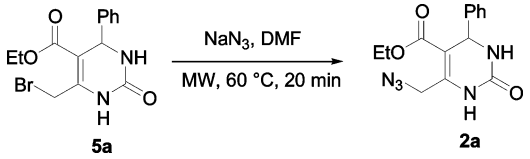


Figure 1. Dihydropyrimidone (DHPM) building blocks used for the bromination/azidation/click reaction sequence.

Scheme 4

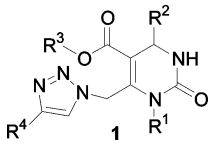


(ii) the success of the azidation step is critically dependent on the quality of the sodium azide. After several trials, we discovered that a fresh batch of high-purity sodium azide (>99% purity) consistently provided the best results.[23] Nevertheless, reaction times of ca. 1 day at room temperature were still required to obtain full conversion, regardless of the solvent that was used (HMPT, DMF, NMP). After considerable experimentation, we found that microwave irradiation[24] of a solution of pure bromo-DHPM **5a** with 1.5 equiv of sodium azide in dry DMF at 60 °C led to full conversion to the azide within 20 min and provided an isolated yield of 82% of pure compound upon precipitation with ice water (Scheme 4). Gratifyingly, we were able to integrate the bromination (**3a** → **5a**) and azidation (**5a** → **2a**) steps into a simple experimental procedure wherein the DMF solution obtained from the bromination under flow-through conditions containing the crude bromo-DHPM **5a** (see above) was directly subjected to azidation under microwave conditions after addition of sodium azide. The azido-DHPM **2a** obtained after precipitation with ice water had >98% purity (via HPLC, ^{1}H NMR) and was obtained in an isolated yield of 73%.

2.2.3. Preparation of 6-(1,2,3-Triazol-1-yl)-dihydropyrimidone Libraries. Our next goal was to establish protocols for the preparation of a diverse set of triazolyl-decorated DHPM libraries of type **1** with four points of diversity (see Scheme 1). For that purpose, a selection of eight DHPMs (Figure 1) were prepared by rapid, automated, microwave-assisted Biginelli multicomponent condensations (cf. Scheme 1), following our previously published protocols.[25]

The DHPM analogues were then subjected to the flow-through bromination/azidation sequence (see previous discussion) to provide the corresponding 6-azidomethyl-DHPMs **2b**−**i**. At this point, it was necessary to isolate the crude azides by precipitation with ice water (ca 40−70% yield, >95% purity via HPLC). Attempts to perform the Cu(I)-catalyzed azide−acetylene ligation ("click chemistry") directly with the nonisolated azides in DMF solution by adding the terminal acetylenes and the copper catalyst met with little success.[26] In all cases, higher product yields were observed by first isolating the crude azides **2**, thereby removing excess sodium azide from the reaction mixture. Azide−acetylene cycloadditions on precursors **2b**−**i** were performed according to the general procedure described previously, using a selection of the terminal acetylenes **4** (see Table 1). Out of the full 8 × 10 = 80 set of possible triazole cycloaddition products, a representative subset of 17 compounds was prepared. To have a uniform workup method available, all cycloadducts were precipitated with water and subsequently purified by flash choromatography. The overall yields (three steps) for the bromination/azidation/click sequence were in the range of 15−46%. Note that no attempt was made to optimize any of the three reaction steps for specific building block combinations and that one standard protocol for all 17 derivatives was used for the three steps (Table 2).

Table 2. Overall Yields of Triazolyl-dihydropyrimidones **1** Prepared by the Three-Step Bromination/Azidation/Click Sequence from Dihydropyrimidones **3b**−**i** (see Figure 1) and Terminal Acetylenes **4** (see Table 1, R^{4}C≡CH)[a]



product	R^1	R^2	R^3	R^4	yield (%)[b]
1bA	Me	phenyl	Et	phenyl	36
1bF	Me	phenyl	Et	pyridin-3-yl	35
1bG	Me	phenyl	Et	$PhOCH_2$	25
1cA	H	Me	Et	phenyl	15
1cG	H	Me	Et	$PhOCH_2$	16
1dD	H	thien-2-yl	Et	2-(CF_3)-phenyl	24
1eE	H	4-(Cl)-phenyl	benzyl	3,5-($F)_2$-phenyl	34
1eF	H	4-(Cl)-phenyl	benzyl	pyridin-3-yl	38
1eG	H	4-(Cl)-phenyl	benzyl	$PhOCH_2$	27
1fA	Me	4-(F)-phenyl	Et	phenyl	29
1fB	Me	4-(F)-phenyl	Et	3-(Me)-phenyl	28
1gA	H	4-(Br)-phenyl	Et	phenyl	35
1gF	H	4-(Br)-phenyl	Et	pyridin-3-yl	46
1hA	Me	phenyl	benzyl	phenyl	33
1hD	Me	phenyl	Et	2-(CF_3)-phenyl	31
1iB	H	3-(NO_2)-phenyl	*i*-Pr	3-(Me)-phenyl	26
1iE	H	3-(NO_2)-phenyl	*i*-Pr	3,5-($F)_2$-phenyl	28

[a] For reaction conditions and workup, see main text and the Experimental Section. [b] Yields are isolated yields of pure compounds purified by flash chromatography.

3. Conclusion

In conclusion, we have reported the decoration of privileged dihydropyrimidone (DHPM) scaffolds at the C6 position with a 1,2,3-triazole pharmacophore. The key step in the synthesis was the Cu(I)-catalyzed azide−acetylene ligation ("click chemistry"), reacting azide-functionalized DHPMs **2** with terminal acetylenes **4**. The required 6-azidomethyldihydropyrimidone precursors **2** were readily prepared using a bromination/azidation sequence that involved a polymer-supported brominating reagent under flow-through conditions and subsequent displacement of the

bromine with azide. The resulting 6-(1,2,3-triazol-1-yl)-methyldihydropyrimidones **1** (27-member library, 4 diversity points) were obtained in moderate overall yields over three steps. By merging multicomponent transformations such as the three-component Biginelli DHPM synthesis with click chemistry applications, highly diverse libraries can rapidly be obtained.

