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Cu(I)-catalyzed one-pot decarboxylation-alkynylation reactions on 1,2,3,4-tetrahydroisoquinolines and one-pot synthesis of triazolyl-1,2,3,4-tetrahydroisoquinolines

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ABSTRACT

A facile and efficient method to introduce alkyne groups to the C-1 position of biologically interesting 1,2,3,4-tetrahydroisoquinolines via direct C—H-functionalization is reported. Various alkynylated N-substituted 1,2,3,4-tetrahydroisoquinolines could be obtained by using copper(I)-chloride as catalyst, alkynoic acids as alkyne source and t-BuOOH as oxidant, in a one-pot two-step decarboxylation- alkynylation reaction in moderate to high yields. Furthermore, a one-pot protocol of a three-step decarboxylation-alkynylation-1,3-dipolar cycloaddition reaction leading to 1-triazolyl-tetrahydroisoquinolines was developed, a hitherto unknown reaction cascade.

1. Introduction

The structural motif of 1,2,3,4-tetrahydroisoquinoline (TIQ) is present in many natural products, such as in mammalian alkaloids (e.g. salsoline carboxylic acid) [1,2], the ecteinascidin family [3–6], spiro-benzoisoquinoline alkaloids (parfumine) [7], and cactus alkaloids [8]. Some derivatives have been determined as pharmacologically active, showing antitumor [9] or anti-HIV activities [10,11], as well as playing an important role in the research to find a treatment for Parkinson 's disease [12,13]. More specifically, in recent years, examples of in position 1 alkynylated TIQs displaying biological activity have been reported repeatedly (Fig. 1). For example, compound **I** was synthesized to target microtubule polymerization [14] and compounds **II** and **III** have been reported as sirtuin inhibitors for treating viral infections [15,16].

Since the biologically and pharmaceutically interesting TIQ derivatives mostly carry a substituent in C1-position, it is of high interest to introduce various functional groups into this position. Classical synthetic routes, such as the Pictet-Spengler, Bischler-Napieralski and Pommeranz-Fritsch reactions [17] have been successful in the synthesis of TIQs for many years. However, the trend in synthetic chemistry goes into the direction of functionalizing simple scaffolds to get to the desired (hetero)cyclic compounds rather than building up the ring system for each compound separately. Furthermore, due to the trend to increase atom efficiency in synthetic processes, direct functionalization reactions of C—H bonds manifested themselves as highly desirable transformations [18–20]. One such method is cross-dehydrogenative-coupling [21,22] which stirred a lot of attention in recent years. Various methods such as alkynylation [23], indolation [24], arylation [25], methoxylation [26], phosphonation [27], cyanation [27,28], and introduction of nitroalkanes [27,29], or malonic esters [30] to the C-1 position of N-substituted TIQs have been reported. The alkyne functionality is here of special interest since the triple bond can be further transformed to other functional groups. Although good results have been reported in all cases, alkynylation reactions on TIQ (Scheme 1, upper part) have only been performed with long alkyl chains (C > 6) or aromatic or bulky substituents, and the substrate scope is limited to *N*-phenyl-, *N*-4-methoxyphenyl- (PMP), and *N*-2-methoxyphenyl-TIQs (OMP) [23]. One reason for that is for sure the fact that shorter chain alkynes are quite volatile and hence difficult to handle (1-pentyne is the shortest 1-alkyne which is liquid at room temperature with a boiling point of 40 °C). However, especially a

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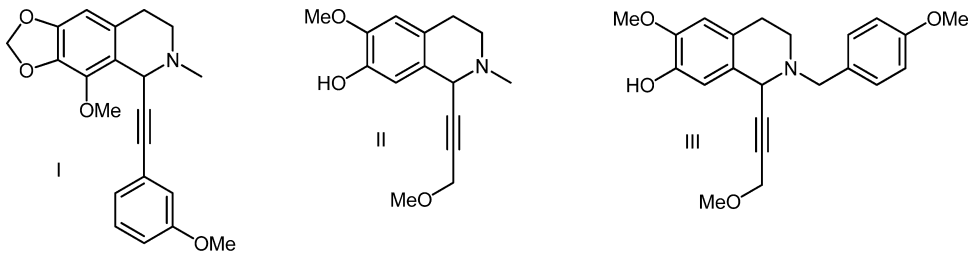
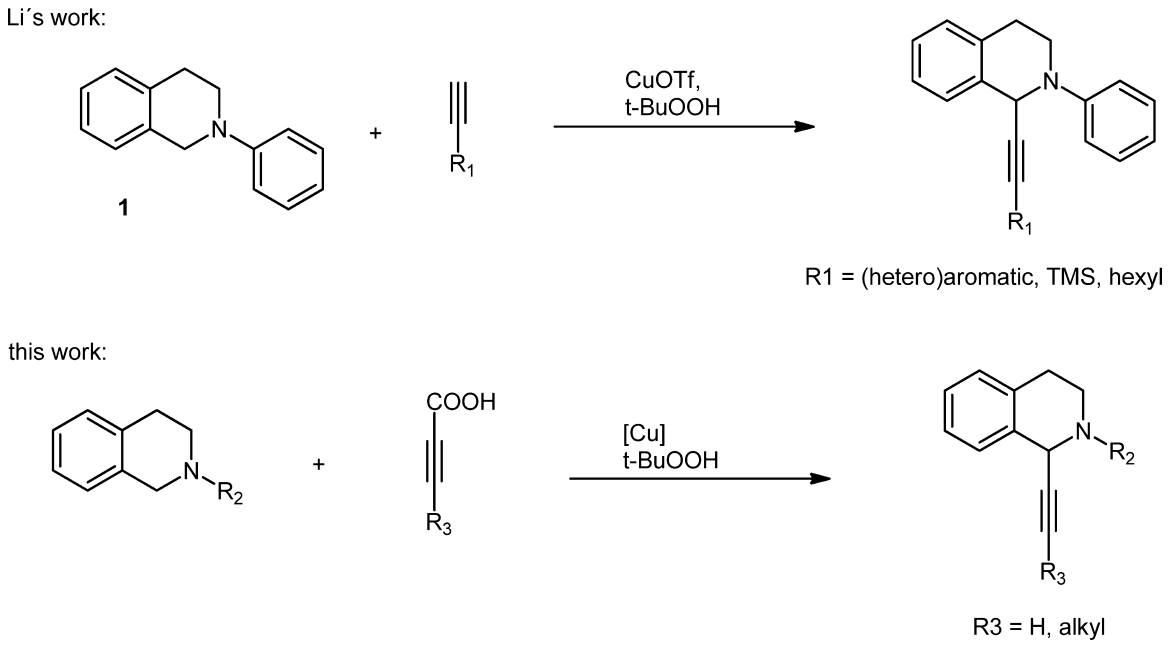


Fig. 1. Examples for 1-alkynylated TIQs displaying biological activity.



