JOC The Journal of Organic Chemistry

ARTICLE

pubs.acs.org/joc

Tandem Catalysis: From Alkynoic Acids and Aryl Iodides to 1,2,3-Triazoles in One Pot

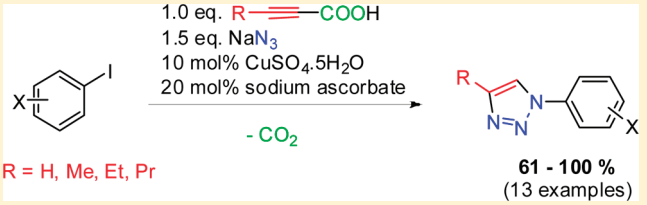
Andrej Kolarovič,*[,†] Michael Schnürch,[‡] and Marko D. Mihovilovic[‡]

[†]Institute of Organic Chemistry, Catalysis and Petrochemistry, Slovak University of Technology, Radlinského 9, 81237 Bratislava, Slovak Republic

[‡]Institute of Applied Synthetic Chemistry, Vienna University of Technology, Getreidemarkt 9/163-OC, 1060 Vienna, Austria

Supporting Information

ABSTRACT: A tandem catalysis protocol based on decarboxylative coupling of alkynoic acids and 1,3-dipolar cycloaddition of azides enables a highly efficient synthesis of a variety of functionalized 1,2,3-triazoles. The three-step, one-pot method avoids usage of gaseous or highly volatile terminal alkynes, reduces handling of potentially unstable and explosive azides to a minimum, and furnishes target structures in excellent yields and a very good purity without the need for additional purification.



INTRODUCTION

Since the first synthesis of an organic compound, synthetic chemists constantly come up with new transformations to allow the construction of almost any desired connection between organic building blocks. However, until recent years, the aspect of environmentally benign reactions was not a major concern in the development of such new transformations. This has certainly changed significantly, and newly developed synthetic methods are evaluated by the synthetic community not only by their usefulness but also by environmental aspects such as atom efficiency, waste production, and energy consumption. In this regard, the combination of two or more synthetic steps into one operation is a very appealing methodology since time, energy, and resources consuming workup and purification steps can be minimized in a synthetic sequence. Additionally, multistep synthesis of complex molecules can be significantly shortened. Tandem catalysis is one of the tools enabling achievement of this goal.[1] Furthermore, placing an emphasis on click chemistry principles in tandem reactions should allow isolation of the target structures in very good purity, avoiding any final purification. The copper(I)-catalyzed 1,3-dipolar cycloaddition of azides and terminal alkynes[2,3] is considered to be the most prominent reaction of the "click" chemistry concept[4] and represents the most straightforward synthesis of 1,2,3-triazoles. This class of valuable compounds has been widely utilized in pharmaceutical, combinatorial, and material chemistry.[5] In recent years, several protocols describing in situ formation of azides have been developed.[6] However, alkynes of low molecular weight are difficult to handle, and their usage under laboratory conditions is somewhat cumbersome due to their low boiling points (Figure 1).[7] The one-pot synthesis of 1,2,3-triazoles from terminal alkynes generated by in situ decarboxylation has not been addressed so far.[8]

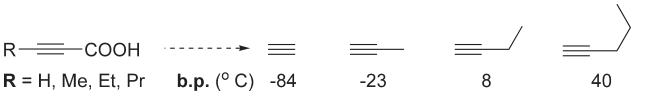


Figure 1. Boiling points of C_2−C_5 terminal alkynes.

Moreover, to ensure a full conversion, one has to use an excess of either gaseous or low-boiling volatile liquid alkyne, thus producing additional waste and decreasing the material efficiency of the overall process. On the other hand, the corresponding alkynoic acids are not volatile, and even propiolic acid, the most simple alkynoic acid, has a very high boiling point (102 °C/267mbar, mp 16−18 °C) and can be easily handled. Additionally, stoichiometric amounts of alkynoic acid should be sufficient, and CO_2 released upon generation of a terminal alkyne in situ can be considered as a harmless human metabolite.

RESULTS AND DISCUSSION

In a quest to develop efficient synthetic protocols, we envisioned that copper(I)-catalyzed decarboxylation of alkynoic acids[9a] ((A), Scheme 1) along with azide formation[10] (B) and their successive fusion to triazoles via 1,3-dipolar cycloaddition[2] (C) might represent an appealing simplification in the synthesis setup and provide much greater efficiency in the formation of 1,4-disubstituted triazoles.

Received: December 19, 2010
Published: March 10, 2011

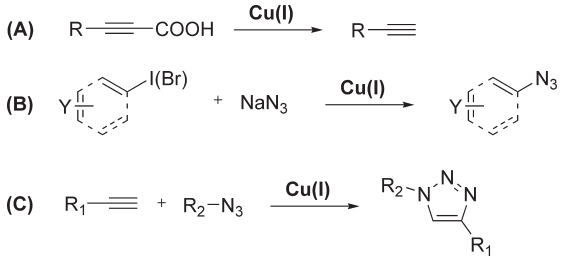
The combination of reactions (B) and (C) in one pot was first realized by Fokin et al.[6a] A series of aryl iodides and alkyl halides (Cl, Br, I) were transformed to the corresponding azides in situ and reacted with various alkynes in good to excellent yield. Organic azides are potentially unstable compounds, and a methodology avoiding their isolation was convenient.[11] It has to be mentioned that in this contribution no gaseous or low boiling alkynes were employed. However, simple acetylene or alkynes of low molecular weight (and therefore also of low boiling point) are often required to get to the desired triazole products. One method to facilitate the usage of short-chained alkynes in click processes could be by substituting them with the corresponding alkynoic acids. Copper-catalyzed decarboxylation of alkynes was recently reported,[9a] and a similar method was applied under reaction conditions compatible with in situ azide formation and triazole formation. We were delighted to observe that only minor modifications of our original decarboxylative protocol[12] were necessary in order to realize a combination of alkynoic acid decarboxylation (A) and azide−alkyne "click chemistry" (C) (Scheme 2).