4. Experimental Section

4.1. General Methods. TLC analysis was performed on Merck precoated 60 F_{254} plates. Flash column chromatography was performed using silica gel 60 (0.035−0.070 mm, Acros). Melting points were obtained on a Gallenkamp melting point apparatus (model MFB-595) in open capillary tubes. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AMX360 or AMX500 instrument in DMSO-d_6, operating at 360 or 500 MHz, respectively. FTIR spectra were recorded on a Unicam Galaxy Series model FTIR 7000 (Mattson Instruments Inc.) spectrometer, using KBr pellets. Mass spectra were taken on a Hewlett-Packard model LC/MSD 1100 series instrument in the positive atmospheric pressure chemical ionization (APCI) mode. Microanalyses were performed on a Carlo Erba model 1106 elemental analyzer. Analytical HPLC analysis was performed on a Shimadzu LC-10 system, equipped with LC10-AT(VP) pumps, an autosampler (S-10AXL), and a dual-wavelength UV detector that was set at 215 and 280 nm (HPLC purities refer to 215 nm). Analytical liquid chromatographic separations were performed on a C18 reversed-phase analytical column (LiChrospher 100 Rp-18, E. Merck, 119 × 3 mm, particle size of 5 μm) at 25 °C using a mobile phase (A, which was a 90:10 (v/v) mixture of water and acetonitrile + 0.1% TFA, and B, which was acetonitrile + 0.1% TFA (HPLC solvents were purchased from Acros with gradient-grade quality; TFA was of analytical reagent grade, Aldrich) at a flow rate of 0.5 mL/min. The following gradient was applied: a linear increase from 30% solution B to 100% B in 7 min, holding at 100% solution B for 2 min.

4.2. Microwave Irradiation Experiments. All microwave irradiation experiments were performed using the Emrys Synthesizer from Biotage AB (Uppsala, Sweden) in the standard sealed-vessel configuration. A detailed description of this single-mode microwave reactor with integrated robotics was recently published.[25]

4.3. Synthesis of Triazolyl-DHPMs 1aA-1aJ from Dihydropyrimidone 2a (Azide−Acetylene Ligation). 4.3.1. General Procedure. A sample of DHPM **2a**[12] (301 mg, 1.0 mmol) was dissolved in anhydrous DMF (5 mL). The appropriate acetylene **4A**−**J** (see Table 1, 1.0 mmol), $CuSO_4 \cdot 5\ H_2O$ (2 mol %, ca. 5 mg), and sodium ascorbate (0.2 mmol, 40 mg) were added and the mixture was irradiated under microwave conditions at 90 °C for 10 min. After rapid gas jet cooling, the reaction mixture was poured onto 100 mL of ice water, and after 2 h, the precipitate was filtered off (for **1aJ**, 4 mL *tert*-BuOH/H_2O 1:1 was used as solvent, and 3.0 equiv of acetylene **4J** were reacted at room temperature for 4 h). Triazoles **1aA**−**1aJ** were obtained in isolated yields of 63−87% (see Table 1) and at >98% purity (HPLC at 215 nm). Analytically pure samples were prepared by recrystallization from ethanol.

4.3.2. Ethyl 2-Oxo-4-phenyl-6-(4-phenyl-[1,2,3]triazol-1-ylmethyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylate (1aA). mp 197−198 °C. ^{1}H NMR (DMSO-d_6): δ 1.05 (t, J = 7.1 Hz, 3H), 4.01 (q, J = 7.1 Hz, 2H), 5.24 (d, J = 3.2 Hz, 1H), 5.52 and 5.71 (2 d, J = 14.0 Hz, 2H), 7.24−7.38 (m, 6H), 7.42−7.50 (m, 2H), 7.83−7.89 (m, 2H), 7.91 (br s, 1H), 8.51 (s, 1H), 9.60 (s, 1H). ^{13}C NMR (90 MHz, DMSO-d_6): δ 165.0, 152.2, 146.4, 144.4, 143.5, 131.0, 129.3, 128.9, 128.3, 128.0, 126.9, 125.6, 122.2, 103.5, 60.5, 54.6, 48.6, 14.3. MS (pos. APCI): m/z 404 (M + 1). Anal. Calcd for $C_{22}H_{21}N_5O_3$: C, 65.50; H, 5.25; N, 17.36. Found: C, 65.38; H, 5.18; N, 17.29.

4.3.3. Ethyl 2-Oxo-4-phenyl-6-(4-*m*-tolyl-[1,2,3]triazol-1-ylmethyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylate (1aB). mp 99−101 °C. ^{1}H NMR (DMSO-d_6): δ 1.05 (t, J = 7.0 Hz, 3H), 2.36 (s, 3H), 4.01 (q, J = 7.0 Hz, 2H), 5.23 (d, J = 3.2 Hz, 1H), 5.52 and 5.69 (2 d, J = 14.0 Hz, 2H), 7.10−7.18 (m, 1H), 7.22−7.40 (m, 6H), 7.60−7.75 (m, 1H), 7.90 (br s, 1H), 8.46 (s, 1H), 9.60 (s, 1H). MS (pos. APCI): m/z 418 (M + 1). Anal. Calcd for $C_{23}H_{23}N_5O_3$: C, 66.17; H, 5.55; N, 16.78. Found: C, 66.03; H, 5.53; N, 16.63.