Scheme 1. Copper-catalyzed alkynylation of 1,2,3,4-tetrahydrosioquinolines.

terminal alkyne functionality would be of high interest for further transformations, such as Huisgen 1,3-dipolar cycloadditions (click reactions) [31–33], leading to triazolyl-derivatives. Decarboxylative coupling methods were also developed in recent years and interesting results have been reported [34–36], especially also using copper catalysis [37–39]. Hence, we hypothesized that a combination of decarboxylative coupling and cross-dehydrogenative coupling could solve the problem of introducing short chained alkynes onto TIQ since the corresponding alkyne-acids are either liquid or solid at room temperature and handling of these compounds is not a problem (Scheme 1, lower part). In fact, the shortest chain representative, propiolic acid, has a boiling point of 102 °C at 200 mmHg and a melting point just below room temperature of 16–18 °C. Herein we report our efforts in this direction.

2. Experimental

2.1. Materials and methods

Unless otherwise noted, chemicals were purchased from commercial suppliers and used without further purification.

Flash column chromatography was performed on silica gel 60 from Merck (40–63 μm) whereas separations were carried out using a Büchi Sepacore™ MPLC system. For TLC aluminum coated silica gel was used and signals were visualized with UV light (254 nm). GC–MS runs were performed on a Thermo Finnigan Focus GC/DSQ II using a standard capillary column BGB 5 (30 m × 0.32 mm ID) and the following settings were used as standard: Injection: 1 μl (hot needle-technique), split-injection (split-ratio:1:8); Flow: 2 ml/min Helium; Injectorblock temperature: 250 °C; MS-Transferline Temperature: 280 °C.

All samples for HR-MS were analyzed by LC-IT-TOF-MS in only positive ion detection mode upon recording of MS and MS/MS spectra. For the evaluation in the following, only positive ionization spectra were used (where the quasi-molecular ion is the one of [M+H]+), and further data or information were not taken into consideration. The following instruments were used: Shimadzu Prominence HPLC, consisting of: solvent degassing unit (DGU-20 A3), binary gradient Pump (2 x LC-20AD), auto-injector (SIL-20A), column oven (CTO-20AC), control module (CBM-20A), and diode array detector (SPD-M20A). MS System: Shimadzu IT-TOF-MS with electrospray interface.

Melting points were determined using a Kofler-type Leica Galen III micro hot stage microscope and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AC 200 (200 MHz) or on a Bruker Avance UltraShield 400 (400 MHz) spectrometer. Chemical shifts are reported as ppm downfield from TMS (tetramethylsilane) as internal standard with multiplicity, number of protons, allocation, and coupling constant(s) in Hertz.

2.2. Starting materials

2.2.1. N-*Phenyl-1,2,3,4-tetrahydroisoquinoline (**1**)*

Copper(I)iodide (39.8 mg, 0.21 mmol, 0.1 equiv.) and potassium phosphate (887.3 mg, 4.18 mmol, 2.09 equiv.) were weighed into a round bottom flask which was evacuated and back filled

with nitrogen for 3 times. 2-Propanol (2 ml), ethylene glycol (0.23 ml), iodobenzene (426.4 mg, 0.23 ml, 2.09 mmol, 1.05 equiv.) and 1,2,3,4-tetrahydroisoquinoline (0.27 g, 0.26 ml, 2.0 mmol, 1 equiv.) were added via a syringe at room temperature. The reaction mixture was heated to 85–90 °C, stirred for 24 h and then allowed to cool to room temperature. Diethyl ether (5 ml) and water (5 ml) were then added to the reaction mixture. The organic layer was extracted by diethyl ether (2 × 20 ml). The combined organic phases were washed with brine and dried over magnesium sulfate. The solvent was removed under vacuo and the crude mixture purified by column chromatography on silica gel (PE:EtOAc = 20:1). Compound **1** was obtained as light brown solid in 83% yield (347 mg, 1.66 mmol). M.p.: 43–46 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm): 3.01 (t, ^3J = 5.8 Hz, 2H), 3.59 (t, ^3J = 5.9 Hz, 2H), 4.44 (s, 2H), 6.85 (t, ^3J = 7.2 Hz, 1H), 7.01 (d, ^3J = 7.9 Hz, 2H), 7.19–7.36 (m, 6H); ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm): 29.83, 47.18, 51.41, 115.80, 119.34, 126.51, 126.69, 127.00, 129.18, 129.83, 135.12, 135.51, 151.17.

2.2.2. N-(4-Methoxyphenyl)-1,2,3,4-tetrahydroisoquinoline (**2**)

Copper(I)iodide (39.8 mg, 0.21 mmol, 0.1 equiv.), potassium phosphate (887.3 mg, 4.18 mmol, 2.09 equiv.) and 4-iodoanisole (489.1 mg, 2.09 mmol, 1.05 equiv.) were put into a round bottom flask which was evacuated and back filled with nitrogen for 3 times. 2-Propanol (2 ml), ethylene glycol (0.23 ml) and 1,2,3,4-tetrahydroisoquinoline (0.27 g, 0.26 ml, 2.0 mmol, 1.0 equiv.) were added via Hamilton syringe at room temperature. The reaction mixture was heated to 85–90 °C, stirred for 24 h and then allowed to cool to room temperature. Diethyl ether (5 ml) and water (5 ml) were then added to the reaction mixture. The organic layer was extracted by diethyl ether (2 × 20 ml). The combined organic phases were washed with brine and dried over magnesium sulfate. The solvent was removed under vacuo and the product purified by column chromatography on silica gel (PE: EtOAc = 20:1). Compound **2** was obtained as white solid in 79% yield (380 mg, 1.58 mmol). M.p.: 89–91 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm): 3.01 (t, ^3J = 5.8 Hz, 2H), 3.47 (t, ^3J = 5.9 Hz, 2H), 3.80 (s, 3H), 4.32 (s, 2H), 6.90 (d, ^3J = 9.2 Hz, 2H), 7.01 (d, ^3J = 9.2 Hz, 2H), 7.11–7.24 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm): 29.11, 48.43, 52.57, 55.59, 114.53, 118.01, 125.93, 126.22, 126.46, 128.61, 134.50, 134.56, 145.31, 153.40.

