The *Sonogashira* Coupling of Polymer-Supported Propargylamine with Aryl Iodides

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The *Sonogashira* coupling reaction of polymer-supported propargylamine (= prop-2-yn-1-amine) with aryl iodides in the presence of the $[Pd(PPh_3)_2]Cl_2$/CuI catalyst system produces 3-arylprop-1-yn-1-amines smoothly at room temperature (*Scheme*). When propargylamine is attached on *Wang* resin through a carbamate linker, the common problems with amino functionality in palladium-catalyzed couplings are overcome. The arylpropynamines are cleaved from the polymer with CF_3COOH and converted into chromatographically easily separable acetamides. Our solid-phase method opens a new pathway toward precursors of pharmacologically interesting arylpropynamines and arylpropanamines.

Introduction. – Aryl- and heteroarylpropanes are common precursors of biologically important natural products, *e.g.*, of lignin [1] and lignans [2]. In addition, some 3-aryl- or 3-heteroarylpropan-1-amine derivatives have been associated with central nervous system stimulating [3], antimalarial [4], positive inotropic [5], and antifungal [6] properties. We embarked on the solid-phase *Sonogashira* coupling reactions of polymer-bound propargylamine (= prop-2-yn-1-amine) with various aryl iodides. The 3-arylpropargylamines obtained in this coupling reaction can be reduced into 3-arylpropan-1-amines of interest. On the other hand, substituted arylpropargylamines themselves are interesting compounds since some of them, or their metabolites, possess selective inhibitory activity toward physiologically significant enzymes, such as aldehyde dehydrogenase [7] and monoamine oxidase B [8].

The *Sonogashira* coupling is an efficient palladium-catalyzed method for constructing aryl- and heteroarylacetylenes [9]. This reaction has been widely studied in liquid-phase synthesis, and due to its general efficiency, *e.g.*, high yields, tolerance of a wide range of functional groups, and a simple one-step procedure, it has in most applications replaced the analogous reaction of copper acetylide, the *Castro – Stephens* reaction [10]. Although the *Sonogashira* coupling in solid-phase reactions has been studied to a lesser extent, there are substantial amount of reports, where the benefits of the use of polymer-supported reagents have been combined with the high performance of this reaction [11 – 24]. On the other hand, both the aryl iodide and the acetylene components have been successfully used as polymer-bound reactants. For example, *Moore* and co-workers generated a resin-bound terminal acetylene by deprotecting the trimethylsilyl group with Bu_4NF, and subjected it to *Sonogashira* conditions with (trimethylsilyl)acetylene-funtionalized aryl iodides [11]. After repeating the reaction cycles, oligomeric arylacetylenes were obtained as final products. *Huang* and *Tour* applied a related sequence-specific methodology in solid-phase synthesis of linear,

oligomeric arylacetylenes by subsequently introducing aryl diiodides and monoprotected phenylenebis[acetylenes] [16]. *Bolton et al.* used *Sonogashira* coupling in the arylation of a polymer-bound olefinic acetylene prior to its *Pauson–Khand* cyclization [12]. *Tulla-Puche* and *Barany* employed an interesting way of proceeding, where both reactants were attached on different resins with *Wang* and allyl linkages [24]; treatment with Pd(0) cleaved the allyl-linked component which subsequently underwent a resin-to-resin transfer *Sonogashira* reaction.

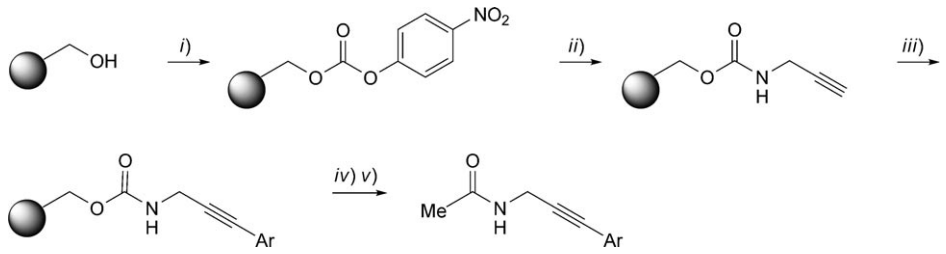
In addition to the general usefulness of solid-phase syntheses owing to the convenient preparation of combinatorial compound libraries by automatization, to their simple reaction conditions and product isolation, as well as to their safety in large scale preparations, the solid-phase versions of *Sonogashira* coupling possess some extra advantages. For example, diyne and other by-product formation is almost avoided when the acetylenic reactant is covalently bound to the polymer. Additionally, reactive functional groups can be protected by using them as attachment sites.