4.3.4. Ethyl 2-Oxo-4-phenyl-6-[4-(3-chlorophenyl)-[1,2,3]-triazol-1-ylmethyl]-1,2,3,4-tetrahydropyrimidine-5-carboxylate (1aC). mp 170−171 °C. ^{1}H NMR (DMSO-d_6): δ 1.05 (t, J = 7.0 Hz, 3H), 4.00 (q, J = 7.0 Hz, 2H), 5.23 (d, J = 3.0 Hz, 1H), 5.52 and 5.70 (2 d, J = 14.0 Hz, 2H), 7.23−7.42 (m, 6H), 7.44−7.52 (m, 1H), 7.82−7.92 (m, 2H), 7.94 (br s, 1H), 8.64 (s, 1H), 9.61 (s, 1H). MS (pos. APCI): m/z 438 (M + 1). Anal. Calcd for $C_{22}H_{20}ClN_5O_3$: C, 60.34; H, 4.60; N, 15.99. Found: C, 60.28; H, 4.56; N, 15.82.

4.3.5. Ethyl 2-Oxo-4-phenyl-6-[4-(2-trifluoromethylphenyl)-[1,2,3]triazol-1-ylmethyl]-1,2,3,4-tetrahydropyrimidine-5-carboxylate (1aD). mp 158−159 °C. ^{1}H NMR (DMSO-d_6): δ 1.05 (t, J = 7.0 Hz, 3H), 4.02 (q, J = 7.0 Hz, 2H), 5.23 (d, J = 3.1 Hz, 1H), 5.60 and 5.68 (2 d, J = 14.0 Hz, 2H), 7.21−7.36 (m, 5H), 7.60−7.68 (m, 1H), 7.74−7.89 (m, 3H), 7.85 (t, J = 7.59 Hz, 2H), 7.91 (br s, 1H), 8.28 (s, 1H), 9.65 (s, 1H); MS (pos. APCI): m/z 472 (M + 1); Anal. Calcd for $C_{23}H_{20}F_3N_5O_3$: C, 58.60; H, 4.28; N, 14.86. Found: C, 58.67; H, 4.20; N, 14.70.

4.3.6. Ethyl 2-Oxo-4-phenyl-6-[4-(3,5-difluorophenyl)-[1,2,3]triazol-1-ylmethyl]-1,2,3,4-tetrahydropyrimidine-5-carboxylate (1aE). mp 213−214.5 °C. ^{1}H NMR (DMSO-d_6): δ 1.04 (t, J = 7.0 Hz, 3H), 4.00 (q, J = 7.0 Hz, 2H), 5.23 (d, J = 3.1 Hz, 1H), 5.52 and 5.70 (2 d, J = 14.0 Hz, 2H), 7.18−7.38 (m, 6H), 7.58−7.68 (m, 2H), 7.89−7.94 (m, 1H), 8.70 (s, 1H), 9.63 (s, 1H). MS (pos. APCI): m/z 440 (M + 1). Anal. Calcd for $C_{22}H_{19}F_2N_5O_3$: C, 60.13; H, 4.36; N, 15.94. Found: C, 60.27; H, 4.16; N, 15.80.

4.3.7. Ethyl 2-Oxo-4-phenyl-6-(4-pyridin-3-yl-[1,2,3]-triazol-1-ylmethyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylate (1aF). mp 204−205 °C. ^{1}H NMR (DMSO-d_6): δ 1.05 (t, J = 7.0 Hz, 3H), 4.01 (q, J = 7.0 Hz, 2H), 5.23 (d, J = 3.0 Hz, 1H), 5.55 and 5.72 (2 d, J = 14.0 Hz, 2H), 6.90−7.10 (m, 3H), 7.15−7.42 (m, 6H), 7.90 (br s, 1H), 8.70 (s, 1H), 9.63 (s, 1H). MS (pos. APCI): m/z 405 (M + 1). Anal. Calcd for $C_{21}H_{20}N_6O_3$: C, 62.37; H, 4.98; N, 20.78. Found: C, 61.99; H, 4.96; N, 20.78.

4.3.8. Ethyl 2-Oxo-4-phenyl-6-(4-phenoxymethyl-[1,2,3]-triazol-1-ylmethyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylate (1aG). mp 159−161 °C. ^{1}H NMR (DMSO-d_6): δ 1.04 (t, J = 7.0 Hz, 3H), 4.00 (q, J = 7.0 Hz, 2H), 5.21 (d, J = 3.2 Hz, 1H), 5.41 (s, 2H), 5.51 and 5.67 (2 d, J = 14.0 Hz, 2H), 7.20−7.38 (m, 5H), 7.48−7.58 (m, 2H), 7.62−7.72 (m, 1H), 7.89 (br s, 1H), 7.93−7.99 (m, 2H), 8.22 (s, 1H), 9.60 (s, 1H). MS (pos. APCI): m/z 434 (M + 1). Anal. Calcd for $C_{23}H_{23}N_5O_4$: C, 63.73; H, 5.35; N, 16.16. Found: C, 63.53; H, 5.33; N, 15.87.

4.3.9. Ethyl 2-Oxo-4-phenyl-6-(4-benzyloxymethyl-[1,2,3]triazol-1-ylmethyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylate (1aH). mp 159−161 °C. ^{1}H NMR (DMSO-d_6): δ 1.03 (t, J = 7.0 Hz, 3H), 4.00 (q, J = 7.0 Hz, 2H), 5.20 (d, J = 3.2 Hz, 1H), 5.41 (s, 2H), 5.49 and 5.66 (2 d, J = 13.9 Hz, 2H), 7.20−7.34 (m, 5H), 7.49−7.58 (m, 2H), 7.63−7.71 (m, 1H), 7.89 (br s, 1H), 7.92−7.98 (m, 2H), 8.22 (s, 1H), 9.60 (s, 1H); MS (pos. APCI): m/z 462 (M + 1). Anal. Calcd for $C_{24}H_{23}N_5O_5$: C, 62.46; H, 5.02; N, 15.18. Found: C, 62.25; H, 4.81; N, 14.85.

