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Synthesis of Polar Aromatic Substituted Terminal Alkynes from Propargyl Amine

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Abstract: A series of small molecules containing polar aromatic substituents and alkynes have been synthesized. One–pot preparations of polar aromatic molecules containing an alkynyl imine and alkynyl amide are reported. A one-pot preparation of a catechol containing an alkynyl amine was also attempted but in our hands it proved much better to synthesize this target molecule via a three step synthesis which we also report here.

Keywords: catechol; alkyne; thiol-alkyne click reaction

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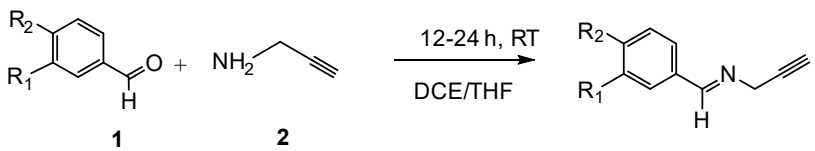
1. Introduction

A series of small molecules containing polar aromatic substituents and propargyl amines were synthesized so that they could potentially be incorporated into hydrogel systems as an approach to developing a better hydrogen bonded and more rigid hydrogel via a thiol-alkyne click reaction [1–6]. Propargyl amines are also an important class of molecules in their own right, and are used as building blocks in heterocyclic chemistry and pharmaceutical chemistry [7,8]. Three main structural aspects of the small molecules to be synthesized were considered: (1) a polar functional group for enhanced hydrogen bonding, (2) an alkyne functional group for attachment to thiol containing hydrogels via the thiol-alkyne click reaction, and (3) ease of synthesis of the small molecule, i.e., where possible, one-pot reactions from inexpensive, commercially available starting materials.

2. Results and Discussion

To satisfy the above criteria, we initially performed reactions between substituted benzaldehydes (**1**) with propargyl amine (**2**) as shown in Scheme 1. Condensation of propargyl amine (**2**) with the aldehydes (**1**) led to the imines (**3**–**8**) in good yield.

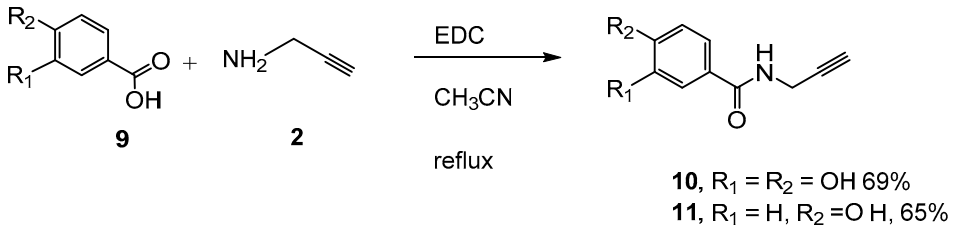


1 **2**

3 R_1 = OH, R_2 = OH, 85%
4 R_1 = H, R_2 = CO_2 H, 93%
5 R_1 = F, R_2 = OH, 90%
6 R_1 = H, R_2 = $NHC(O)CH_3$, 87%
7 R_1 = H, R_2 = CO_2CH_3, 89%
8 R_1 = H, R_2 = OH, 88%

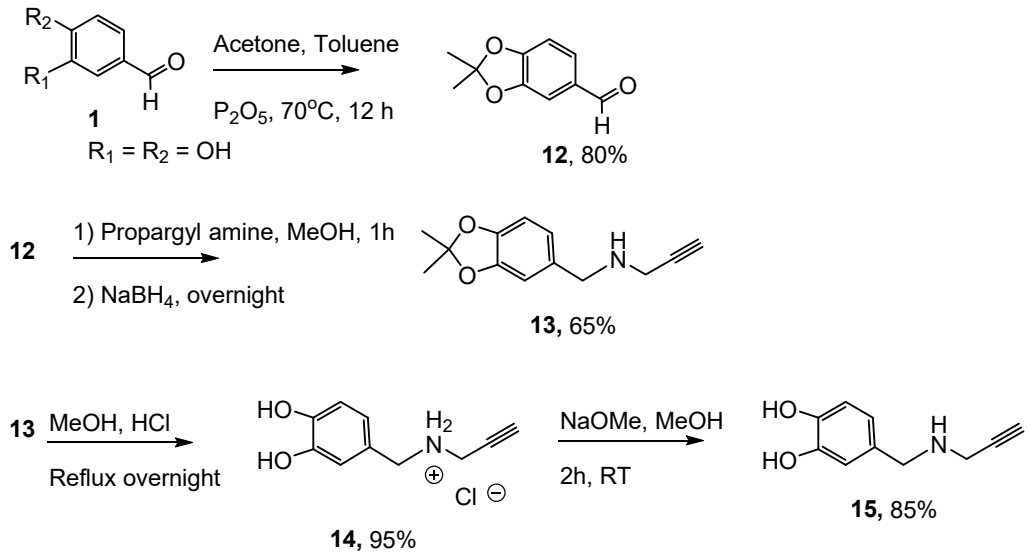
Scheme 1. Preparation of propargyl imines from propargyl amine.