So far, there are no reports of the *Sonogashira* reaction of polymer-bound unsubstituted propargylamines. *De Mesmaeker* and co-workers studied the coupling of propargylamine with aryl iodides in solution and observed formation of the desired arylacetylene in an excellent yield, but only when the propargylamine was introduced into the reaction as a (*tert*-butoxy)carbonyl-protected derivative [25]. Additionally, *Khan* and *Grinstaff* used amide and carbamate derivatives of propargylamine, among them *N*-(trifluoroacetyl)- and *N*-[(*tert*-butoxy)carbonyl]propargylamine, in the coupling reaction with polymer-bound 5-iodouridines in a modification study of oligonucleotides [14].

To avoid polymer-bound propargylamine acting as a competing base with the tertiary amine, typically Et_3N, used in the coupling, we concentrated our efforts on reactions of propargylamine attached to the *Wang* resin through a carbamate linkage (*Scheme*). Among the several reactions available to bind amines covalently to the polymer, the carbamate method has been used in syntheses of low molecular-mass compounds, *e.g.*, 1,2,3-triazoles [26], and in the solid-phase synthesis of oligomeric peptides [27]. On the other hand, this method enables quantitative cleavage of the amine products from the polymeric support under relatively mild conditions with 50% CF_3COOH in CH_2Cl_2. Herein, we report the use of *Wang*-resin-bound propargylamine as a masked amino derivative in the *Sonogashira* coupling reaction with aryl iodides and the isolation and purification of the 3-arylpropargylamine products as easily separable acetamides (*Scheme*).

Results and Discussion. – We started our studies by searching a suitable polymeric support and an effective and reproducible attachment method for propargylamine. For example, we coupled propargylamine to trityl chloride resin by the corresponding method for 2-chlorotrityl chloride resin [28]. The ^{1}H-NMR spectrum of the cleaved CF_3COO^- salt was identical to the corresponding salt prepared from commercial propargylamine. However, the standard *Sonogashira* conditions with $[Pd(PPh_3)_4]$ or $[Pd(PPh_3)_2]Cl_2$ as a catalyst and CuI as a co-catalyst [18][29] for this polymer-bound acetylene did not give a trace of the desired arylacetylene. Considering these results with the studies of *De Mesmacker* and co-workers [25], it can be assumed that the probable reason for this failure is the amino functionality in the linkage. Polymer-

Scheme. *Coupling of Propargylamine to* Wang *Resin, the* Sonogashira *Reaction, Cleavage, and Acetylation*



i) 4-Nitrophenyl carbonochloridate, pyridine, CH_2Cl_2, r.t., 2 h. *ii*) $HC{\equiv}CCH_2NH_2$, DMF, 0° to r.t., 20 h. *iii*) ArI (3–5 equiv.), $[Pd(PPh_3)_2]Cl_2$ (0.2 equiv.), CuI (0.4 equiv.), Et_3N/1,4-dioxane 1:2, r.t., 20–73 h. *iv*) CF_3COOH/CH_2Cl_2 1:1, r.t., 2 h. *v*) $^iPr_2NEt/Ac_2O$ 1:1, cat. *N*,*N*-dimethylpyridin-4-amine (DMAP), r.t., 2 h.

supported propargylamine is a secondary amine, which is a stronger base than free propargylamine. Therefore, it is possible that the polymer-bound propargylamine is acting in the reaction as an amine base, analogously to the Et_3N used the in solution phase, rather than as an acetylenic nucleophile. On the other hand, suppression of the coupling reaction caused by direct interaction of the N-atom with the palladium complex, as postulated by *Santelli* and co-workers [30], cannot be excluded. In addition, *Erdélyi* and *Gogoll* discussed about the amine-mediated decomposition of the catalyst as a competing process [19]. Moreover, steric factors can play an important role in these reactions. *Nakamura et al.* performed straightforward *Sonogashira* couplings in solution with heteroaryl bromides and *N*,*N*-diisopropylpropargylamine [31]. Additionally, *Santelli* and co-workers obtained the best results with bulky, tertiary amines [30]. Hence, it is conceivable that the bulkiness of the amine overcomes its high basicity in the reaction.

After these preliminary experiments, we decided to test propargylamine attached to the *Wang* resin with a carbamate linker. This polymer-supported amine was routinely prepared by a two-step procedure [26] from the *Wang* resin, 4-nitrophenyl carbonochloridate (=4-nitrophenyl chloroformate), and pyridine in CH_2Cl_2 and a subsequent reaction of the isolated 4-nitrophenyl carbonate resin with propargylamine in DMF (*Scheme*). The success of the attachment can be monitored by FT-IR by means of the characteristic terminal-alkyne signals at 3290 cm^{-1} and 2100 cm^{-1} and the strong carbamate C=O peak at 1710 cm^{-1}. This light yellow *Wang*-carbamate resin shows the expected stability in air at room temperature, but it was stored in a desiccator over silica gel due to the requirements of dry conditions in the subsequent palladium-catalyzed reactions.