4.3.10. Ethyl 2-Oxo-4-phenyl-6-(4-hydroxymethyl-[1,2,3]-triazol-1-ylmethyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylate (1aI). mp 169−171 °C. ^{1}H NMR (DMSO-d_6): δ 1.06 (t, J = 7.0 Hz, 3H), 4.00 (q, J = 7.0 Hz, 2H), 4.51 (d, J = 5.3 Hz, 2H), 5.19−5.24 (m, 2H), 5.42 and 5.66 (2 d, J = 14.0 Hz, 2H), 7.19−7.38 (m, 5H), 7.82−7.94 (m, 2H), 7.87 (br s, 1H), 7.91 (s, 1H), 9.54 (s, 1H). MS (pos. APCI): m/z 358 (M + 1). Anal. Calcd for $C_{17}H_{19}N_5O_4$: C, 57.14; H, 5.36; N, 19.60. Found: C, 56.74; H, 5.40; N, 19.19.

4.3.11. Ethyl 2-Oxo-4-phenyl-6-(4-trimethylsilanyl-[1,2,3]triazol-1-ylmethyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylate (1aJ). mp 119−121 °C. ^{1}H NMR (DMSO-d_6): δ 0.24 (s, 9H), 1.04 (t, J = 7.0 Hz, 3H), 4.00 (q, J = 7.0 Hz, 2H), 5.18−5.23 (m, 1H), 5.50 and 5.63 (2 d, J = 13.0 Hz, 2H), 7.21−7.36 (m, 5H), 7.88 (br s, 1H), 8.02 (s, 1H), 9.51 (s, 1H). MS (pos. APCI): m/z 400 (M + 1). Anal. Calcd for $C_{19}H_{25}N_5O_3Si$: C, 57.10; H, 6.31; N, 17.53. Found: C, 57.04; H, 6.28; N, 17.47.

4.4. Thermal Cycloaddition of Azide 2a with Phenylacetylene 4A under Catalyst-Free Conditions. A sample of DHPM **2a** (301 mg, 1.0 mmol) was dissolved in 5 mL of anhydrous DMF. After the addition of acetylene **4A** (102 mg, 1.0 mmol), the reaction mixture was irradiated under microwave conditions at 150 °C for 3 h. Subsequent purification of the crude reaction mixture by flash chromatography ($CHCl_3$/MeOH 5:1) provided 120 mg (30%) of an inseparable mixture of syn and anti triazole cycloadducts (ratio 3:5 by both HPLC and ^{1}H NMR measurements). ^{1}H NMR (syn + anti) (DMSO-d_6): δ 0.88 (t, J = 7.1 Hz, 3H, syn), 1.05 (t, J = 7.0 Hz, 3H, anti), 4.02 (q, J = 7.0 Hz, 2H, anti), 3.81 (q, J = 7.0 Hz, 2H, syn), 5.20 (d, J = 3.3 Hz, 1H, syn), 5.23 (d, J = 3.3 Hz, 1H, anti), 5.48 and 5.61 (2 d, J = 14.2 Hz, 2 H, syn), 5.52 and 5.71 (2 d, J = 14.0 Hz, 2H, anti), 7.25−7.60 (m, 14 H, syn + anti), 7.85−7.91 (m, 3H, syn + anti), 7.95 (s, 1 H, syn), 8.50 (s, 1H, anti), 9.35 (br s, 1H, syn), 9.59 (br s, 1H, anti).

4.5. Preparation of Macroporous Perbromide Resin 7.[20] A sample of 1.0 g (ca. 3.5 mmol) of Amberlyst A-26, Br-form resin (3.5 mequiv/g, Aldrich Product 51,376-8) was washed two times each with 5 mL of H_2O, 5 mL of MeOH, and 2 mL of acetone and dried under vacuum at room temperature overnight. Subsequently, 25 mL of dry CCl_4 and 1.68 g (10.5 mmol) of elemental bromine were added and the reaction mixture was stirred for 2 h at 40 °C. The resin was filtered, washed two times with 5 mL of dry CCl_4, and dried under vacuum at room temperature overnight to provide odorless orange resin beads. This resin could be stored for several weeks at 4 °C without any loss of activity.

4.6. Bromination of Dihydropyrimidone 3a under Flow-Through Conditions. A sample of DHPM **3a** (260 mg, 1.0 mmol) was dissolved in 5 mL of anhydrous DMF. The solution was passed three times (residence time of ca. 30 s per cycle) through a cartridge (0.9 mm i.d.) that was filled with ca. 1.0 g of perbrominated resin **7** (see previous discussion), leading to a 96% conversion by HPLC. After pouring the mixture onto ice water, the formed precipitate was filtered to provide DHPM **5a** (254 mg, 75%) in 97% purity (HPLC). The recycling of the perbromide resin was performed under batch conditions as described in the aforementioned experiment.

4.7. Azidation of Bromomethyldihydropyrimidone 5a. A sample of DHPM **5a**[16] (339 mg, 1.0 mmol) was dissolved in 5 mL of anhydrous DMF. Subsequently, sodium azide (Aldrich Product 19,993-1, >99% purity) (1.5 mmol, 98 mg) was added and the mixture was irradiated under microwave conditions at 60 °C for 20 min. After the mixture was cooled, it was poured onto 100 mL of ice water and stirred for 5 min, and, after standing for 30 min, the precipitate was filtered to provide 247 mg (82%) of azide **2a** in >98% purity (HPLC). All spectral (^{1}H NMR, IR) and analytical data were identical to the literature values.[12]

4.8. Preparation of Azidodihydropyrimidone 2a by a Combined Bromination/Azidation Step of 3a. A sample of DHPM **3a** (260 mg, 1.0 mmol) was dissolved in 4 mL of anhydrous DMF. The solution was passed three times (residence time of ca. 30 s per cycle) through a cartridge (0.9 mm i.d.) that was filled with ca. 1.0 g of perbrominated resin **7,** leading to a 96% conversion by HPLC. Subsequently, the mixture was passed through a cartridge filled with 1 g of basic alumina and eluted with an additional quantity of 2 mL of DMF. After the addition of sodium azide (1.5 mmol, 98 mg), the reaction mixture was irradiated under microwave conditions at 60 °C for 20 min. After cooling to ambient temperature, the mixture was poured onto 100 mL of ice water, stirred for 5 min, and allowed to stand for 30 min at room temperature. The precipitate was filtered to provide 220 mg (73%) of azide **2a** (>98% purity, HPLC).