The target compounds **3** and **5** were obtained in excellent yields. These data suggest the applicability of this protocol for both aryl- and alkyl-substituted alkynoic acids. Having demonstrated the compatibility of decarboxylation and 1,3-dipolar cycloaddition, the next aim was to combine all three steps (A), (B), and (C) in a one-pot protocol. We decided to use a slightly modified procedure described by Fokin et al. for the in situ azide formation.[6a,13] We were pleased to find that under these conditions our one-pot azide formation−decarboxylation−cycloaddition proceeded in excellent yields (Scheme 3).

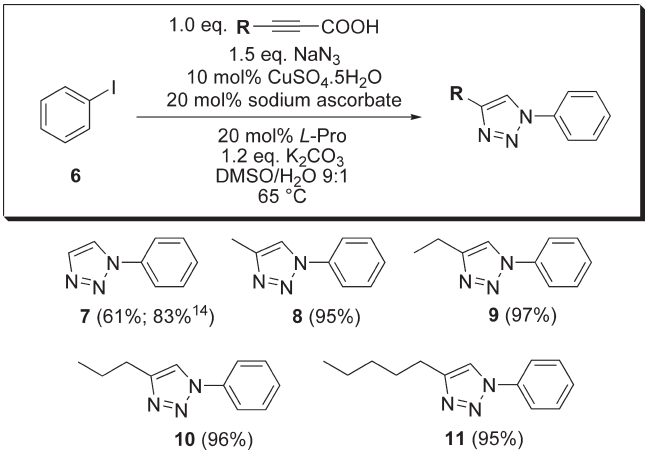
Moreover, in all cases the isolated compounds were of very high purity, and no additional purification was required.[15] Experiments were executed in simple 4 mL vials equipped with a screw-cap septum, and no particular precautions to avoid leakage of generated gases were taken. In the case of triazole **7**, the 61% yield was less satisfactory.[16] Obviously, a free alkyne site in propynoic acid enables coordination to Cu(I) catalyst and subsequent "click" reaction prior to decarboxylation.[17] We observed formation of acid **13** (vide infra) as a side product in a yield of 7%, indicating that complete decarboxylation had not been achieved in this particular example.[18] Both products were of interest to us, since 4,5-unsubstituted triazole **7** represents the simplest example which can be obtained via this protocol and the acid functionality in compound **13** can be used for further modification. Hence, we attempted to find conditions leading to selectivity for one product over the other. For the sake of better yields, we omitted in situ formation of azide **1**, and after a short screening of reaction conditions we devised two complementary protocols enabling either a nondecarboxylative or decarboxylative pathway (Table 1, entries 4 and 6, respectively).

In a control experiment,[19] it was proven that acid **13** itself is not prone to decarboxylation, which indicates that 1-phenyltriazole **7** is formed from phenyl azide and in situ formed acetylene. Under standard "click" conditions (entry 1), acid **13** was isolated as a major product. Our attempt to suppress decarboxylation of acid **12** by adding 2 equiv of AcOH (entry 2) failed, and the overall reactivity was lowered. Chemoselectivity of the nondecarboxylative protocol leading to acid **13** turned out to be rather sensitive to the amount of sodium ascorbate. For instance, usage of 25 mol % of the reagent was already reflected in a partial decarboxylation of **12** and a successive cycloaddition (entry 1), indicating that the decarboxylative process is favored by presence of a base. On the other hand, cutting the amount of sodium ascorbate down to

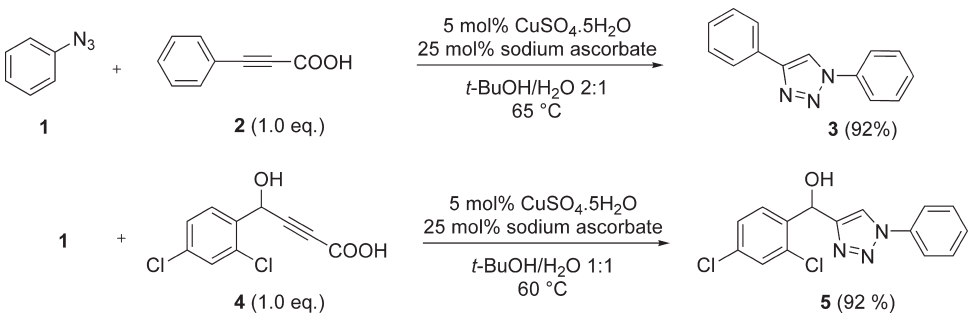
Scheme 1. Copper(I)-Catalyzed Reactions Selected for Tandem Catalysis



Scheme 3. Low Molecular Weight Alkynes Generated in Situ and Utilized in the Synthesis of 1,2,3-Triazoles