We observed the formation of coupling products from the *Wang*-carbamate resin and aryl iodides (see *Scheme*) with satisfying yields when we applied the *Sonogashira* procedure for polymer-bound aryl iodide with phenylacetylene in solution [15]; in this method, $[Pd(PPh_3)_2]Cl_2$ and CuI constitute the catalyst system and dry 1,4-dioxane/Et_3N 2:1 the solvent. Three- to five-fold excess of aryl iodides over the polymer-bound propargylamine was used in our studies. The couplings proceeded at room temperature,

typically within 20–73 h. The use of amine base as the co-solvent was crucial. Our initial trials of the same *Wang*-carbamate resin with iodobenzene in THF with $[Pd(PPh_3)_2]Cl_2$ and in DMF with $[Pd(PPh_3)_4]$, wherein only *ca.* 1.5 equiv. of Et_3N with respect to the polymer-bound propargylamine was used, did not give a trace of the desired coupling product.

After the cleavage of the polymer moiety with CF_3COOH/CH_2Cl_2 1:1, the 3-arylpropargylamines were liberated from their CF_3COO^- salts with *N*,*N*-diisopropylethylamine and immediately acetylated with Ac_2O (*Scheme*). To ensure complete acetylation within 2 h, a catalytic amount of *N*,*N*-dimethylpyridine-4-amine (DMAP) was added into the mixture. The products were acetylated to facilitate purification by the subsequent flash chromatography thus avoiding the sluggish separation of free amines by silica gel column chromatography. A typical eluent system was an AcOEt/acetone gradient, which gave good separation of these relatively polar acetamides. However, the purity of the acetamide with a MeO group at the *meta* position of the aryl moiety (*Table*, *Entry 11*) was, according to LC/UV detection at 210 nm, only 79% due to inseparable impurities.

Table. *Yields and Primary Analysis Data of* N-*(3-Arylpropargyl)acetamides Obtained* from *Various Aryl Iodides after Loading of Propargylamine to* Wang *Resin,* Sonogashira *Coupling, Cleavage, and Acetylation*

Entry	Aryl group	^{1}H-NMR $\delta(ArC{\equiv}CC\mathit{H}_2)$[a])	^{13}C-NMR $\delta(Ar\mathit{C}{\equiv}\mathit{C}CH_2)$[b])	FT-IR C=O (acetamide) [cm^{-1}][c])	Yield [%][d])
1	Ph	4.21	82.6; 87.2	1651	41
2	4-$NO_2C_6H_4$	4.28	80.9; 92.8	1643	52
3	4-CNC_6H_4	4.25	81.1; 91.9	1642	60
4	2-ClC_6H_4	4.28	76.2; 92.8	1633	55
5	3-BrC_6H_4	4.21	80.9; 89.0	1636	55
6	3-$CHOC_6H_4$	4.25	81.3; 88.8	1656	44
7	4-FC_6H_4	4.18	81.4; 87.0	1646	15
8	pyridin-3-yl	4.25	79.4; 90.7	1657	47
9	3-ClC_6H_4	4.21	81.0; 88.9	1634	51
10	4-ClC_6H_4	4.20	81.3; 88.5	1634	36
11	3-$MeOC_6H_4$	4.19	82.5; 87.0	1655	24

[a]) 300 MHz, (D_6)acetone; *d*, $J = 5-6$ Hz. [b]) 75 MHz, (D_6)acetone. [c]) KBr pellets. [d]) Yield of the isolated acetamide.

In general, the best results were obtained with aryl iodides containing electron-withdrawing substituents, the highest yield being 60% with 4-iodobenzonitrile, after loading of propargylamine to *Wang* resin, coupling, cleavage, and acetylation (*Table*, *Entry 4*). The 1-chloro-2-iodobenzene, and 1-bromo-3-iodobenzene gave both 55% yield (*Entries 4* and *5*) of the coupling product after cleavage and acetylation, suggesting that the position of the substituent at the aromatic ring does not play an important role in the success of the coupling. Furthermore, the latter reactant showed total selectivity of the I- over the Br-substituent as a leaving group. The only exception of the general rule was the reactivity of 1-fluoro-4-iodobenzene: with the high electronegativity of the F-atom, a better yield than the obtained 15% (*Entry 7*) would

have been expected. Of course, it is possible that the high electron withdrawal surpasses unexpected side reactions as well.