4.9. Preparation of the Triazolyldihydropyrimidone Library 1. 4.9.1. General Procedure. A 1.0 mmol sample of the corresponding DHPMs **3b**−**i** (Figure 1, Table 2) was dissolved in 4 mL of anhydrous DMF and passed three times through a cartridge that was filled with 1 g of the perbromide resin **7** (see previous discussion). Subsequently, the mixture was passed through a second cartridge that was filled with 1 g of basic alumina and eluted with 2 mL of anhydrous DMF. To this mixture, 1.5 mmol (98 mg) of sodium azide

(99% purity) were added and irradiated under microwave conditions at 60 °C for 25 min. After gas-jet cooling to room temperature, the reaction mixture was poured onto ice water, and after 2 h, the precipitate was filtered and dried. Subsequently, 1.0 mmol of the corresponding acetylene **4** (see Table 1), $CuSO_4 \cdot 5H_2O$ (4 mol %, ca. 10 mg), sodium ascorbate (0.35 mmol, 70 mg), and 5 mL of anhydrous DMF were added to the crude azide **2** and irradiated at 85 °C for 20 min. After the mixture was cooled to room temperature, it was poured onto 70 mL of ice water and subsequently extracted two times with 10 mL of ethyl acetate and once with 10 mL of dichloromethane (DCM). The combined organic phases were washed with brine and water, dried (Na_2SO_4), and subsequently evaporated. The crude cycloaddition products were purified by flash chromatography using ethyl acetate/DCM or DCM/methanol solvent mixtures to provide the library compounds **1** in a yield of 15−46% and high purity (>98%; see Table 2). The structural identity and purity of all library compounds was confirmed by ^{1}H NMR, mass spectroscopy (MS), and HPLC analysis.

4.9.2. Ethyl 1-Methyl-2-oxo-4-phenyl-6-(4-phenyl-[1,2,3]-triazol-1-ylmethyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylate (1bA). ^{1}H NMR (DMSO-d_6): δ 1.10 (t, J = 7.0 Hz, 3H), 3.10 (s, 3H), 4.06−4.11 (m, 2H), 5.23−5.27 (m, 1H), 5.90 and 6.05 (2 d, J = 15.0 Hz, 2H), 7.20−7.50 (m, 10H), 8.16−8.17 (m, 1H), 8.57 (s, 1H). MS (pos APCI): m/z 418.3 (M + 1).

4.9.3. Ethyl 1-Methyl-2-oxo-4-phenyl-6-(4-pyridin-3-yl-[1,2,3]triazol-1-ylmethyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylate (1bF). ^{1}H NMR (DMSO-d_6): δ 1.09 (t, J = 7.0 Hz, 3H), 3.10 (s, 3H), 4.07 (q, J = 7.0 Hz, 2H), 5.24 (d, J = 3.6 Hz, 1H), 5.90 and 6.08 (2 d, J = 15.0 Hz, 2H), 7.20−7.50 (m, 9H), 8.16 (d, J = 3.7 Hz, 1H), 8.71 (s, 1H). MS (pos APCI): m/z 419.2 (M + 1).

4.9.4. Ethyl 1-Methyl-2-oxo-6-(4-phenoxymethyl-[1,2,3]-triazol-1-ylmethyl)-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate (1bG). ^{1}H NMR (DMSO-d_6): δ 1.09 (t, J = 7.0 Hz, 3H), 3.08 (s, 3H), 4.06 (q, J = 7.0 Hz, 2H), 5.14 (s, 2H), 5.23 (d, J = 3.6 Hz, 1H), 5.80 and 5.99 (2 d, J = 15.0 Hz, 2H), 6.90−7.40 (m, 10H), 8.16 (d, J = 3.8 Hz, 1H), 8.22 (s, 1H). MS (pos APCI): m/z 448.3 (M + 1).

4.9.5. Ethyl 2-Oxo-4-methyl-6-(4-phenyl-[1,2,3]triazol-1-ylmethyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylate (1cA). ^{1}H NMR (DMSO-d_6): δ 1.16 (t, J = 5.2 Hz, 6H), 4.00−4.30 (m, 3H), 5.40 and 5.63 (2 d, J = 13.0 Hz, 2H), 6.80−7.50 (m, 4H), 7.86 (d, J = 7.7 Hz, 1H), 8.50 (s, 1H), 9.38 (br s, 1H). MS (pos. APCI): m/z 342.3 (M + 1).

4.9.6. Ethyl 2-Oxo-4-methyl-6-(4-phenoxymethyl-[1,2,3]-triazol-1-ylmethyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylate (1cG). ^{1}H NMR (DMSO-d_6): δ 1.09−1.20 (m, 6H), 4.00−4.30 (m, 3H), 5.12 (br s, 2H), 5.35 and 5.67 (2 d, J = 13.0 Hz, 2H), 7.20−7.50 (m, 6H), 8.49 (s, 1H), 9.37 (s, 1H). MS (pos. APCI): m/z 372.3 (M + 1).

4.9.7. Ethyl 2-Oxo-4-(thien-2-yl)-6-[4-(2-trifluoromethylphenyl)-[1,2,3]triazol-1-ylmethyl]-1,2,3,4-tetrahydropyrimidine-5-carboxylate (1dD). ^{1}H NMR (DMSO-d_6): δ 1.13−1.19 (m, 4H), 1.98 (s, 1H), 3.90−4.20 (m, 3H), 5.50 (d, J = 3.4 Hz, 1H), 5.58 and 5.70 (2 d, J = 14.0 Hz, 2H), 6.90−7.00 (m, 2H), 7.38−7.42 (m, 1H), 7.60−7.90 (m, 4H), 8.00 (br s, 1H), 8.25 (s, 1H). MS (pos. APCI): m/z 478.3 (M+1).