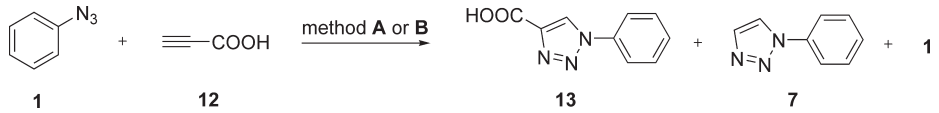


Scheme 2. Copper(I)-Catalyzed Decarboxylation−Cycloaddition Sequence



dx.doi.org/10.1021/jo1024927 |J. Org. Chem. 2011, 76, 2613–2618

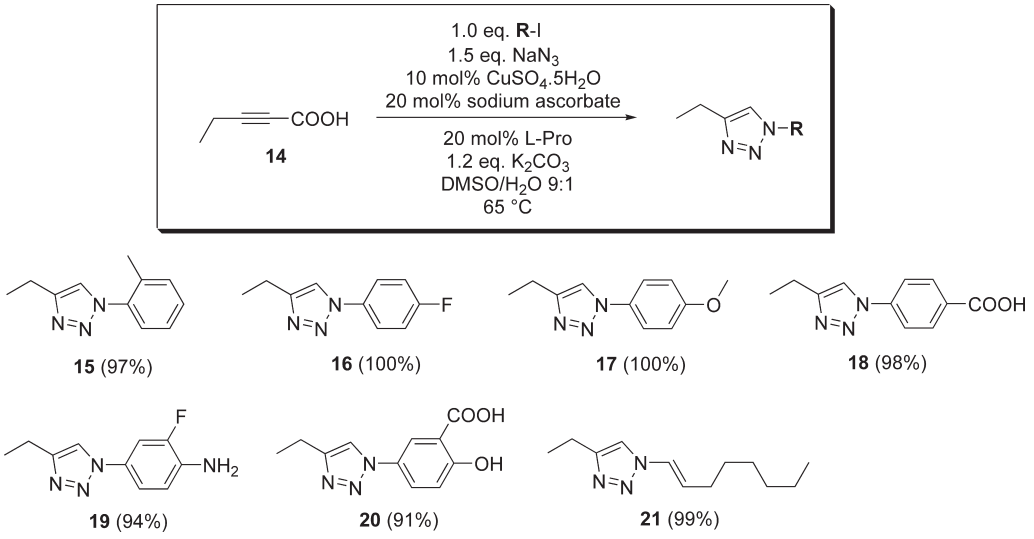
Table 1. Alternation in Reaction Conditions Allows Both Non-decarboxylative and Decarboxylative Pathways



entry	method[a]	modification[b]	time (h)	13[c] (%)	7 (%)	1 (%)
1	**A**		17	62	12	
2	**A**	+ 2 equiv of AcOH	17	41	25	13
3	**A**	+ 0.2 equiv of **12**	21	51	20	
4	**A**	+ 0.2 equiv of **12**, − 15 mol % of Na ascorbate	17	**>99**		
5	**B**		18	22	53	12
6	**B**	+ 0.2 equiv of **12**, + 15 mol % of CuCl	22	*d*	**83**	

[a] Method A: 1.0 equiv of **12**, 5 mol % of $CuSO_4 \cdot 5H_2O$, 25 mol % of sodium ascorbate, *t*-BuOH/H_2O 1:1, rt. Method B: 1.0 equiv of **12**, 5 mol % of CuCl, 2.0 equiv of Et_3N, MeCN, rt. [b] Reagents added ("+") or cut ("−") in addition to the amounts reported in the corresponding method. [c] Yields were determined for crude isolated mixtures by means of ^1H NMR. [d] Undetermined, workup with satd aq $NaHCO_3$.

Scheme 4. Modifications of the Iodide Coupling Partner for in Situ Azide Formation

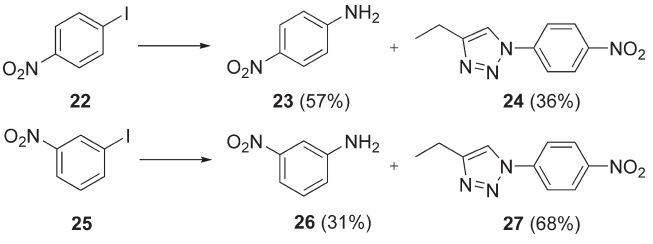


10 mol % in combination with a slight excess of acid **12** afforded triazole **13** in almost quantitative yield (entry 4). As we described previously,[9a] decarboxylation of 2-alkynoic acids is efficiently catalyzed by CuCl−Et_3N, which served as basis for conditions leading to **7** selectively (entry 6). However, 20 mol % of the catalyst had to be used to achieve satisfactory chemoselectivity.

Having investigated the scope of the alkynoic acid coupling partner, a series of different aryl and alkenyl iodides were used for the azide forming step and butynoic acid **14** for the in situ generation of 1-butyne (Scheme 4).

The decarboxylative protocol was found to tolerate a variety of structural patterns and yielded almost quantitative amounts of the target structures in excellent purity.[15,20] Substrates bearing either electron-donating (products **15** and **17**) or -withdrawing groups (products **16** and **18**) or even one of each type (products **19** and **20**) underwent smooth conversion, and the method turned out to be insensitive to unprotected carboxylic acid, amino, and phenol groups. As expected, decarboxylation occurred solely at alkynoic acids and was not observed for benzoic acid subunits of structures **18** and **20**. However, attempts to employ substrates **22** and **25** containing a strong electron-withdrawing nitro group were less satisfactory, and the reaction yielded significant amounts of related anilines **23** and **26**, respectively (Scheme 5).

Scheme 5. Unexpected Formation of Nitroanilines 23 and 26



First we hypothesized that a collapse of a triazole ring was responsible for the side reaction, as this was previously observed in case of sulfonyl azides, i.e., azides substituted with an

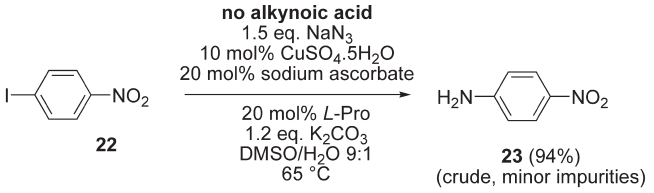
dx.doi.org/10.1021/jo1024927 |*J. Org. Chem.* 2011, 76, 2613–2618

electron-withdrawing group.[21] However, experiments with exclusion of 2-pentynoic acid **14** proved that 1-butyne was not responsible for reduction to anilines, and a different reaction mechanism was involved (Scheme 6).

Moreover, additional screening of reaction parameters revealed that neither sodium ascorbate nor DMSO was necessary for a complete conversion to aniline **23**. A closely related reaction was reported by Peng et al.,[22] who observed unexpected reduction of azide **28** to amine **29** in the presence of Cu(II)−sodium ascorbate (Scheme 7).