The reaction of 4-iodoanisole (=1-iodo-4-methoxybenzene) did not give the desired coupling product at all, neither at room temperature overnight nor even after 92 h at 70°. However, 3-iodoanisole (=1-iodo-3-methoxybenzene), where the substituent acts mainly as σ-acceptor, gave a 24% yield after attachement, coupling at room temperature, cleavage, and acetylation (*Entry 11*). According to this observation, the coupling reaction is retarded more strongly when electron density is donated by conjugation.

In addition, the coupling reaction of 3-iodobenzaldehyde proceeded successfully (*Entry 6*). After the cleavage from the polymer, the product was released from its CF_3COO^- salt and acetylated immediately at $-100°$. This exceptional acetylation procedure was applied to avoid rapid polymerization of the aminoaldehyde at room temperature. The corresponding acetylated derivative obtained could be routinely purified by silica gel column chromatography. Generally, all the acetylenic acetamides prepared were sufficiently stable when stored under dry conditions at room temperature.

Interpreting the ^{1}H-NMR spectra of the acetamides derived from the coupling products is rather straightforward. In all spectra, the CH_2 group of the propynyl moiety gives a *d* at δ 4.2–4.3 with a coupling constant of 5–6 Hz arising from the coupling with the amide NH proton. In the case of the 2-chloro-substituted product, also the signal of the amide NH proton is visible as a broad signal in the aromatic region. In the ^{13}C-NMR spectrum of the 4-fluoro-substituted product, the F-atom couples strongly to all C-atoms of the aromatic ring.

Conclusions. – We have combined the advantages of the efficient solid-phase-synthesis methodology and the wide applicability of palladium-catalyzed coupling reactions in the *Sonogashira* reaction of polymer-supported propargylamine with aryl iodides. The amino group that is problematic in the *Sonogashira* coupling is easily converted into a mildly cleavable carbamate linker at the attachment to the *Wang* resin. The reactions proceed generally with moderate to good yields at room temperature, and the use of base, *e.g.*, Et_3N, as the co-solvent is necessary. Our solid-phase method provides new possibilities for the syntheses of pharmacologically interesting carbocyclic and heterocyclic 3-arylprop-2-yn-1-amines and 3-arylpropan-1-amines.

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Experimental Part

General. Reagents were obtained from *Aldrich*, *Fluka*, *Acros*, and *Riedel-de Haën*. *Wang* resin (polymer-bound 4-(benzyloxy)benzyl alcohol, loading 0.64–1.1 mmol/g; 100–200 or 200–400 mesh; cross-linked with 1% divinylbenzene) was commercially available from *NovaBiochem*. The yields are based on the actual loading of the commercial resin. The solvent 1,4-dioxane was dried by distilling over Na, or dry 1,4-dioxane from *Acros* was used. Et_3N was predried with $CaSO_4$ and distilled over P_2O_5. Otherwise, commercial-grade reagents and solvents were used without further purification or drying. TLC: *Merck* aluminium sheets coated with silica gel *60* F_{254} (SiO_2); visualization by UV at 254 nm.

Column chromatography (CC): *Merck silica gel 60*, SiO_2; 230–400 mesh HPLC: *Acquity-UPLC-BEH-C_{18}* column (1.7 μm, 2.1 × 50 mm; *Waters*), column oven set at 40°; eluents 0.1% aq. HCO_2H soln. and MeCN, linear gradient 5–90% MeCN within 4 min; flow rate 1.0 ml/min. M.p.: *Electrothermal-IA9100* digital melting-point apparatus; uncorrected. LC/UV Analyses: *Waters Acquity UPLC* instrument equipped with an *Acquity* photodiode-array UV detector at 210 nm (40 scans/min). IR Spectra: *Bruker-Vertex-70* FT-IR spectrometer; KBr technique; $\tilde{\nu}$ in cm^{-1}. NMR Spectra: *Varian-Mercury-300-Plus* spectrometer; in (D_6)acetone; chemical shifts δ in ppm rel. to Me_4Si (= 0.00 ppm) in the ^1H spectra (300 MHz) and rel. to (D_6)acetone (= 29.84 ppm) in the ^{13}C spectra (75 MHz). GLC/MS: *Hewlett-Packard-HP-5890A* gas chromatograph equipped with an *HP-5970* mass-selective detector; capillary column *HP5-MS* (12 m × 0.25 mm); carrier gas He; oven temp. program: 100° (0 min), 20°/min, 310° (3 min); injection and detection temp. 250 and 280°, resp.; in *m/z* (rel. %). Elemental analyses: *Robertson Microlit Laboratories Inc.*, Madison, N. J.