4.9.8. Benzyl 2-Oxo 4-(4-chlorophenyl)-6-[4-(3,5-difluoro-phenyl)-[1,2,3]triazol-1-ylmethyl]-1,2,3,4-tetrahydropyrimidine-5-carboxylate (1eE). ^{1}H NMR (DMSO-d_6): δ 5.05 (q, J = 12.5 Hz, 2H), 5.25 (d, J = 3.1 Hz, 1H), 5.50 and 5.72 (2 d, J = 14.0 Hz, 2H), 7.01−7.42 (m, 12H), 7.94 (br s, 1H), 8.64 (s, 1H), 9.75 (s, 1H). MS (pos. APCI): m/z 536.3 (M + 1).

4.9.9. Benzyl 2-Oxo-4-(4-chlorophenyl)-6-(4-pyridin-3-yl-[1,2,3]triazol-1-ylmethyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylate (1eF). ^{1}H NMR (DMSO-d_6): δ 5.06 (q, J = 12.4 Hz, 2H), 5.25 (d, J = 3.1 Hz, 1H), 5.51 and 5.76 (2d, J = 14.0 Hz, 2H), 7.01−7.42 (m, 13H), 7.94 (br s, 1H), 8.61 (s, 1H), 9.74 (s, 1H). MS (pos. APCI): m/z 501.2 (M + 1).

4.9.10. Benzyl 2-Oxo-4-(4-chlorophenyl)-6-(4-phenoxymethyl-[1,2,3]triazol-1-ylmethyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylate (1eH). ^{1}H NMR (DMSO-d_6): δ 4.90−5.20 (m, 4H), 5.24 (d, J = 3.1 Hz, 1H), 5.48 and 5.69 (2 d, J = 14.0 Hz, 2H), 6.95−7.45 (m, 14H), 7.92 (br s, 1H), 8.14 (s, 1H), 9.72 (s, 1H). MS (pos. APCI): m/z 530.3 (M + 1).

4.9.11. Ethyl 1-Methyl-2-oxo-4-(4-fluorophenyl)-6-(4-phenyl-[1,2,3]triazol-1-ylmethyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylate (1fA). ^{1}H NMR (DMSO-d_6): δ 1.09 (t, J = 7.0 Hz, 3H), 4.08 (q, J = 7.0 Hz, 2H), 5.25 (d, J = 3.7 Hz, 1H), 5.88 and 6.01 (2 d, J = 14.0 Hz, 2H), 7.10−7.55 (m, 9H), 7.87 (m, 3H), 8.16 (br s, 1H), 8.51 (s, 1H). MS (pos. APCI): m/z 436.3 (M + 1).

4.9.12. Ethyl 1-Methyl-2-oxo-4-(4-fluorophenyl)-6-(4-m-tolyl-[1,2,3]triazol-1-ylmethyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylate (1fB). ^{1}H NMR (DMSO-d_6): δ 1.15 (t, J = 7.0 Hz, 3H), 2.35 (s, 3H), 3.09 (s, 3H), 4.06 (q, J = 7.0 Hz, 2H), 5.26 (d, J = 3.6 Hz, 1H), 5.88 and 6.07 (2 d, J = 14.0 Hz, 2H), 7.10−7.50 (m, 6H), 7.60−7.80 (m, 2H), 8.18 (d, J = 3.6 Hz, 1H), 8.54 (s, 1H). MS (pos. APCI): m/z 450.4 (M + 1).

4.9.13. Ethyl 2-Oxo-4-(4-bromophenyl)-6-(4-phenyl-[1,2,3]triazol-1-ylmethyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylate (1gA). ^{1}H NMR (DMSO-d_6): δ 1.07 (t, J = 7.0 Hz, 3H), 4.00 (q, J = 7.0 Hz, 2H), 5.23 (d, J = 3.2 Hz, 1H), 5.50 and 5.69 (2 d, J = 14.0 Hz, 2H), 7.10−7.60 (m, 7H), 7.86 (d, J = 7.2 Hz, 2H), 7.92 (br s, 1H), 8.50 (s, 1H), 9.65 (s, 1H). MS (pos. APCI): m/z 478.1 (M + 1).

4.9.14. Ethyl 2-Oxo-4-(4-bromophenyl)-6-(4-pyridin-3-yl-[1,2,3]triazol-1-ylmethyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylate (1gF). ^{1}H NMR (DMSO-d_6): δ 1.05 (t, J = 7.0 Hz, 3H), 4.02 (q, J = 7.0 Hz, 2H), 5.22 (d, J = 2.8 Hz, 1H), 5.53 and 5.72 (2 d, J = 14.0 Hz, 2H), 7.10−7.70 (m, 6H), 7.93 (br s, 1H), 8.24−8.35 (m, 1H), 8.67 (s,1H), 9.66 (s, 1H). MS (pos. APCI): m/z 483.2 (M + 1).

4.9.15. Benzyl 1-Methyl-2-oxo-4-phenyl-6-(4-phenyl-[1,2,3]triazol-1-ylmethyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylate (1hA). ^{1}H NMR (DMSO-d_6): δ 3.11 (s, 3H), 5.10−5.17 (m, 1H), 5.27 (d, J = 3.1 Hz, 1H), 5.90 and 6.08 (2 d, J = 14.0 Hz, 2H), 7.01−7.61 (m, 15H), 7.84 (br s,

1H), 8.16 (s, 1H), 8.51 (s, 1H). MS (pos. APCI): *m*/*z* 480.1 (M + 1).

4.9.16. Benzyl 1-Methyl-2-oxo-4-phenyl-6-[4-(2-trifluoromethylphenyl)-[1,2,3]triazol-1-ylmethyl]-1,2,3,4-tetrahydropyrimidine-5-carboxylate (1hD). ^{1}H NMR (DMSO-d_6): δ 3.10 (s, 3H), 5.13 (d, J = 3.0 Hz, 2H), 5.29 (d, J = 3.0 Hz, 1H), 5.99 and 6.01 (2 d, J = 15.0 Hz, 2H), 7.10−7.40 (m, 10H), 7.60−7.90 (m, 4H), 8.18 (br s, 1H), 8.25 (s, 1H). MS (pos. APCI): *m*/*z* 548.3 (M + 1).