2.2.3. N-Benzyl-1,2,3,4-tetrahydroisoquinoline (**3**)

To an argon degassed solution of TIQ (2.66 g, 2.53 ml, 20 mmol, 1.0 equiv.) and TEA (6.07 g, 8.4 ml, 60 mmol, 3.0 equiv.) in 50 ml dry DCM, benzylbromide (5.13 g, 3.4 ml, 30 mmol, 1.5 equiv.) was added at 0 °C. After 10 min, the reaction mixture was warmed to r.t. and stirred under argon for 5 h. The reaction mixture was quenched with aq. saturated sodium carbonate solution, and extracted three times with EtOAc. The collected organic layers were washed twice with brine, dried over sodium sulfate, filtered and evaporated. The crude product was purified via column chromatography (PE:$CHCl_3$ = 3:1). Compound **3** was obtained as pale yellow solid in 82% yield (3680 mg, 16.5 mmol). M.p: 35–37 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm) = 2.79 (t, ^3J = 5.8 Hz, 2H), 2.95 (t, ^3J = 5.9 Hz, 2H), 3.69 (s, 2H), 3.74 (s, 2H), 6.98–7.07 (m, 1H), 7.08–7.49 (m, 8H); ^{13}C NMR (50 MHz, APT, $CDCl_3$) δ (ppm): 29.13, 50.62, 56.10, 62.79, 125.51, 126.04, 126.59, 127.01, 128.24, 128.63, 129.00, 134.32, 134.89, 138.39.

2.3. General procedure for the decarboxylation/alkynylation reaction on 1,2,3,4-tetrahydroisoquinolines

A mixture of copper chloride (0.02 mmol, 2 mg), 2-phenyl-1,2,3,4-tetrahydroisoquinoline (0.4 mmol, 83.7 mg) was flushed with Ar for about 2 min. Then the alkynoic acid (0.2–1.2 mmol) and *tert*-butyl hydroperoxide (0.04 ml, 5–6 M in decane) were added via syringe at room temperature. The temperature was then raised to 50 °C over 10–15 min. The mixture was stirred at this temperature for 2 days and then cooled to room temperature. The resulting suspension was diluted with CH_2Cl_2 and filtrated. The solvent was evaporated ant the residue was purified by column chromatography.

2.3.1. 1-(Ethyn-1-yl)-2-phenyl-1,2,3,4-tetrahydroisoquinoline (**4**)

Compound **4** was obtained as colorless oil using PE:$CHCl_3$ (3:1) as eluent in 90% yield (42 mg, 0.18 mmol). ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm): 2.31 (d, 1H), 2.83–3.22 (m, 2H), 3.47–3.75 (m, 2H), 5.46 (s, 1H), 6.75–7.42 (m, 9H); ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm): 29.43, 43.72, 52.15, 73.37, 83.48, 117.17, 120.43, 126.96, 127.86, 128.03, 129.61, 129.81, 134.89, 135.46, 149.91; HR-MS: 234.1271 (Calc. $[M+H]^+$: 234.1277).

2.3.2. 1-(Propyn-1-yl)-2-phenyl-1,2,3,4-tetrahydroisoquinoline (**5**)

Compound **5** was obtained as light yellow oil using PE:$CHCl_3$ (3:1) as eluent in 80% yield (40 mg, 0.16 mmol). ^{1}H NMR (200 MHz, d6-DMSO) δ (ppm): δ = 1.74 (d, ^3J = 9.7 Hz, 3H), 2.88–3.12 (m, 2H), 3.52–3.75 (m, 2H), 5.64 (s, 1H), 6.79–7.50 (m, 9H); ^{13}C NMR (50 MHz, d6-DMSO) δ (ppm): 2.76, 27.57, 41.57, 49.71, 78.45, 79.68, 115.28, 118.22, 125.53, 126.51, 126.91, 128.18, 128.53, 133.44, 135.45, 148.55; HR-MS: 248.1422 (Calc. $[M+H]^+$: 248.1434).

2.3.3. 1-(Butyn-1-yl)-2-phenyl-1,2,3,4-tetrahydroisoquinoline (**6**)

Compound **6** was obtained as light yellow oil using PE:$CHCl_3$ (3:1) as eluent in 90% yield (47 mg, 0.18 mmol). ^{1}H NMR (200 MHz, d6-DMSO) δ (ppm): 0.97 (t, ^3J = 3.7 Hz), 2.11 (dq, ^3J = 3.8 Hz, ^4J = 1.0 Hz, 2H), 2.85–3.13 (m, 2H), 3.35–3.62 (m, 1H), 3.67–3.92 (m, 1H), 5.64 (s, 1H), 6.83 (t, ^3J = 3.7 Hz, 1H), 7.01–7.42 (m, 8H); ^{13}C NMR (50 MHz, d6-DMSO) δ (ppm): 12.81, 14.29, 29.13, 43.52, 51.94, 78.71, 86.86, 116.76, 119.57, 126.46, 127.29, 127.60, 129.15, 129.36, 134.52, 136.54, 149.88; HR-MS: 262.1584 (Calc. $[M+H]^+$: 262.1590).

2.3.4. 1-(Pentyn-1-yl)-2-phenyl-1,2,3,4-tetrahydroisoquinoline (**7**)

Compound **7** was obtained as orange oil using PE:$CHCl_3$ (4:1) as eluent in 85% yield (47 mg, 0.17 mmol). ^{1}H NMR (200 MHz, d6-DMSO) δ (ppm): 0.81 (t, ^3J = 3.7 Hz, 3H), 1.34 (sext, ^3J = 3.6 Hz, 2H), 2.09 (dt, ^3J = 3.3 Hz, J = 1 Hz, 2H), 2.87–3.20 (m, 2H), 3.31-3.83 (m, 2H), 5.66 (s, 1H), 6.83 (t, ^3J = 3.6 Hz, 1H), 7.03–7.41 (m, 8H); ^{13}C NMR (50 MHz, APT, $CDCl_3$) δ (ppm): 13.72, 20.56, 22.36, 28.76, 42.68, 51.12, 116.75, 119.50, 126.62, 127.59, 128.02, 129.32, 129.57; HR-MS: 276.1744 (Calc. $[M+H]^+$: 276.1747).