Loading of Propargylamine to Wang *Resin through a Carbamate Linker.* Propargylamine was attached to the *Wang* resin according to a reported procedure [26] suitable for primary and secondary amines with minor modifications. *Wang* resin (polymer-bound 4-(benzyloxy)benzyl alcohol loading 0.64–1.1 mmol/g) was swelled in CH_2Cl_2 (12 ml/g resin). Pyridine (1.15 ml/g resin) was added, and then 4-nitrophenyl carbonochloridate (5 equiv.) in CH_2Cl_2 (7.5 ml/g). The mixture was stirred at r.t. for 2 h, filtered, and washed with CH_2Cl_2 (5 × 5 ml/g resin). The resulting carbonate resin was added immediately into the soln. of propargylamine (5 equiv.) in DMF (1:60; *v/v*) at 0°. The mixture was stirred at r.t. for 20 h. After filtering, the resin was washed twice (2 × 5 ml/g resin) each with DMF, MeOH, THF, Et_2O, and CH_2Cl_2, and dried *in vacuo*.

Sonogashira *Coupling of Polymer-Bound Propargylamine with Aryl Iodides in Solution: General Procedure 1 (G.P.1)*. Polymer-bound propargylamine (600–1000 mg, 0.64–1.1 mmol/g), aryl iodide (3–5 equiv.), and CuI (60–70 mg, 0.4 equiv.) were mixed with anh. 1,4-dioxane (10 ml) and anh. Et_3N (5 ml) under Ar. $[Pd(PPh_3)_2]Cl_2$ (95–120 mg, 0.2 equiv.) was added under a gentle flow of Ar. The mixture was stirred at r.t. for 20–73 h. After filtering, the resin was washed with 2 × 10 ml of each DMF, MeOH, THF, Et_2O, and CH_2Cl_2, and dried in *vacuo*.

Cleavage and Acetylation of the Coupling Product: General Procedure 2 (G.P.2) Polymer-bound coupling product (600–800 mg) was stirred in CF_3COOH/CH_2Cl_2 1:1 (5 ml) at r.t. for 2 h. After filtering, the resin was washed successively with CH_2Cl_2 and MeOH. The filtrate was concentrated to give the crude product which was dissolved in *N,N*-diisopropylethylamine (1 ml) and Ac_2O (1 ml). A cat. amount of DMAP was added, and the mixture was stirred at r.t. for 2 h. The solvents were evaporated twice with EtOH (10 ml) to give the crude acetylated product, which was subjected to CC (SiO_2).

N-*(3-Phenylprop-2-yn-1-yl)acetamide.* According to the *G.P.1*, with polymer-bound propargylamine (806 mg, 1.1 mmol/g), iodobenzene (500 μl, 915 mg, 4.49 mmol), CuI (72.1 mg, 0.379 mmol), and $[Pd(PPh_3)_2]Cl_2$ (120 mg, 0.171 mmol) for 44 h. Cleavage (749 mg) and acetylation according to the *G.P.2* followed by CC (SiO_2, AcOEt/hexane 3:1) gave the known [32] compound (57.8 mg, 41%). Pale yellow solid. M.p. 72–73° ([24]: 78.2–79.4°). R_f 0.41 (acetone/AcOEt 1:4). FT-IR: 695, 763, 1029, 1295, 1542, 1651, 3299. ^1H-NMR: 1.93 (*s*, 3 H); 4.21 (*d*, *J* = 5.4, 2 H); 7.32–7.42 (*m*, 5 H). ^{13}C-NMR: 22.7; 29.7; 82.6; 87.2; 123.9; 129.1; 129.3; 132.3; 169.8. GLC/MS: 173, 158, 130 (100), 103.

N-*[3-(4-Nitrophenyl)prop-2-yn-1-yl]acetamide.* According to the *G.P.1*, with polymer-bound propargylamine (804 mg, 1.1 mmol/g), 1-iodo-4-nitrobenzene (804 mg, 3.68 mmol), CuI (71.7 mg, 0.376 mmol), and $[Pd(PPh_3)_2]Cl_2$ (123 mg, 0.175 mmol) for 44 h. Cleavage (755 mg) and acetylation according to the *G.P.2* followed by CC (SiO_2, AcOEt) gave the product (93.8 mg, 52%). Yellow crystals. M.p. 137–138°. R_f 0.38 (acetone/AcOEt 1:4). FT-IR: 687, 857, 1280, 1347, 1540, 1643, 3308. ^1H-NMR: 1.95 (*s*, 3 H); 4.28 (*d*, *J* = 5.1, 2 H); 7.66 (*d*, *J* = 9.0, 2 H); 8.23 (*d*, *J* = 9.0, 2 H). ^{13}C-NMR: 22.7; 29.7; 80.9; 92.8; 124.5; 130.6; 133.4; 148.1; 169.9. GLC/MS: 218 (100), 203, 175, 129, 103. Anal. calc. for $C_{11}H_{11}N_2O_3$ (219.22): C 60.55, H 4.62, N 12.84; found: C 60.70, H 4.77, N 12.55.