4.9.17. Isopropyl 2-Oxo-4-(3-nitrophenyl)-6-(4-m-tolyl-[1,2,3]triazol-1-ylmethyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylate (1iB). ^{1}H NMR (DMSO-d_6): δ 0.93 (d, J = 6.2 Hz, 3H), 1.14 (d, J = 6.2 Hz, 3H), 2.35 (s, 3H), 4.85 (q, J = 6.0 Hz, 2H), 5.40 (d, J = 3.2 Hz, 1H), 5.50 and 5.69 (2 d, J = 14.0 Hz, 2H), 7.10−8.20 (m, 10H), 8.49 (s, 1H), 9.74 (s, 1H). MS (pos. APCI): *m*/*z* 477.4 (M + 1).

4.9.18. Isopropyl 2-Oxo-4-(3-nitrophenyl)-6-[4-(3,5-difluorophenyl)-[1,2,3]triazol-1-ylmethyl]-1,2,3,4-tetrahydropyrimidine-5-carboxylate (1iE). ^{1}H NMR (DMSO-d_6): δ 0.91 (t, J = 6.0 Hz, 3H), 1.13 (t, J = 6.0 Hz, 3H), 4.82 (q, J = 6.0 Hz, 1H), 5.40 (d, J = 2.2 Hz, 1H), 5.54 and 5.69 (2 d, J = 13.0 Hz, 2H), 7.10−8.30 (m, 9H), 8.73 (s, 1H), 9.78 (s, 1H). MS (pos. APCI): *m*/*z* 497.2 (M + 1).

Acknowledgment. This work was supported by the Austrian Science Fund (FWF, No. P15582). B.K. (Institute for Single Crystals, Kharkov, Ukraine) thanks the Austrian Academic Exchange Service (ÖAD) for a scholarship. We also thank Dr. Bimbisar Desai for valuable suggestions regarding polymer-supported bromination reagents and Biotage AB (Uppsala, Sweden) for the use of the Emrys Synthesizer.