The authors reported that in the absence of sodium ascorbate, azide **28** could not be reduced to amine **29** in the presence of Cu(I) catalysts, which is in contrast to our observations. Very recently, three articles describing copper-mediated aminations of aryl halides utilizing azides as an amino source appeared.[23] However, the mechanism of the redox process was not disclosed. On the basis of our investigations, we hypothesize that a strong electron-withdrawing nitro group makes 1-azido-4-nitrobenzene (formed in situ) prone to reduction, and water serves as a hydrogen donor required for the transformation to 4-nitroaniline **23** (Scheme 6). On the basis of this assumption, we devised a one-pot procedure using dry DMSO, which furnished triazole **24** in a far better yield, although aniline **23** was still present as a minor side product (Scheme 8; compare with Scheme 5).

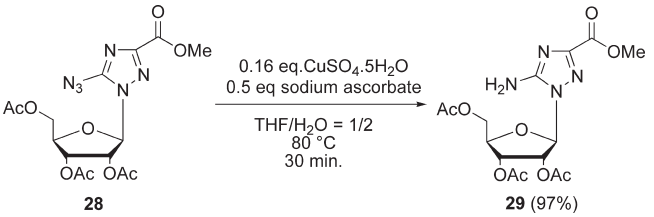
Scheme 6. Reaction with Exclusion of 2-Pentynoic Acid, Alternation of Reaction Parameters



DMF/H_2O 9:1 instead of DMSO/H_2O 9:1 — 96% (crude)

10 mol%CuCl instead of 10 mol% $CuSO_4.5H_2O$, no sodium ascorbate — 93% (crude)

Scheme 7. Unexpected Reduction of Azide 28 Reported by Peng et al.[22]



On the other hand, utilization of $CuSO_4 \cdot 5H_2O$/sodium ascorbate in dry DMSO results in a much less appealing ratio of **24**/**23** 56:44, which might be attributed to the water present in the catalyst. Investigations regarding this transformation are ongoing.

CONCLUSION

In summary, the present study illustrates the feasibility and broad applicability of decarboxylative Cu(I)-catalyzed azide−alkyne cycloadditions under tandem catalysis conditions. Moreover, reaction setup and execution of the three-step, one-pot sequence is simple and provides the target 1,2,3-triazoles in excellent yields and purity. Additionally, this transformation tolerates a wide range of functional groups on the azide part, and also a series of alkynoic acids of different chain length could be applied. 1-Azido-4-nitrobenzene formed in situ underwent a reductive pathway to 4-nitroaniline **23**; however, exclusion of water enabled synthesis of the desired triazole **24** in a good yield. The further application of alkynoic acids as easy to handle masked alkynes is under investigation in our laboratory.

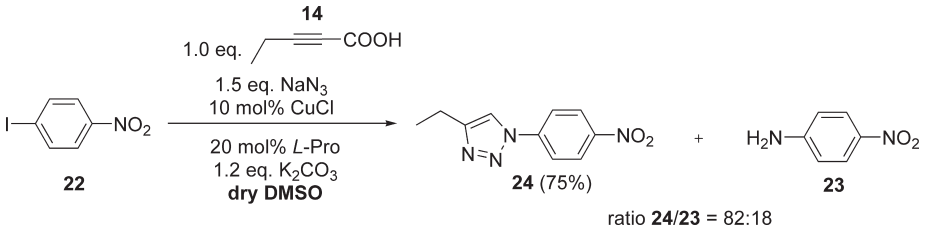
EXPERIMENTAL SECTION

General Methods. ^{1}H NMR and ^{13}C NMR spectra were measured at 200 and 50 MHz, respectively, with TMS as internal standard. Melting points are uncorrected. All reactions were carried under ambient atmosphere, in a closed vial. The reagents were used directly as obtained commercially.

1,4-Diphenyl-1*H*-1,2,3-triazole (3)[24]**.** $CuSO_4 \cdot 5H_2O$ (8.5 mg, 5 mol %, 0.034 mmol), sodium ascorbate (34 mg, 25 mol %, 0.17 mmol), acid **2** (100 mg, 0.684 mmol), water (0.5 mL), azidobenzene **1** (87 mg, 1.0 equiv; 94% purity), and *t*-BuOH (1 mL) were sequentially added to a 4 mL vial. The vial was closed with a screw-cap containing a once perforated septum, enabling release of overpressure. The mixture was stirred at 65 °C for 16 h, diluted with ethyl acetate (60 mL), washed with brine (10 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to afford 139 mg (92%) of triazole **3** as a pale yellow solid; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.33−7.59 (m, 6H), 7.78−7.82 (m, 2H), 7.90−7.94 (m, 2H), 8.20 (s, 1H); MS (EI) m/z 221.05 [M^+].

(2,4-Dichlorophenyl)(1-phenyl-1*H*-1,2,3-triazol-4-yl)methanol (5). $CuSO_4 \cdot 5H_2O$ (2.5 mg, 5 mol %, 0.010 mmol), sodium ascorbate (10 mg, 25 mol %, 0.051 mmol), acid **4** (50 mg, 0.204 mmol), water (0.5 mL), azidobenzene **1** (26 mg, 1.0 equiv; 94% purity), and *t*-BuOH (0.5 mL) were sequentially added to a 4 mL vial. The vial was closed with a screw-cap containing a once perforated septum, enabling release of overpressure. The mixture was stirred at 60 °C for 17 h and then was quenched with water (3 mL), sonicated (3 min), and stirred at rt for 0.5 h. The precipitated product was filtered off and dried under reduced pressure to afford 60 mg (92%) of triazole **5** as a pale-brown powder: ^{1}H NMR (200 MHz, $CDCl_3$) δ 4.73 (bs, 1H), 6.43 (s, 1H), 7.29−7.51 (m, 5H), 7.62−7.67 (m, 3H), 7.76 (d, J = 8.2 Hz, 1H); ^{1}H