2.3.5. 1-(Heptyn-1-yl)-2-phenyl-1,2,3,4-tetrahydroisoquinoline (**8**)

Compound **8** was obtained as orange oil using PE:EtOAc (20:1) as eluent in 75% yield (46 mg, 0.15 mmol). ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm): 0.78–1.02 (m, 3H), 1.22–1.56 (m, 6H), 1.99 (t, 2H), 2.86–3.27 (m, 2H), 3.51–3.87 (m, 2H), 5.45 (s, 1H), 6.90 (m, 1H), 7.02–7.48 (m, 8H); ^{13}C NMR (50 MHz, APT, $CDCl_3$) δ (ppm): 13.94, 18.69, 28.34, 28.86, 29.69, 30.68, 31.19, 43.13, 51.75, 119.32, 125.32, 126.08, 126.26, 126.92, 126.99, 127.20, 127.28, 128.75, 128.79, 128.91, 128.98, 132.04; HR-MS: 304.2064 (Calc. $[M+H]^+$: 304.2060).

2.3.6. 1-(Ethyn-1-yl)-2-(4-methoxyphenyl)-1,2,3,4-tetrahydroisoquinoline (**9**)

Compound **9** was obtained as light brown oil using $CHCl_3$ as eluent in 53% yield (28 mg, 0.11 mmol). ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm): 2.30 (d, ^3J = 2,1 Hz), 2.89 (td, ^3J = 3.5 Hz, ^3J = 3.5 Hz,

^3J = 16.3 Hz, 2H), 3.12 (td, ^3J = 8.3 Hz, ^3J = 8.3 Hz, ^3J = 16.6 Hz, 2H), 3.53 (dd, ^3J = 3.6 Hz, ^3J = 8,4 Hz, 3H), 5.32 (d, ^3J = 1,9 Hz, 1H), 6.84–6,93 (m, 2H); ^{13}C NMR (50 MHz, APT, $CDCl_3$) δ (ppm): 28.91, 43.83, 53.54, 55.54, 73.40, 82.65, 114.41, 119.86, 126.19, 127.29, 127.32, 129.11, 133.95, 134.92, 143.83, 154.24; HR-MS: 264.1375 (Calc. $[M+H]^+$: 264.1383).

*2.3.7. 2-(4-Methoxyphenyl)-1-propynyl-1,2,3,4-tetrahydroisoquinoline (**10**)*

Compound **10** was obtained as redbrown oil using $CHCl_3$ as eluent in 47% yield (39 mg, 0.14 mmol). ^{1}H NMR (200 MHz, $CDCl_3$): δ (ppm): 1.73 (d, ^3J = 2.2 Hz, 3H), 2.87 (td, ^3J = 16.2 Hz, ^4J = 3.6 Hz, ^4J = 3.6 Hz, 1H), 3.10 (ddd, ^3J = 16.5 Hz, ^4J = 9.7 Hz, ^4J = 6.8 Hz, 1H), 3.50–3.61 (m, 2H), 3.78 (s, 3H), 5.26 (d, ^4J = 1.9 Hz, 1H), 6.81–6.92 (m, 2H), 7.11–7.31 (m, 4H); ^{13}C NMR (50 MHz, APT, $CDCl_3$): δ (ppm): 3.75, 28.83, 44.02, 53.42, 55.56, 78.08, 81.31, 114.34, 119.57, 126.04, 126.96, 127.33, 128.99, 133.86, 136.20, 144.09, 153.88; HR-MS: 278.1535 (Calc. $[M+H]^+$: 278.1539).

*2.3.8. 1-Butynyl-2-(4-methoxyphenyl)-1,2,3,4-tetrahydroisoquinoline (**11**)*

Compound **11** was obtained as light orange oil using $CHCl_3$ as eluent in 67% yield (39 mg, 0.13 mmol). ^{1}H NMR (200 MHz, $CDCl_3$): δ (ppm): 1.05 (t, ^3J = 7.4 Hz, 3H), 2.14 (dq, ^3J = 7.5 Hz, ^4J = 2 Hz, 2H), 2.82–3.29 (m, 2H), 3.40–3.71 (m, 2H), 3.82 (s, 3H), 5.31 (s, 1H), 6.91 (d, ^3J = 9 Hz, 2H), 7.09 (d, ^3J = 9 Hz, 2H), 7.15–7.37 (m, 4H); ^{13}C NMR (50 MHz, APT, $CDCl_3$): δ (ppm): 12.68, 14.23, 29.11, 44.24, 53.87, 55.76, 78.40, 87.48, 114.47, 120.11, 126.20, 127.10, 127.56, 129.17, 134.06, 136.47, 144.41, 154.19; HR-MS: 292.1698 (Calc. $[M+H]^+$: 292.1696).

*2.3.9. 2-(4-Methoxyphenyl)-1-pentynyl-1,2,3,4-tetrahydroisoquinoline (**12**)*

Compound **12** was obtained as orange oil using $CHCl_3$ as eluent in 57% yield (52 mg, 0.17 mmol). ^{1}H NMR (200 MHz, $CDCl_3$): δ (ppm): 0.83 (t,^3J = 7.3 Hz, 3H'), 1.24–1.49 (m, 2H), 2.05 (dt, ^3J = 6.7 Hz, ^4J = 2.1 Hz, 2H), 2.87 (td, ^3J = 16.3 Hz, ^4J = 2.1 Hz, 1H), 3.09 (ddd, ^3J = 16.5 Hz, ^4J = 9.9 Hz, ^4J = 6.7 Hz, 1H), 3.41–3.58 (m, 2H), 3.77 (s, 3H), 5.28 (s, 1H), 6.82–6.91 (m, 2H), 6.99–7.09 (m, 2H), 7.11–7.31 (m, 4H); ^{13}C NMR (50 MHz, APT, $CDCl_3$): δ (ppm): 13.42, 20.82, 22.25, 29.04, 44.07, 53.80, 55.63, 79.10, 85.87, 114.34, 119.97, 126.04, 126.93, 127.43, 129.01, 133.87, 136.35, 144.31, 154.06; HR-MS: 306.1840 (Calc. $[M+H]^+$: 306.1852).

*2.3.10. 1-(Heptyn-1-yl)-2-(4-methoxyphenyl)-1,2,3,4-tetrahydroisoquinoline (**13**)*

Compound **13** was obtained as orange oil using $CHCl_3$ as eluent in 71% yield (47 mg, 0.14 mmol). ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm): 0.83 (t, 3J = 6.4 Hz, ^3J = 6.4 Hz, 3H), 1.11-1.45 (m, 6H), 2.07(dt, ^3J = 6.8 Hz, ^3J = 6.9 Hz, ^4J = 1.9 Hz, 2H), 2.87 (td, ^3J = 16.3 Hz, 4J = 3.5 Hz, ^4J = 3.5 Hz, 1H), 3.09 (ddd, ^3J = 16.5 Hz, 4J = 9.7 Hz, ^4J = 6.8 Hz, 1H), 3.45-3.58 (m, 2H), 3.77 (s, 3H), 5.28 (s, 1H), 6.86 (d, ^3J = 9.1 Hz, 2H), 7.04 (d, ^3J = 9.1 Hz, 2H), 7.10-7.30 (m, 4H); ^{13}C NMR (50 MHz, APT, $CDCl_3$) δ (ppm): 14.01, 18.75, 22.18, 28.44, 29.04, 30.90, 44.02, 53.81, 55.54, 78.93, 86.02, 114.27, 119.97, 126.00, 126.89, 127.41, 128.97, 133.82, 136.28, 144.27, 154.04; HR-MS: 334.2162 (Calc. $[M+H]^+$: 334.2165).