References and Notes

(1) Rouhi, A. M. *Chem. Eng. News* **2004**, *82* (7), 63−65.
(2) Kolb, H. C.; Finn, M. G.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2001**, *40*, 2004−2021.
(3) Kolb, H. C.; Sharpless, K. B. *Drug Discovery Today* **2003**, *8*, 1128−1137.
(4) (a) Huisgen, R. In *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; Wiley: New York, 1984; Vol. 1, pp 1−117. (b) Sha, C.-K.; Mohanakrishnan, A. K. In *Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry Toward Heterocycles and Natural Products*; Padwa, A., Pearson, W. H., Eds.; Wiley: New York, 2003; pp 623−680.
(5) For examples of biologically active 1,2,3-triazoles, see the following: (a) Alvarez, R.; Velazquez, S.; San, F.; Aquaro, S.; De, C.; Perno, C. F.; Karlsson, A.; Balzarini, J.; Camarasa, M. J. *J. Med. Chem.* **1994**, *37*, 4185−4194. (b) Velazquez, S.; Alvarez, R.; Perez, C.; Gago, F.; De, C.; Balzarini, J.; Camarasa, M. J. *Antiviral Chem. Chemother.* **1998**, *9*, 481−489. (c) 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. (d) 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.; Fischer, M. H.; Weber, A. E. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 2111−2114.
(6) Tornøe, C. W.; Christensen, C.; Meldal, M. *J. Org. Chem.* **2002**, *67*, 3057−3064.
(7) Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2002**, *41*, 2596−2599.
(8) For recent applications of Cu(I)-catalyzed azide acetylene cycloadditions, see: (a) Lewis, W. G.; Green, L. G.; Grynszpan, F.; Radić, Z.; Carlier, P. R.; Taylor, P.; Finn, M. G.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2002**, *41*, 1053−1057. (b) Wang, Q.; Chan, T. R.; Hilgraf, R.; Fokin, V. V.; Sharpless, K. B.; Finn, M. G. *J. Am. Chem. Soc.* **2003**, *125*, 3192−3193. (c) Lee, L. V.; Mitchell, M. L.; Huang, S.-J.; Fokin, V. V.; Sharpless, K. B.; Wong, C.-H. *J. Am. Chem. Soc.* **2003**, *125*, 9588−9589. (c) Link, A. J.; Tirrell, D. A. *J. Am. Chem. Soc.* **2003**, *125*, 11164−11165. (d) Speers, A. E.; Adam, G. C.; Cravatt, B. F. *J. Am. Chem. Soc.* **2003**, *125*, 4686−4687. (e) Speers, A. E.; Cravatt, B. F. *Chem. Biol.* **2004**, *11*, 535−546. (f) Seo, T. S.; Li, Z.; Ruparel, H.; Ju, J. *J. Org. Chem.* **2003**, *68*, 609−612. (g) Löber, S.; Rodriguez-Loaiza, P.; Gmeiner, P. *Org. Lett.* **2003**, *5*, 1753−1755. (g) Tornøe, C. W.; Sanderson, S. J.; Mottram, J. C.; Coombs, G. H.; Meldal, M. *J. Comb. Chem.* **2004**, *6*, 312−324.
(9) For recent reviews, see the following: (a) Kappe, C. O. *Acc. Chem. Res.* **2000**, *33*, 879−888. (b) Kappe, C. O. *QSAR Comb. Sci.* **2003**, *22*, 630−645. (c) Kappe, C. O.; Stadler, A. *Org. React.* **2004**, *63*, 1−117.
(10) (a) Armstrong, R. W.; Combs, A. P.; Tempest, P. A.; Brown, S. D.; Keating, T. A. *Acc. Chem. Res.* **1996**, *29*, 123−131. (b) Dax, S. L.; McNally, J. J.; Youngman, M. A. *Curr. Med. Chem.* **1999**, *6*, 255−270. (c) Dömling, A.; Ugi, I. *Angew. Chem., Int. Ed.* **2000**, *39*, 3168−3210. (d) Hulme, C.; Gore, V. *Curr. Med. Chem.* **2003**, *10*, 51−80. (e) Dömling, A. *Curr. Opin. Chem. Biol.* **2002**, *6*, 306−313.
(11) Kappe, C. O. *Eur. J. Med. Chem.* **2000**, *35*, 1043−1052.
(12) Kappe, C. O. *Liebigs Ann. Chem.* **1990**, 505−507.
(13) For a recent example of microwave-assisted click chemistry, see the following: Pérez-Balderas, F.; Ortega-Muñoz, M.; Morales-Sanfrutos, J.; Hernández-Mateo, F.; Calvo-Flores, F. G.; Calvo-Asín, J. A.; Isac-García, J.; Santoyo-González, F. *Org. Lett.* **2003**, *5*, 1951−1954.
(14) For general references on controlled microwave synthesis, see the following: Kappe, C. O. *Angew. Chem., Int. Ed.* **2004**, *43*, in press, and references therein.
(15) (a) Katritzky, A. R.; Singh, S. K. *J. Org. Chem.* **2002**, *67*, 9077−9079. (b) Chen, J.; Rebek, J. *Org. Lett.* **2002**, *4*, 327−329.
(16) Zigeuner, G.; Hamberger, H.; Blaschke, H.; Sterk, H. *Monatsh. Chem.* **1966**, *97*, 1408−1421.
(17) (a) Zigeuner, G.; Knopp, C.; Blaschke, H. *Monatsh. Chem.* **1976**, *107*, 587−603. (b) George, T.; Tahilramani, R.; Metha, D. V. *Synthesis* **1975**, 405−407. (c) Ashby, J.; Griffiths, D. *J. Chem. Soc., Perkin Trans 1* **1975**, 657−662. (d) Zigeuner, G.; Knopp, C. *Monatsh. Chem.* **1970**, *101*, 1541−1546. (e) Bullock, E.; Carter, R. A.; Cochrane, R. M.; Gregory, B.; Shields, D. C. *Can. J. Chem.* **1977**, *55*, 895−905. (f) Lewandowski, K.; Murer, P.; Svec, F.; Fréchet, J. M. J. *J. Comb. Chem.* **1999**, *1*, 105−112.
(18) (a) Drewry, D. H.; Coe, D. M.; Poon, S. *Med. Res. Rev.* **1999**, *19*, 97−148. (b) Ley, S. V.; Baxendale, I. R.; Bream, R. N.; Jackson, P. S.; Leach, A. G.; Longbottom, D. A.; Nesi, M.; Scott, J. S.; Storer, R. I.; Taylor, S. J. *J. Chem. Soc., Perkin Trans 1* **2000**, 3815−4195. (c) Kirschning, A.; Monenschein, H.; Wittenberg, R. *Angew. Chem., Int. Ed.* **2001**, *40*, 650−679. (d) Flynn, D. L.; Berk, S. C.; Makara, G. M. *Curr. Opin. Drug Discovery Dev.* **2002**, *5*, 580−593. (e) Ley, S. V.; Baxendale, I. R. *Nat. Rev. Drug Discovery* **2002**, *1*, 573−586.
(19) (a) Hafez, A. M.; Taggi, A. E.; Lectka, T. *Chem.—Eur. J.* **2002**, *8*, 4114−4119. (b) Hodge, P. *Curr. Opin. Chem. Biol.* **2003**, *7*, 362−373. (c) Jas, G.; Kirschning, A. *Chem.—Eur. J.* **2003**, *9*, 5708−5723.
(20) Cacchi, S.; Caglioti, L. *Synthesis* **1979**, 64−66.

(21) (a) Bongini, A.; Cianelli, G.; Contento, M.; Manescalchi, F. *Synthesis* **1980**, 143−146. (b) Smith, K.; James, D. M.; Matthews, I.; Bye, M. R. *J. Chem. Soc., Perkin Trans. 1* **1992**, 1877−1878. (c) Parlow, J. J. *Tetrahedron Lett.* **1995**, *36*, 1395−1396.

(22) We have also investigated the use of commercially available perbromide resin **7** (1.0 mmol Br_3/g, Aldrich 33,809-5) for the bromination step. Although the selectivities were similar to the freshly prepared resin, we find that the residence times needed to achieve high conversions were significantly longer. The brominating resin prepared according to our protocol (see Experimental Section for details) remained active for several weeks without losing any activity.

(23) Both sodium azide of >99.99% purity (Aldrich Product 43,845-6) and >99% purity (Aldrich Product 19,993-1), obtained fresh from the supplier, provided good results. Older bottles and/or of lower purity gave unsatisfactory results.

(24) For a recent example of microwave-assisted bromide-azide displacement, see the following: Singh, P. N. D.; Muthukrishnan, S.; Murthy, R. S.; Klima, R. F.; Mandel, S. M.; Hawk, M.; Yarbrough, N.; Gudmundsdottir, A. D. *Tetrahedron Lett.* **2003**, *44*, 9169−9171.

(25) (a) Stadler, A.; Kappe, C. O. *J. Comb. Chem.* **2001**, *3*, 624−630. (b) Kappe, C. O.; Stadler, A. In *Combinatorial Chemistry, Part B*; Bunin, B. B., Morales, G., Eds.; Elsevier: Amsterdam, 2003; Chapter 11, pp 197−223.

(26) Sodium azide is known to form a complex with Cu ions and dimethylformamide (DMF). For details, see: (a) Baruah, S. D.; Dass, N. N. *Makromol. Chem.* **1981**, *182*, 3591−3601. (b) Maggio, F.; Cavasino, F. P. *Ann. Chim.* **1961**, *51*, 1392−1398.

CC0498938