Scheme 8. Optimized Conditions for a One-Pot Synthesis of Triazole 24



dx.doi.org/10.1021/jo1024927 |J. Org. Chem. 2011, 76, 2613–2618

NMR (200 MHz, DMSO-d_6) δ 6.16 (d, J = 4.6 Hz, 1H), 6.49 (d, J = 4.8 Hz, 1H), 7.41−7.59 (m, 5H), 7.75−7.86 (m, 3H), 8.58 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 65.0, 119.7, 120.5, 127.6, 128.9, 128.9, 129.2, 129.7, 132.7, 134.2, 136.7, 138.0, 150.0; ESI-MS (m/z) calcd for $C_{15}H_{12}N_3OCl_2$ $[M + H]^+$ 320.0352, found 320.0357.

General Procedure for Synthesis of Triazoles 7−11, 15−17, 19, and 21. L-Proline (16 mg, 20 mol %, 0.14 mmol), $CuSO_4 \cdot 5H_2O$ (17 mg, 10 mol %, 0.068 mmol), sodium ascorbate (27 mg, 20 mol %, 0.14 mmol), NaN_3 (67 mg, 1.5 equiv, 1.0 mmol), K_2CO_3 (114 mg, 1.20 equiv, 0.825 mmol), alkynoic acid (1.0 equiv, 0.69 mmol), aryl (alkenyl) iodide (1.0 equiv, 0.69 mmol), DMSO (2.25 mL), and water (0.25 mL) were sequentially added to a 4 mL vial. The vial was closed with a screw-cap containing a once-perforated septum, enabling release of overpressure. The mixture was stirred slowly (250 rpm) at 65 °C for 20−24 h and then added to a mixture of concd NH_4OH (5 mL), water (10 mL), and ethyl acetate (40 mL). The aqueous phase was extracted with ethyl acetate (20 mL), and the combined organic extracts were washed with brine (4 × 10 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to afford the corresponding triazole.

1-Phenyl-1*H*-1,2,3-triazole (7):[7] pale brown solid (61%); mp =53 °C (*n*-hexane; colorless fine crystals); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.39−7.56 (m, 3H), 7.72−7.76 (m, 2H), 7.84 (s, 1H), 8.00 (s, 1H); ^{1}H NMR (200 MHz, DMSO-d_6) δ 7.45−7.64 (m, 3H), 7.89−7.93 (m, 2H), 7.98 (s, 1H), 8.83 (s, 1H); MS (EI) m/z 145.04 $[M^+]$; ESI-MS (m/z) calcd for $C_8H_8N_3$ $[M + H]^+$ 146.0713, found 146.0712.

4-Methyl-1-phenyl-1*H*-1,2,3-triazole (8):[25] yellow solid (95%); mp = 69−71 °C (petroleum ether; colorless needles); ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.44 (s, 3H), 7.37−7.54 (m, 3H), 7.69−7.73 (m, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 10.7, 119.3, 120.2, 128.3, 129.5, 137.0, 143.9; MS (EI) m/z 159.05 $[M^+]$; ESI-MS (m/z) calcd for $C_9H_{10}N_3$ $[M + H]^+$ 160.0869, found 160.0867.

4-Ethyl-1-phenyl-1*H*-1,2,3-triazole (9): yellow liquid (97%); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.34 (t, J = 7.6 Hz, 3H), 2.84 (q, J = 7.6 Hz, 2H), 7.37−7.54 (m, 3H), 7.68−7.74 (m, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 13.5, 18.9, 118.4, 120.1, 128.2, 129.5, 137.1, 150.3; MS (EI) m/z 173.09 $[M^+]$; ESI-MS m/z calcd for $C_{10}H_{12}N_3$ $[M + H]^+$ 174.1026, found 174.1028.

4-Propyl-1-phenyl-1*H*-1,2,3-triazole (10): pale brown amorphous solid (96%); ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.95 (t, J = 7.4 Hz, 3H), 1.76 (sextet, J = 7.4 Hz, 2H), 2.71 (t, J = 7.4 Hz, 2H), 7.29−7.46 (m, 3H), 7.64−7.72 (m, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 13.6, 22.4, 27.4, 118.7, 120.0, 128.1, 129.4, 137.0, 148.7; MS (EI) m/z = 187.08 $[M^+]$; ESI-MS m/z calcd for $C_{11}H_{14}N_3$ $[M + H]^+$ 188.1182, found 188.1186.

4-Pentyl-1-phenyl-1*H*-1,2,3-triazole (11): yellow oil (95%); ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.91 (t, J = 6.9 Hz, 3H), 1.35−1.42 (m, 4H), 1.74 (m, 2H), 2.79 (t, J = 7.7 Hz, 2H), 7.37−7.54 (m, 3H), 7.70−7.75 (m, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 13.8, 22.2, 25.4, 28.9, 31.2, 118.7, 120.1, 128.2, 129.4, 137.0, 148.9; MS (EI) m/z = 215.12 $[M^+]$; ESI-MS m/z calcd for $C_{13}H_{18}N_3$ $[M + H]^+$ 216.1495, found 216.1501.

4-Ethyl-1-(2-methylphenyl)-1*H*-1,2,3-triazole (15): pale green oil (97%); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.35 (t, J = 7.5 Hz, 3H), 2.21 (s, 3H), 2.85 (q, J = 7.6 Hz, 2H), 7.30−7.39 (m, 4H), 7.47 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 13.4, 17.6, 18.7, 121.7, 125.6, 126.4, 129.3, 131.1, 133.3, 136.5, 149.3; ESI-MS m/z calcd for $C_{11}H_{14}N_3$ $[M + H]^+$ 188.1182, found 188.1186.