N-*[3-(4-Cyanophenyl)prop-2-yn-1-yl]acetamide.* According to the *G.P.1*, with polymer-bound propargylamine (823 mg, 1.1 mmol/g), 4-iodobenzonitrile (511 mg, 2.58 mmol), CuI (70.9 mg, 0.372 mmol), and $[Pd(PPh_3)_2]Cl_2$ (120 mg, 0.171 mmol) for 72 h. Cleavage (749 mg) and acetylation according to the *G.P.2* followed by CC (SiO_2, acetone/AcOEt 1:5) gave the product (97.7 mg, 60%). Colorless crystals. M.p. 159–161°. R_f 0.38 (acetone/AcOEt 1:4). FT-IR: 677, 842, 1275, 1539, 1642, 2227,

3308. ^{1}H-NMR: 1.9 (*s*, 3 H); 4.25 (*d*, *J* = 6.0, 2 H); 7.59 (*d*, *J* = 8.7, 2 H); 7.77 (*d*, *J* = 8.7, 2 H). ^{13}C-NMR: 22.7; 29.7 81.1; 91.9; 112.5; 118.9; 128.7; 133.1; 169.8. GLC/MS: 198, 183, 155 (100). Anal. calc. for $C_{12}H_{10}N_2O$ (198.22): C 72.71, H 5.08, N 14.13; found: C 71.63, H 4.96, N 13.37.

N-*[3-(2-Chlorophenyl)prop-2-yn-1-yl]acetamide.* According to the *G.P.1*, with polymer-bound propargylamine (1006 mg, 0.74 mmol/g), 1-chloro-2-iodobenzene (460 µl, 898 mg, 4.32 mmol), CuI (60.5 mg, 0.318 mmol), and $[Pd(PPh_3)_2]Cl_2$ (108 mg, 0.154 mmol) for 18 h. Cleavage (815 mg) and acetylation according to the *G.P.2* followed by CC (SiO_2, hexane/AcOEt 1:4) gave the product (68.3 mg, 55%). Yellow crystals. M.p. 106–108°. R_f 0.42 (acetone/AcOEt 1:4). FT-IR: 669, 758, 1063, 1278, 1544, 1633, 3294. ^{1}H-NMR: 1.95 (*s*, 3 H); 4.28 (*d*, *J* = 5.4, 2 H); 7.28–7.40 (*m*, 2 H); 7.45–7.52 (*m*, 2 H); 7.6–7.7 (br., NH). ^{13}C-NMR: 22.7; 29.7; 76.2; 92.8; 123.5; 127.8; 130.1; 130.6; 134.4; 169.8. GLC/MS: 209, 207 (100), 166, 164, 130, 101. Anal. calc. for $C_{11}H_{10}ClNO$ (207.66): C 63.62, H 4.85, N 6.75; found: C 63.53, H 5.08, N 6.55.

N-*[3-(3-Bromophenyl)prop-2-yn-1-yl]acetamide.* According to the *G.P.1*, with polymer-bound propargylamine (815 mg, 1.1 mmol/g), 1-bromo-3-iodobenzene (340 µl, 754 mg, 2.67 mmol), CuI (77.8 mg, 0.409 mmol), and $[Pd(PPh_3)_2]Cl_2$ (120 mg, 0.171 mmol) for 22 h. Cleavage (770 mg) and acetylation according to the *G.P.2* followed by CC (SiO_2, AcOEt, acetone/AcOEt 1:5) gave the product (117 mg, 55%). Yellow crystals. M.p. 89–91°. R_f 0.42 (acetone/AcOEt 1:4). FT-IR: 678, 773, 1242, 1294, 1558, 1636, 3065, 3249. ^{1}H-NMR: 1.93 (*s*, 3 H); 4.21 (*d*, *J* = 5.7, 2 H); 7.28–7.42 (*m*, 3 H); 7.52–7.57 (*m*, 1 H). ^{13}C-NMR: 22.7; 29.6; 80.9; 89.0; 122.6; 126.1; 131.18; 131.25; 132.3; 134.8; 169.8. GLC/MS: 253, 251, 238, 236, 210, 208 (100), 130, 102, 75. Anal. calc. for $C_{11}H_{10}BrNO$ (252.11): C 52.41, H 4.00, N 5.56; found: C 52.17, H 3.79, N 5.28.