*2.3.11. 1-(Ethyn-1-yl)-2-benzyl-1,2,3,4-tetrahydroisoquinoline (**14**)*

Compound **14** was obtained as light brown oil using PE:$CHCl_3$ (3:2) as eluent in 81% yield (40 mg, 0.16 mmol). ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm): 2.47 (d, 1H), 2.70–3.12 (m, 4H), 3.87 (dt, 2H), 4.60 (s, 1H), 7.08–7.50 (m, 9H); ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm): 29.20, 45.68, 53.86, 59.64, 74.91, 81.92, 126.15, 127.36, 127.49, 127.82, 128.60, 129.37, 134.27, 135.34, 138.48; HR-MS: 248.1428 (Calc. $[M+H]^+$: 248.1434).

*2.3.12. 1-(Propyn-1-yl)-2-benzyl-1,2,3,4-tetrahydroisoquinoline (**15**)*

Compound **15** was obtained as light yellow oil using PE:$CHCl_3$ (3:2) as eluent in 70% yield (37 mg, 0.14 mmol). ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm): 1.89 (s, 3H), 2.66–3.09 (m, 4H), 3.86 (m, 2H), 4.54 (s, 1H), 7.05–7.50 (m, 9H); ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm): 4.08, 29.29, 45.80, 54.47, 59.74, 77.47, 82.72, 126.06, 127.09, 127.41, 128.01, 128.60, 129.29, 129.55, 134.19, 136.54, 138.87; HR-MS: 262.1588 (Calc. $[M+H]^+$: 262.1590).

*2.3.13. 1-(Butyn-1-yl)-2-benzyl-1,2,3,4-tetrahydroisoquinoline (**16**)*

Compound **16** was obtained as light yellow oil using PE:$CHCl_3$ (3:2) as eluent in 90% yield (50 mg, 0.18 mmol). ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm): 1.19 (t, ^3J = 7.4 Hz, 3H), 2.18–2.35 (dq, ^3J = 7.4 Hz, ^4J = 2.2 Hz, 2H), 2.70-3.05 (m, 4H), 3.86 (dt, ^3J = 17.3 Hz, ^3J = 8.4 Hz, 2H), 4.56 (s, 1H), 7.08–7.50 (m, 9H); ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm): 12.91, 14.67, 26.80, 29.32, 45.87, 51.99, 54.37, 77.49, 88.78, 126.03, 127.03, 127.40, 128.02, 128.58, 129.24, 129.60, 134.19, 136.59, 138.85; HR-MS: 276.1747 (Calc. $[M+H]^+$: 276.1742).

*2.3.14. 1-(Pentyn-1-yl)-2-benzyl-1,2,3,4-tetrahydroisoquinoline (**17**)*

Compound **17** was obtained as light yellow oil using PE:$CHCl_3$ (3:2) as eluent in 66% yield (38 mg, 0.13 mmol). ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm): 0.91 (t, ^3J = 7.2 Hz, 3H), 1.46 (sext, ^3J = 7.2 Hz, 2H), 2.12 (dt, ^3J = 6.8 Hz, ^4J = 2.1 Hz, 2H) 2.56–3.07 (m, 4H), 3.75 (dt, ^3J = 16.9 Hz, ^3J = 7.5 Hz, 2H), 4.45 (s, 1H), 6.93–7.38 (m, 9H); ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm): 13.89, 21.17, 22.73, 29.30, 45.84, 54.37, 59.72, 78.28, 87.30, 125.96, 126.96, 127.35, 127.97, 128.53, 129.18, 129.54, 134.13, 136.59, 138.80; HR-MS: 290.1892 (Calc. $[M+H]^+$: 290.1903).

*2.3.15. 1-(Heptyn-1-yl)-2-benzyl-1,2,3,4-tetrahydroisoquinoline (**18**)*

Compound **18** was obtained as light yellow oil using PE:$CHCl_3$ (3:2) as eluent in 80% yield (51 mg, 0.16 mmol). ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm): 0.92 (t, 3H), 1.29-1.62 (m, 6H), 2.17–2.30 (m, 2H), 2.70–3.08 (m, 4H), 3.86 (dt, 2H), 4.56 (s, 1H), 7.05–7.50 (m, 9H); ^{13}C NMR (50 MHz, $CDCl_3$): 14.25, 19.03, 22.39, 28.87, 29.21, 31.32, 45.76, 54.28, 59.63, 78.04, 87.41, 125.86, 126.87, 127.26, 127.88, 128.44, 129.08, 129.45, 134.03, 136.48, 138.71; HR-MS: 318.2206 (Calc. $[M+H]^+$: 318.2216).

2.4. General procedure for the one-pot decarboxylation/alkynylation/click reaction on 1,2,3,4-tetrahydroisoquinolines

A mixture of copper chloride (0.02 mmol, 2 mg), 2-phenyl-1,2,3,4-tetrahydroisoquinoline (0.4 mmol, 83.7 mg) was flushed with Ar for about 2 min. Then propiolic acid (0.2 mmol, 0.012 ml) and *tert*-butyl hydroperoxide (0.04 ml, 5–6 M in decane) were added via syringe at room temperature. The temperature was then raised to 50 °C over 10–15 min. The mixture was stirred at this temperature for 2 days and then Ph-N_3 was added (Attention: Adding an azide to a peroxide can lead to explosions. Hence, this protocol should only be used in small scale) to the existing reaction mixture and stirred for another two days under same conditions. The product was purified via precipitation using a solvent of 200 ml PE and 5 ml EE.