4-Ethyl-1-(4-fluorophenyl)-1*H*-1,2,3-triazole (16): pale yellow solid (100%); mp =74−75 °C (*n*-hexane; pale brown needles); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.26 (t, J = 7.6 Hz, 3H), 2.75 (q, J = 7.6 Hz, 2H), 7.11 (m, 2H), 7.59−7.66 (m, 2H), 7.68 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 13.4, 18.8, 116.3 (d, J = 25 Hz), 118.6, 122.1 (d, J = 10 Hz), 133.4, 150.4, 162.0 (d, J = 245 Hz); ESI-MS m/z calcd for $C_{10}H_{11}N_3F$ $[M + H]^+$ 192.0932, found 192.0935.

4-Ethyl-1-(4-methoxyphenyl)-1*H*-1,2,3-triazole (17): pale yellow solid (100%); mp = 63 °C (*n*-hexane; colorless fine crystals); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.22 (t, J = 7.5 Hz, 3H), 2.70 (q, J = 7.6 Hz, 2H), 3.72 (s, 3H), 6.86 (d, J = 8.8 Hz, 2H), 7.49 (d, J = 8.8 Hz, 2H), 7.60 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 13.4, 18.8, 55.3, 114.3, 118.5, 121.6, 130.4, 150.0, 159.2; ESI-MS m/z calcd for $C_{11}H_{14}N_3O$ $[M + H]^+$ 204.1131, found 204.1137.

4-(4-Ethyl-1*H*-1,2,3-triazol-1-yl)-2-fluoroaniline (19): brown oil (94%); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.31 (t, J = 7.6 Hz, 3H), 2.80 (q, J = 7.6 Hz, 2H), 3.95 (bs, 2H), 6.84 (dd, J = 8.8, 8.8 Hz, 1H), 7.21−7.27 (m, 1H), 7.39 (dd, J = 2.4, 11.4 Hz, 1H), 7.59 (s, 1H) ; ^{13}C NMR (50 MHz, $CDCl_3$) δ 13.4, 18.8, 108.5 (d, J = 23.0 Hz), 116.5 (d, J = 5.0 Hz), 116.6 (d, J = 3.0 Hz), 118.5, 127.9 (d, J = 9.0 Hz), 135.1 (d, J = 12.5 Hz), 150.1, 150.7 (d, J = 240 Hz); ESI-MS m/z calcd for $C_{10}H_{12}N_4F$ $[M + H]^+$ 207.1041, found 207.1044.

(*E*)-4-Ethyl-1-(oct-1-enyl)-1*H*-1,2,3-triazole (21): yellow liquid (99%); ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.88 (m, 3H), 1.27 (m, 9H), 1.45 (m, 2H), 2.20 (ddt, J = 1.4, 7.2, 7.2 Hz, 2H), 2.75 (q, J = 7.6 Hz, 2H), 6.13 (dt, J = 7.4, 14.2 Hz, 1H), 7.07 (dt, J = 1.4, 14.4 Hz, 1H), 7.46 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 13.4, 13.8, 18.8, 22.3, 28.5, 28.7, 29.4, 31.4, 117.2, 122.3, 124.1, 149.6; ESI-MS m/z calcd for $C_{12}H_{22}N_3$ $[M + H]^+$ 208.1808, found 208.1817.

1-Phenyl-1*H*-1,2,3-triazole-4-carboxylic acid (13). $CuSO_4 \cdot 5H_2O$ (20 mg, 5 mol %, 0.081 mmol), sodium ascorbate (32 mg, 10 mol %, 0.16 mmol), water (0.5 mL), azidobenzene (207 mg, 1.0 equiv, 1.63 mmol; 94% purity), *t*-BuOH (0.5 mL), and propiolic acid (127 μL, 1.2 euiv., 1.96 mmol; 95% purity) were sequentially added to a 4 mL vial. The vial was closed with a screw-cap containing a septum. The mixture was mildly stirred (250 rpm) at rt for 21 h. It was then quenched with satd $NaHCO_3$ (25 mL), washed with diisopropyl ether (20 mL), acidified with 0.5 M aq solution of H_2SO_4 ,and extracted with ethyl acetate (80 mL and 2 × 40 mL). The combined organic solutions were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to afford acid **13** as a pale yellow solid (309 mg, 100%): mp = 132−134 °C (toluene/*n*-hexane); ^{1}H NMR (200 MHz, DMSO-d_6) δ = 7.48−7.65 (m, 3H), 7.97 (d, J = 7.6 Hz, 2H), 9.40 (s, 1H), 13.34 (s, 1H); ^{13}C NMR (50 MHz, acetone-d_6) δ = 122.4, 128.4, 131.0, 131.6, 138.5, 142.3, 162.7; ESI-MS m/z calcd for $C_9H_8N_3O_2$ $[M + H]^+$ 190.0611, found 190.0620.

General Procedure for Synthesis of Triazoles 18 and 20. The reaction was setup as above, but 2.20 equiv (208 mg, 1.51 mmol) of K_2CO_3 was used. Workup: the mixture was added to a solution of 0.5 M H_2SO_4 (6 mL), brine (9 mL), and ethyl acetate (40 mL). The aqueous phase was extracted with ethyl acetate (20 mL), and the combined organic extracts were washed with brine (4 × 10 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to afford the corresponding triazole.

4-(4-Ethyl-1*H*-1,2,3-triazol-1-yl)benzoic acid (18): pale brown solid (98%); mp = 280−284 °C (EtOH; sublimation upon heating); ^{1}H NMR (200 MHz, DMSO-d_6) δ 1.27 (t, J = 7.6 Hz, 3H), 2.74 (q, J = 7.6 Hz, 2H), 8.03 (d, J = 8.8 Hz, 2H), 8.13 (d, J = 8.8 Hz, 2H), 8.70 (s, 1H), 13.21 (bs, 1H); ^{13}C NMR (50 MHz, DMSO-d_6) δ 13.3, 18.5, 119.3, 119.7, 130.2, 131.0, 139.7, 149.9, 166.4; ESI-MS m/z calcd for $C_{11}H_{12}N_3O_2$ $[M + H]^+$ 218.0924, found 218.0920.