N-*[3-(3-Formylphenyl)prop-2-yn-1-yl]acetamide.* According to the *G.P.1*, with polymer-bound propargylamine (808 mg, 1.1 mmol/g), 3-iodobenzaldehyde (633 mg, 2.73 mmol), CuI (72.4 mg, 0.380 mmol), and $[Pd(PPh_3)_2]Cl_2$ (120 mg, 0.171 mmol) for 22 h. After cleavage (777 mg) according to the *G.P.2*, and concentration, the residue was cooled to −100° in a liq. N_2/EtOH bath, and Ac_2O (1.0 ml), *N*,*N*-diisopropylethylamine (1.0 ml), and a cat. amount of DMAP were added. The mixture was stirred in the cooling bath from −100° to r.t. for 22 h. After evaporation with EtOH (2 × 10 ml), the residue was subjected to CC (SiO_2, hexane/AcOEt 1:2, AcOEt, acetone/AcOEt 1:10) gradient to give the product (76.1 mg, 44%). Red-brown oil. R_f 0.37 (acetone/AcOEt 1:4). FT-IR: 685, 1160, 1282, 1542, 1656, 1700, 3063, 3281. ^{1}H-NMR: 1.9 (*s*, 3 H); 4.25 (*d*, *J* = 5.4, 2 H); 7.54–7.74 (*m*, 3 H); 7.87–7.93 (*m*, 1 H); 10.0 (*s*, 1 H). ^{13}C-NMR: 22.7; 29.7; 81.3; 88.8; 124.9; 129.7; 130.3; 133.2; 137.6; 137.8; 170.0; 192.4. GLC/MS: 201 (100), 186, 158, 130, 77. Anal. calc. for $C_{12}H_{11}NO_2$ (201.22): C 71.63, H 5.51, N 6.96; found: C 69.22, H 5.08, N 6.36.

N-*[3-(4-Fluorophenyl)prop-2-yn-1-yl]acetamide.* According to the *G.P.1*, with polymer-bound propargylamine (811 mg, 1.1 mmol/g), 1-fluoro-4-iodobenzene (510 µl, 982 mg, 4.42 mmol), CuI (69.6 mg, 0.365 mmol), and $[Pd(PPh_3)_2]Cl_2$ (120 mg, 0.171 mmol) for 24 h. Cleavage (762 mg) and acetylation according to the *G.P.2* followed by CC (SiO_2, AcOEt) gave the product (24.1 mg, 15%). Pale yellow crystals. M.p. 105°. R_f 0.41 (acetone/AcOEt 1:4). FT-IR: 728, 817, 817, 840, 1094, 1221, 1507, 1547, 1646, 3296. ^{1}H-NMR: 1.91 (*s*, 3 H); 4.18 (*d*, *J* = 5.4, 2 H); 7.09–7.18 (*m*, 2 H); 7.42–7.49 (*m*, 2 H). ^{13}C-NMR (*o*, *m*, *p*, *ipso* with respect to F): 22.7; 29.5; 81.4; 87.0; 116.5 (*d*, $^2J(C_o,F) = 22.2$); 120.3 (*d*, $^4J(C_p,F) = 3.4$); 134.5 (*d*, $^3J(C_m,F) = 8.3$); 163.3 (*d*, $^1J(C_{ipso},F) = 245.9$); 169.7. GLC/MS: 191, 176, 148 (100), 133. Anal. calc. for $C_{11}H_{10}FNO$ (191.20): C 69.10, H 5.27, N 7.33; found: C 67.44, H 4.56, N 6.95.

N-*[3-(Pyridin-3-yl)prop-2-yn-1-yl]acetamide.* According to the *G.P.1*, with polymer-bound propargylamine (804 mg, 1.1 mmol/g), 3-iodopyridine (547 mg, 2.67 mmol), CuI (85.5 mg, 0.449 mmol), and $[Pd(PPh_3)_2]Cl_2$ (121 mg, 0.172 mmol) for 22 h. Cleavage (762 mg) and acetylation according to the *G.P.2* followed by CC (SiO_2, acetone/AcOEt 1:2) gave the product (67.6 mg, 47%). Dark red oil. R_f 0.19 (acetone/AcOEt 1:4). FT-IR: 705, 1286, 1409, 1545, 1657, 3057, 3266. ^{1}H-NMR: 1.95 (*s*, 3 H); 4.25 (*d*, *J* = 5.4, 2 H); 7.37 (*ddd*, *J* = 0.9, 4.8, 7.8, 1 H); 7.78 (*td*, *J* = 1.8, 8.1, 1 H); 8.54 (*dd*, *J* = 1.7, 5.0, 1 H); 8.59 (*d*, *J* = 1.5, 1 H). ^{13}C-NMR: 22.7; 29.7; 79.4; 90.7; 120.8; 124.1; 139.2; 149.6; 152.8; 169.9. GLC/MS: 174, 159, 131 (100), 105, 104, 79. Anal. calc. for $C_{10}H_{10}N_2O$ (174.20): C 68.95, H 5.79, N 16.08; found: C 66.00, H 5.88, N 14.78.