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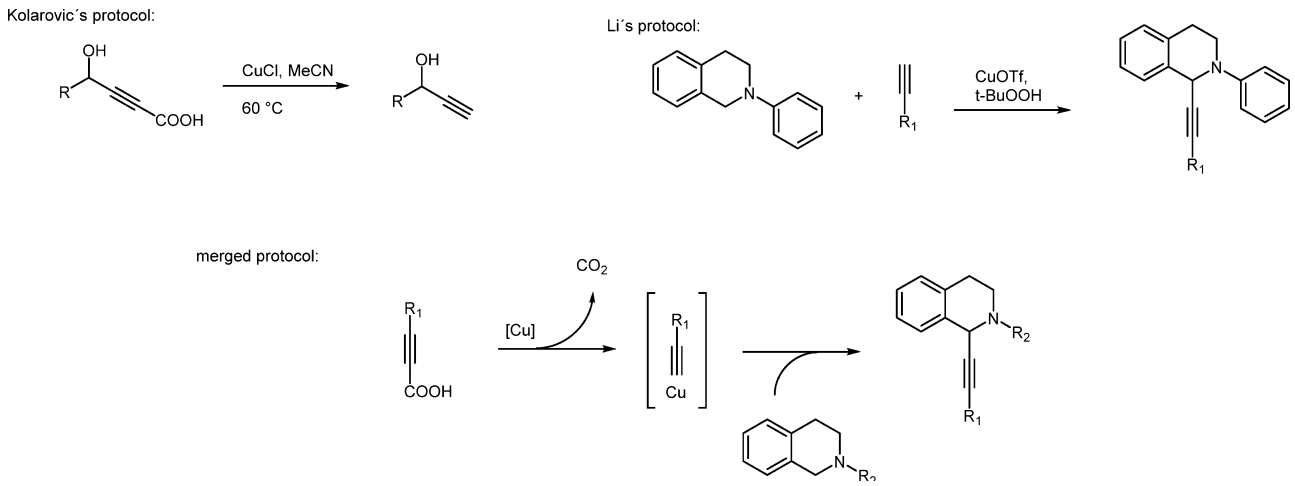


Scheme 2. A proposed merged decarboxylation and alkynylation protocol.

2.4.1. 2-Phenyl-1-(1-phenyl-1H-1,2,3-triazol-4-yl)-1,2,3,4-tetrahydroisoquinoline
(***19***)

Compound **19** was obtained as light brown solid in 90% yield (127 mg, 0.36 mmol). M.p.: 146–149 °C; ^{1}H NMR (d6-DMSO, 200 MHz) δ (ppm): 2.95–3.12 (m, 2H), 3.57–3.87 (m, 2H), 6.18 (s, 1H), 6.68 (t, *J* = 3 Hz, 1H), 6.91-7.04 (m, 2H), 7.10–7.62 (m, 10H), 7.76–7.88 (m, 2H), 8.66 (s, 1H); ^{13}C NMR (50 MHz, d-6-DMSO) δ (ppm): 27.67, 41.98, 54.66, 114.11, 117.45, 119.95, 120.68, 126.15, 126.95, 127.94, 128.43, 128.60, 129.10, 129.88, 134.98, 136.35, 136.62, 148.80, 150.68; HR-MS: 353.1749 (Calc. [M+H]$^+$: 353.1761).

2.4.2. -(4-Methoxyphenyl)-1-(1-phenyl-1H-1,2,3-triazol-4-yl)-1,2,3,4-tetrahydroiosquinoline
(***20***)

Compound **20** was obtained as light brown solid in 50% yield (191 mg, 0.20 mmol). M.p.: 150–151 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm): 2.80–3.10 (m, 2H), 3.33–3.62 (m, 2H), 3.65 (s,3H), 5.93 (s, 1H), 6.73 (d, *J* = 9 Hz, 2H), 6.88 (d, *J* = 9 Hz, 2H), 7.06–7.43 (m, 7H), 7.49–7.58 (m, 3H); ^{13}C NMR (50 MHz, APT, $CDCl_3$) δ (ppm): 28.49, 44.50, 55.61, 57.36, 114.57, 118.42, 119.78, 120.35, 126.26, 127.01, 128.24, 128.52, 128.68, 129.60, 134.81, 135.99, 137.04, 143.94, 151.14, 153.36; HR-MS: 383.1856 (Calc. [M+H]$^+$: 383.1866).

3. Results and discussion

Starting point for our investigations was a protocol published by Kolarovic and coworkers in 2009, which reported copper-catalyzed decarboxylation of 2-alkynoic acids (Scheme 2, upper left) [39]. Since this decarboxylation reaction and the C1-alkynylation reaction on TIQ reported by Li et al. (Scheme 2 upper right) [23] are both copper catalyzed, it was tried to investigate a one-pot protocol, where the alkyne source first undergoes decarboxylation and then couples with the 1,2,3,4-tetrahydroisoquinoline substrate (Scheme 2 bottom).

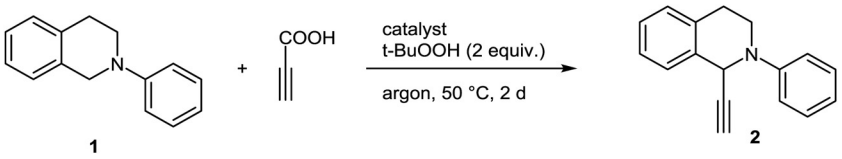
The first decarboxylation-alkynylation experiments were carried out applying the conditions reported by Li using *N*-phenyl-1,2,3,4-tetrahydroisoquinoline **1** as substrate, CuOTf as catalyst (10 mol%), t-BuOOH (2 equiv. as 5.5 M solution in dodecane) as oxidant but otherwise neat conditions under argon atmosphere. It has to be noted that the alkyne is the limiting reagent since in the original protocol by Li 1 equiv. alkyne and 2 equiv. TIQ derivative were used [23]. In contrast to the Li report, propiolic acid was used as alkyne source which gave an encouraging 33% yield of alkynylated product (Table 1, entry 1). Variation of catalyst revealed that $Cu(NO_3)_2{\cdot}3H_2O$, CuCN and CuCl were performing significantly better (entries 2–4). Interestingly CuBr (entry 5) gave only trace amounts of product even though CuCl gave the highest yield of 61% (entry 4). With $Fe(NO_3)_2{\cdot}9H_2O$ as catalyst no product was detected via GC–MS (entry 6) although we successfully used this catalyst in indolation reactions of TIQ [40,41].