5-(4-Ethyl-1*H*-1,2,3-triazol-1-yl)-2-hydroxybenzoic acid (20): pale brown solid (91%); mp = 229−234 °C (EtOH/H_2O); ^{1}H NMR (200 MHz, DMSO-d_6) δ 1.22 (t, J = 7.6 Hz, 3H), 2.67 (q, J = 7.6 Hz, 2H), 7.08 (d, J = 9.0 Hz, 1H), 7.92 (dd, J = 2.6, 8.8 Hz, 1H), 8.17 (d, J = 2.6 Hz, 1H), 8.44 (s, 1H), 11.76 (bs, 2H); ^{13}C NMR (50 MHz, DMSO-d_6): δ = 13.5, 18.6, 113.9, 118.4, 119.7, 121.4, 127.1, 128.8, 149.5, 160.7, 171.2; ESI-MS m/z calcd for $C_{11}H_{12}N_3O_3$ $[M + H]^+$ 234.0873, found 234.0885.

4-Nitroaniline (23). Prepared by a modified general procedure for triazoles **7**−**11**, **15**−**17**, **19**, and **21**; the modification: no alkynoic acid was added: brown solid (94%); ^{1}H NMR (200 MHz, $CDCl_3$) δ = 4.38 (bs, 2H), 6.62 (d, J = 9.2 Hz, 2H), 8.07 (d, J = 9.0 Hz, 2H).

4-Ethyl-1-(4-nitrophenyl)-1*H*-1,2,3-triazole (24). Prepared by a modified general procedure for triazoles **7**−**11**, **15**−**17**, **19**, and **21**; the following modifications were undertaken: CuCl (7 mg, 10 mol %) and DMSO (2.5 mL) were used instead of $CuSO_4 \cdot 5H_2O$ and aqueous DMSO, respectively, and sodium ascorbate was not added: pale yellow solid (75%); mp = 144−145 °C (toluene); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.35 (t, J = 7.6 Hz, 3H), 2.85 (q, J = 7.6 Hz, 2H), 7.86 (s, 1H), 7.96 (d, J = 9.0 Hz, 2H), 8.38 (d, J = 9.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.5, 19.0, 118.6, 120.2, 125.5, 141.4, 146.9, 151.6; ESI-MS m/z calcd for $C_{10}H_{11}N_4O_2$ $[M + H]^+$ 219.0877, found 219.0894.

■ ASSOCIATED CONTENT

Supporting Information. ^{1}H and ^{13}C NMR spectra of compounds **3**, **5**, **8**−**11**, **13**, **15**−**21**, and **24**. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author
*E-mail: andrej.kolarovic@stuba.sk.

■ ACKNOWLEDGMENT

This work was supported by VEGA under contract no. 1/0340/10 and by the Slovak Academic Information Agency (Action Austria-Slovakia).

■ REFERENCES

(1) Selected reviews: (a) Felpin, F. X.; Fouquet, E. *ChemSusChem* **2008**, *1*, 718–724. (b) Wasilke, J. Ch.; Obrey, S. J.; Baker, R. T.; Bazan, G. C. *Chem. Rev.* **2005**, *105*, 1001–1020. (c) Fogg, D. E.; Dos Santos, E. N. *Coord. Chem. Rev.* **2004**, *248*, 2365–2379.

(2) (a) Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2002**, *41*, 2596–2599. (b) Tornøe, C. W.; Christensen, C.; Meldal, M. *J. Org. Chem.* **2002**, *67*, 3057–3064.

(3) For examples of ruthenium-catalyzed azide−alkyne cycloaddition, see: (a) Tam, A.; Arnold, U.; Soellner, M. B.; Raines, R. T. *J. Am. Chem. Soc.* **2007**, *129*, 12670–12671. (b) Boren, B. C.; Narayan, S.; Rasmussen, L. K.; Zhang, L.; Zhao, H.; Lin, Z.; Jia, G.; Fokin, V. V. *J. Am. Chem. Soc.* **2008**, *130*, 8923–8930.

(4) Kolb, H. C.; Finn, M. G.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2001**, *40*, 2004–2021.

(5) Selected reviews: (a) Holub, J. M.; Kirshenbaum, K. *Chem. Soc. Rev.* **2010**, *39*, 1325–1337. (b) Meldal, M.; Tornøe, C. W. *Chem. Rev.* **2008**, *108*, 2952–3015. (c) Spiteri, A. D.; Moses, J. E. *ChemMedChem* **2008**, *3*, 715–723. (d) Wu, P.; Fokin, V. V. *Aldrichim. Acta* **2007**, *40*, 7–17.

(6) For example: (a) Feldman, A. K.; Colasson, B.; Fokin, V. V. *Org. Lett.* **2004**, *6*, 3897–3899. (b) Chittaboina, S.; Xie, F.; Wang, Q. *Tetrahedron Lett.* **2005**, *46*, 2331–2336. (c) Ceylan, S.; Klande, T.; Vogt, C.; Friese, C.; Kirschning, A. *Synlett* **2010**, 2009–2013.

(7) "Click" approach using acetylene gas: Wu, L. Y.; Xie, Y. X.; Chen, Z. S.; Niu, Y. N.; Liang, Y. M. *Synlett* **2009**, 1453–1456.