N-*[3-(3-Chlorophenyl)prop-2-yn-1-yl]acetamide.* According to the *G.P.1*, with polymer-bound propargylamine (806 mg, 1.1 mmol/g), 1-chloro-3-iodobenzene (550 µl, 1060 mg, 4.45 mmol), CuI

(69.7 mg, 0.366 mmol), and $[Pd(PPh_3)_2]Cl_2$ (122 mg, 0.172 mmol) for 22 h. Cleavage (806 mg) and acetylation according to the *G.P.2* followed by CC (SiO_2, AcOEt) gave the product (93.0 mg, 51%). Pale yellow crystals. M.p. 84–85°. R_f 0.36 (acetone/AcOEt 1:4). FT-IR: 679, 776, 1097, 1240, 1295, 1562, 1634, 3066, 3249. ^{1}H-NMR: 1.93 (*s*, 3 H); 4.21 (*d*, *J* = 5.7, 2 H); 7.34–7.44 (*m*, 4 H). ^{13}C-NMR: 22.7; 29.5; 81.0; 88.9; 125.8; 129.4; 130.8; 130.8; 131.1; 131.9; 134.6; 169.7. GLC/MS: 209, 207, 194, 192, 166, 164 (100), 130, 102. Anal. calc. for $C_{11}H_{10}ClNO$ (207.66): C 63.62, H 4.85, N 6.75; found: C 63.35, H 5.13, N 6.48.

N-*[3-(4-Chlorophenyl)prop-2-yn-1-yl]acetamide.* According to the *G.P.1*, with polymer-bound propargylamine (814 mg, 1.1 mmol/g), 1-chloro-4-iodobenzene (1076 mg, 4.51 mmol), CuI (73.0 mg, 0.383 mmol), and $[Pd(PPh_3)_2]Cl_2$ (122 mg, 0.172 mmol) for 22 h. Cleavage (814 mg) and acetylation according to the *G.P.2* followed by CC (SiO_2, AcOEt) gave the product (67.8 mg, 36%). Pale yellow solid. M.p. 128–130°. R_f 0.35 (acetone/AcOEt 1:4). FT-IR: 619, 750, 828, 1089, 1250, 1296, 1634, 2854, 2922, 3254. ^{1}H-NMR: 1.92 (*s*, 3 H); 4.20 (*d*, *J* = 5.1, 2 H); 7.36–7.46 (*m*, 4 H). ^{13}C-NMR: 22.7; 29.6; 81.3; 88.5; 122.7; 129.6; 133.9; 134.6; 169.7. GLC/MS: 209, 207, 194, 192, 166, 164 (100), 149, 130, 113, 102. Anal. calc. for $C_{11}H_{10}ClNO$ (207.66): C 63.62, H 4.85, N 6.75; found: C 63.84, H 5.41, N 6.23.

N-*[3-(3-Methoxyphenyl)prop-2-yn-1-yl]acetamide.* According to the *G.P.1*, with polymer-bound propargylamine (804 mg, 1.1 mmol/g), 1-iodo-3-methoxybenzene (530 µl, 1040 mg, 4.44 mmol), CuI (71.4 mg, 0.375 mmol), and $[Pd(PPh_3)_2]Cl_2$ (118 mg, 0.168 mmol) for 21 h. Cleavage (804 mg) and acetylation according to the *G.P.2* followed by CC (SiO_2, AcOEt) gave the product (56 mg, purity by LC/UV 79%, *i.e.*, 44 mg of pure product, 24%). Brown yellow oil. R_f 0.36 (acetone/AcOEt 1:4). FT-IR: 1041, 1203, 1288, 1655, 2932, 3279. ^{1}H-NMR: 1.92 (*s*, 3 H); 3.80 (*s*, 3 H); 4.19 (*d*, *J* = 5.4, 2 H); 6.85–7.03 (*m*, 3 H); 7.16–7.31 (*m*, 1 H). ^{13}C-NMR: 22.7; 29.6 (overlapped with (D_6)acetone); 55.6; 82.5; 87.0; 115.5; 117.2; 122.4; 124.7; 130.42; 130.44; 160.5. GLC/MS: 203 (100), 202, 188, 160, 145, 130. Anal. calc. for $C_{12}H_{13}NO_2$ (203.24): C 70.92, H 6.45, N 6.89; found: C 69.27, H 6.68, N 4.80.

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