We continued optimization using CuCl and added various solvents (1 ml in every case). When using THF the yield dropped to 36% (Entry 7). On the other hand, CH_2Cl_2 and MeCN led to a significant increase to 78% (Entry 8) and 90% (Entry 9) respectively. It was then tried to lower the catalyst amount in MeCN to 5 mol% but the yield dropped to 30% in this experiment (Entry 10). Increasing catalyst loading to 15% had no significant influence (Entry 11). Also changes in the ratio of TIQ to propiolic acid were investigated. Using 4 equivalents of TIQ slightly improved the yield to 94% and to a slightly higher TON of 9.4 (Entry 12). Using equimolar amounts gave a reduced yield of 33% (Entry 13) and still lower yield of 12% was obtained using 0.5 equiv. TIQ (Entry 14, amount of propiolic acid was doubled). Hence it was decided to stick to the initial ratio of 2 equivalents TIQ substrate, since it is the best compromise between yield and materials economy. Finally the influence of temperature was investigated. At 35 °C (Entry 15) no conversion was detected whereas at 75 °C the yield was as high as at 50 °C (Entry 16). Reducing the reaction time to 24 h led to lower yield as well (Entries 17 & 18) which demonstrated that the long reaction time of 2 days is required.

The screening experiments were all carried out using propiolic acid as alkyne component partner. Hence, the reaction could proceed either via initial CDC at the free C—H side of the triple bond followed by decarboxylation or via initial decarboxylation forming eventually a Cu-acetylide which then undergoes the alkynylation process. When experiments were carried out with longer chained 2-alkynoic acids high yields of the alkynylated products were achieved still (see Table 2, entries 2–5), indicating that the first step is indeed the decarboxylation reaction. All alkynoic acids applied gave good yields using *N*-phenyl-tetrayhdroisoquinoline **1** as substrate (Table 2, entries 1–5). Most importantly, products **4**-**6**, where the corresponding alkyne would be gaseous or volatile at room temperature gave good yields of 90% for **4**, 80% for **5**, and 90% for **6**. This demonstrates the added value of this method as compared to the previously published protocol [23]. Also pentynoic acid and octynoic acid gave good yields of 85% and 75% respectively (Entries 4 & 5).

It was also tested whether the reaction would work using removable N-protecting groups instead of phenyl. Gratifyingly

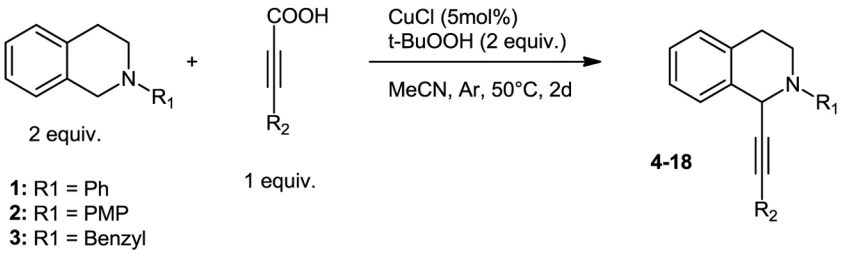
Table 1
Parameter Optimization under argon.



Entry	Catalyst	Solvent	T [°C]	1 [mmol]	Yield [%]	TON
1	$(CuOTf)_2$ toluene complex	Neat	50	0.4	33	3.3
2	$Cu(NO_3)_2{\cdot}3H_2O$	Neat	50	0.4	50	5
3	CuCN	Neat	50	0.4	55	5.5
4	CuCl	Neat	50	0.4	61	6.1
5	CuBr	Neat	50	0.4	Traces	–
6	$Fe(NO_3)_2{\cdot}9H_2O$	Neat	50	0.4	n.p.	–
7	CuCl	THF	50	0.4	36	3.6
8	CuCl	CH_2Cl_2	50	0.4	78	7.8
9	CuCl	MeCN	50	0.4	90	9
10	CuCl	MeCN	50	0.4	30[a]	6
11	CuCl	MeCN	50	0.4	92[b]	6.1
12	CuCl	MeCN	50	0.8	94	9.4
13	CuCl	MeCN	50	0.2	33	3.3
14	CuCl	MeCN	50	0.2	12[c]	2.4
15	CuCl	MeCN	35	0.4	–	–
16	CuCl	MeCN	75	0.4	90	9
17	CuCl	MeCN	50	0.4	52[d]	5.2
18	CuCl	MeCN	75	0.4	60[d]	6.0

Standard conditions: 10 mol% catalyst, 50 °C, 0.2 mmol propiolic acid (1 equiv.), 0.4 mmol **1** (2 equiv.), t-BuOOH (0.4 mmol, 2 equiv.), 2 days.
[a] 5 mol% catalyst used.
[b] 15 mol% catalyst used.
[c] 0.4 mmol propiolic acid instead of 0.2 mmol.
[d] 1 day reaction time instead of 2 days; n.p.: no product formation.

Table 2
Decarboxylation/Alkynylation products.



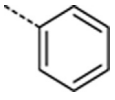
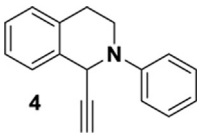
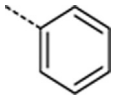
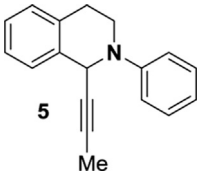
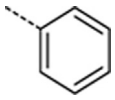
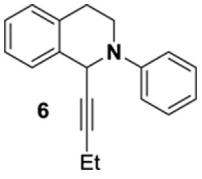
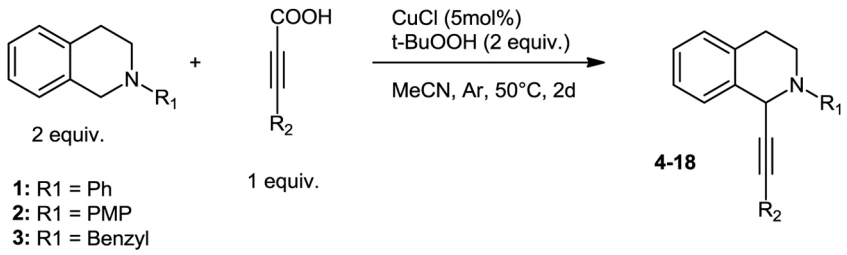
Entry	R^1	R^2	Product	Yield
1		–H	 4	90%
2		Me	 5	80%
3		C_2H_5	 6	90%

Table 2 (*Continued*)