(8) Examples of in situ desilylation of TMS-alkynes and consecutive cycloaddition with an azide: (a) Aucagne, V.; Leigh, D. A. *Org. Lett.* **2006**, *8*, 4505–4507. (b) Hu, M.; Li, J.; Yao, S. Q. *Org. Lett.* **2008**, *10*, 5529–5531. (c) Fletcher, J. T.; Waltz, S. E.; Keeney, M. E. *Tetrahedron Lett.* **2008**, *49*, 7030–7032. (d) Fiandanese, V.; Bottalico, D.; Marchese, G.; Punzi, A.; Capuzzolo, F. *Tetrahedron* **2009**, *65*, 10573–10580. (e) Beltrán, E.; Serrano, J. L.; Sierra, T.; Giménez, R. *Org. Lett.* **2010**, *12*, 1404–1407. (f) Cuevas, F.; Oliva, A. I.; Pericàs, M. A. *Synlett* **2010**, 1873–1877.

(9) (a) Kolarovič, A.; Fáberová, Z. *J. Org. Chem.* **2009**, *74*, 7199–7202. Additional examples of decarboxylative couplings of alkynoic acids:(b) Moon, J.; Jang, M.; Nam, H.; Ju, J.; Moon, J. H.; Jung, H. M.; Lee, S. *Org. Lett.* **2008**, *10*, 945–948. (c) Moon, J.; Jang, M.; Lee, S. *J. Org. Chem.* **2009**, *74*, 1403–1406. (d) Kim, H.; Lee, P. H. *Adv. Synth. Catal.* **2009**, *351*, 2827–2832. (e) Yu, M.; Pan, D.; Jia, W.; Chen, W.; Jiao, N. *Tetrahedron Lett.* **2010**, *51*, 1287–1290. (f) Jia, W.; Jiao, N. *Org. Lett.* **2010**, *12*, 2000–2003. (g) Feng, Ch.; Loh, T. P. *Chem. Commun.* **2010**, *46*, 4779–4781. (h) Zhang, W. W.; Zhang, X. G.; Li, J. H. *J. Org. Chem.* **2010**, *75*, 5259–5264. (i) Park, K.; Bae, G.; Moon, J.; Choe, J.; Song, K. H.; Lee, S. *J. Org. Chem.* **2010**, *75*, 6244–6251. (j) Park, K.; Bae, G.; Park, A.; Kim, Y.; Choe, J.; Song, K. H.; Lee, S. *Tetrahedron Lett.* **2011**, *52*, 576–580. Recent review on decarboxylative coupling reactions: (k) Gooβen, L. J.; Collet, F.; Gooβen, K. *Isr. J. Chem.* **2010**, *50*, 617–629.

(10) Zhu, W.; Ma, D. *Chem. Commun.* **2004**, 888–889.

(11) Scriven, E. F. V.; Turnbull, K. *Chem. Rev.* **1988**, *88*, 297–368.

(12) Here we were inspired by the original paper of Sharpless and Fokin;[2a] in our original work,[9a] decarboxylation of alkynoic acids was accomplished by 5 mol % of CuCl/3 equiv of Et_3N in MeCN at 60 °C.

(13) The difference is that Fokin et al. used 1.2 equiv of NaN_3 (versus 1.5 equiv of NaN_3) and 0.2 equiv of Na_2CO_3 (versus 1.2 equiv of K_2CO_3).

(14) Yield obtained under modified reaction conditions, starting from azidobenzene **1** (Table 1, entry 6).

(15) In the Supporting Information we provide spectra of crude products.

(16) Slightly better yields of 64−71% were observed when Cs_2CO_3 was employed instead of K_2CO_3 or if iodobenzene was added with a 2 h delay (66−68%).

(17) Illustrative Cu(I)-catalyzed "click" reactions of propynoic acid: (a) Xie, J.; Seto, C. T. *Bioorg. Med. Chem.* **2007**, *15*, 458–473. (b) Mindt, T. L.; Schibli, R. *J. Org. Chem.* **2007**, *72*, 10247–10250. (c) Maisonial, A.; Serafin, P.; Traikia, M.; Debiton, E.; Thery, V.; Aitken, D. J.; Lemoine, P.; Viossat, B.; Gautier, A. *Eur. J. Inorg. Chem.* **2008**, 298–305. (d) White, J. R.; Price, G. J.; Schiffers, S.; Raithby, P. R.; Frost, C. G.; Plucinski, P. K. *Tetrahedron Lett.* **2010**, *51*, 3913–3917.

(18) Purity of triazole **7** was not compromised since during a basic workup acid **13** remained in the aqueous phase.

(19) Stirring of acid **13** with 20 mol % of CuCl/2.0 equiv of Et_3N in MeCN at rt for 3 days did not furnish any detectable amount of 1-phenyltriazole **7**.

(20) Compound **20** was slightly more contaminated with byproduct.

(21) For the most recent review, see: Lu, P.; Wang, Y. *Synlett* **2010**, 165–173. Related calculations: Yoo, E. J.; Ahlquist, M.; Kim, S. H.; Bae, I.; Fokin, V. V.; Sharpless, K. B.; Chang, S. *Angew. Chem., Int. Ed.* **2007**, *46*, 1730–1733.

(22) Xia, Y.; Li, W.; Qu, F.; Fan, Z.; Liu, X.; Berro, Ch.; Rauzy, E.; Peng, L. *Org. Biomol. Chem.* **2007**, *5*, 1695–1701.

(23) (a) Monguchi, Y.; Maejima, T.; Mori, S.; Maegawa, T.; Sajiki, H. *Chem.—Eur. J.* **2010**, *16*, 7372–7375. (b) Zhao, H.; Fu, H.; Qiao, R. *J. Org. Chem.* **2010**, *75*, 3311–3316. (c) Markiewicz, J. T.; Wiest, O.; Helquist, P. *J. Org. Chem.* **2010**, *75*, 4887–4890.

(24) Tao, Ch. Z.; Cui, X.; Li, J.; Liu, A. X.; Liu, L.; Guo, Q. X. *Tetrahedron Lett.* **2007**, *48*, 3525–3529.

(25) Raghavendra, M. S.; Lam, Y. *Tetrahedron Lett.* **2004**, *45*, 6129–6132.