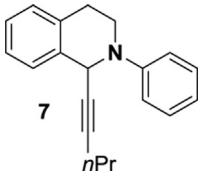
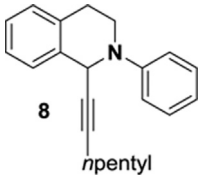
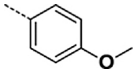
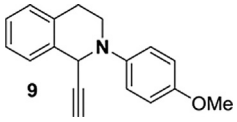
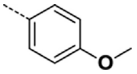
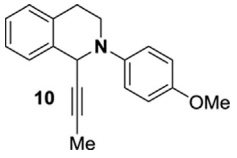
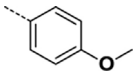
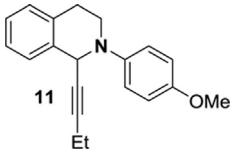
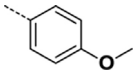
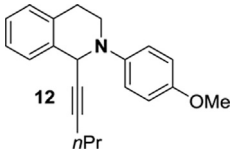
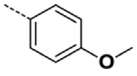
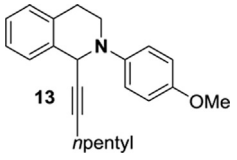
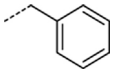
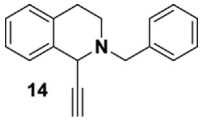
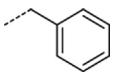
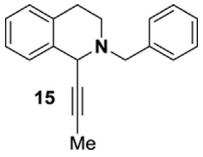
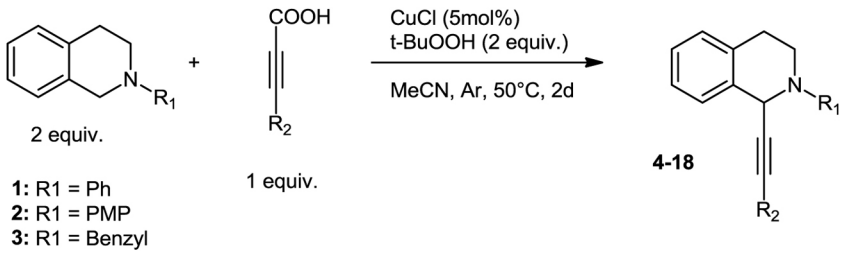
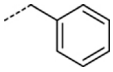
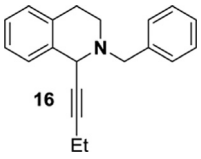
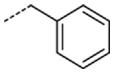
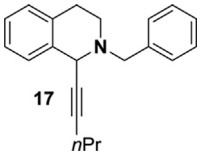
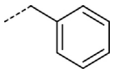
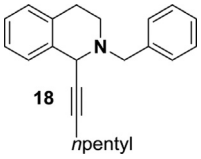
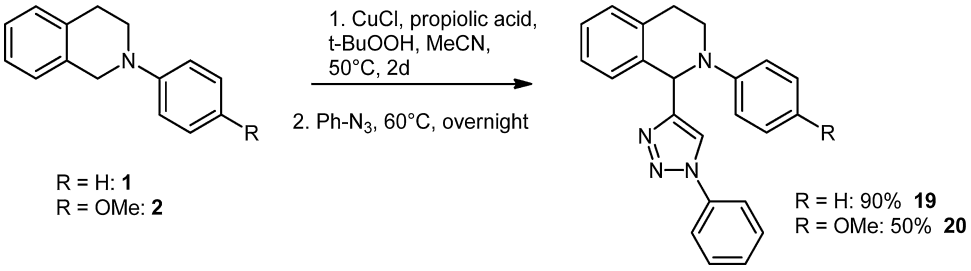
Entry	R^1	R^2	Product	Yield
4		nC_3H_7	 **7** *n*Pr	85%
5		nC_5H_{11}	 **8** *n*pentyl	75%
6		–H	 **9**	53%
7		Me	 **10** Me	47%
8		C_2H_5	 **11** Et	67%
9		nC_3H_7	 **12** *n*Pr	57%
10		nC_5H_{11}	 **13** *n*pentyl	71%
11		–H	 **14**	81%
12		Me	 **15** Me	70%

Table 2 (*Continued*)



Entry	R^1	R^2	Product	Yield
13		C_2H_5	 **16**	90%
14		nC_3H_7	 **17**	66%
15		nC_5H_{11}	 **18**	80%



Scheme 3. Domino catalysis towards triazines **19** and **20**.

both, PMP (entries 6–10) and benzyl (entries 11–15) were tolerated. Protecting the nitrogen as amide (using acetyl) or carbamate (using Boc) led to a complete shutdown of the reaction. In the case of the PMP protecting group, the yield was significantly lower as compared to the unsubstituted phenyl group in all cases. Propiolic acid gave the lowest yield of 53%, significantly lower as compared to the 90% obtained with the *N*-phenyl group (Entry 6). Only in the case of octynoic acid a similar yield was obtained (71% entry 10 vs. 75% respectively entry 5). For the benzyl protecting group the yields were very similar as compared to the phenyl protecting group in all cases and 66–90% yield were obtained (Entries 11–15). It has to be mentioned that in case of the benzyl protecting group, a second benzylic position adjacent to nitrogen is present in the molecule and regioselectivity of alkynylation could be an issue. However, in all cases we observed exclusive alkynylation of the TIQ ring, showing that the alkynylation selectively occurs at the C-1 position of the tetrahydroisoquinoline.

Since terminal alkyne functions were successfully introduced to the C-1 position of TIQ, it was further explored if a subsequent Huisgen 1,3-dipolar cycloaddition with azides (often referred to as "click reaction") would be possible [31–33]. Initially, we started from isolated **2** and submitted it to the same conditions used for the decarboxylation-alkynylation process (CuCl and azidobenzene in MeCN) but in the absence of oxidant. After stirring overnight at 60 °C the desired click-product was obtained in quantitative yield by precipitation from an EtOAc/EtOH mixture in a 100% regioselective fashion. Since this experiment was successful, we attempted a cascade of decarboxylation and alkynylation reaction, adding azidobenzene to the reaction mixture after 2d. This resulted in 90% yield of click-product **19** (Scheme 3). Hence, a three step, one-pot decarboxylation-alkynylation-1,3-dipolar cycloaddition sequence could be realized giving excellent yield of the target compound. Interestingly, the three step one-pot protocol using PMP as protecting group gave a lower yield of **20** of 50%. However, if it is taken into account that **9**, the intermediate towards **20**, was isolated in 53% yield (Table 1, entry 6), the 50% overall yield after three steps indicates that the cycloaddition works almost quantitatively.

4. Conclusions

In conclusion, we have developed a protocol for alkynylation of *N*-phenyl-, *N*-PMP- and *N*-benzyl-1,2,3,4-tetrahydroisoquinolines in the C1-position, using alkynoic acids as alkyne source. Hence, short chain alkynes can be introduced without the need for

gaseous reagents, enabling an operationally very simple protocol. In addition, a three-step one-pot-procedure leading to triazolyl-1,2,3,4-tetrahydroisoquinolines was elaborated, when using propiolic acid as the alkyne source. In this cascade reaction approach, all steps are catalyzed by simple CuCl, which makes this protocol economically very attractive.

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