Likewise, the coupling of propargyl amine (**2**) with the benzoic acids (**9**) using EDC as a coupling agent led to the amides (**10**, **11**) also in good isolated yield (Scheme 2).



Scheme 2. Preparation of propargyl amides from propargylamine.

Preparation of the amine (**15**) proved much more complicated. There is a reported literature procedure for reductive amination of 3,4-dihydroxybenzaldehyde with propargyl amine [9], but the reported yield is low (31%). The product is reported as a red solid, which seems unlikely for a pure compound with just a benzene ring or alkyne as a chromophore and it could be that this material also contains some charge transfer complexes produced under these conditions. When we performed the literature reaction, we isolated mixtures of amine **15** and what we think may possibly be the catecholboronate dimer. Rather than spend a lot of time trying to rigorously identify this byproduct, we chose to investigate an alternate, straightforward route for the preparation of compound **15** (Scheme 3. See Supplementary Materials). Ultimately, to obtain pure amine (**15**), we found that we first had to protect the catechol (**1**, $R_1 = R_2 = OH$) as previously reported acetonide (**12**) [10,11], which was then subjected to reductive amination to produce (**13**) as shown in Scheme 3. Acetonide (**13**) was deprotected to yield ammonium salt (**14**) which was then deprotonated to yield the desired amine (**15**).



Scheme 3. Optimized preparation of amine **15**.

3. Experimental

General Methods

NMR spectra were obtained on a Bruker 400 MHz spectrometer and mass spectrometry was performed on a Thermo LTQ Orbitrap XL. All reagents and materials were obtained from the suppliers listed below. Fischer Scientific: sodium sulfate; Acros: 1,2-Dichloroethane, 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide, propargylamine; Sigma Aldrich: all aromatic aldehydes and acids; Cambridge Isotope Laboratories: Dimethyl Sulfoxide-d_6 + 0.05% v/v TMS. Compounds **3**, **10** and **15** are also described in a patent [12].

(E)-4-((Prop-2-yn-1-ylimino)methyl)benzene-1,2-diol (**3**). To a solution of 3,4-dihydroxybenzlaldehyde (0.200 g, 1.45 mmol) in 5:1 DCE:THF (6 mL), propargylamine (**2**) (111 µL, 1.74 mmol, 1.2 eq) was added dropwise. Fifteen minutes into the reaction, a grey solid started to precipitate. The reaction mixture was stirred for 2 h at room temperature under nitrogen. The resulting precipitate was filtered under vacuum, washed with 5:1 DCE:THF solution (3 × 5 mL), and dried under high vacuum. Compound **3** was isolated as a tan solid (0.218 g, 1.24 mmol, 85%). ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 9.14 (br s, 2H), 8.29 (s, 1H), 7.21 (s, 1H), 7.00 (d, *J* = 8.0 Hz, 1H), 6.78 (d, *J* = 8.0 Hz, 1H), 4.38 (dd, *J* = 2.5, 1.7 Hz, 2H), 3.37 (t, *J* = 2.5 Hz, 1H). ^{13}C-NMR (101 MHz, DMSO-d_6) δ: 162.17, 149.01, 146.02, 127.87, 121.82, 115.81, 114.20, 80.97, 77.36, 47.08. HRMS (EI) for $C_{10}H_9NO_2$ 176.0712 $[M + H]^+$, found 176.0713.

(E)-4-((prop-2-yn-1-ylimino)methyl)benzoic acid (**4**). To a solution of 4-carboxybenzadehyde (0.200 g, 1.33 mmol) in 1,2-dichloroethane (10 mL), propargylamine (103 µL, 1.60 mmol, 1.2 eq) was added dropwise and the reaction was magnetically stirred under nitrogen overnight at room temperature. The resulting precipitate was filtered, washed with DCE (3 × 5 mL), and dried under high vacuum. Compound **4** was isolated as a light tan solid (0.232 g, 1.23 mmol, 93%). ^{1}H-NMR (400 Hz, DMSO-d_6) δ: 8.62 (t, *J* = 1.9 Hz, 1H), 8.01 (m, 2H), 7.88 (m, 2H), 4.55 (m, 2H), 3.48 (t, *J* = 2.5 Hz, 1H). ^{13}C-NMR (101 MHz, DMSO-d_6) δ: 167.52, 161.87, 139.43, 133.93, 130.10, 128.50, 80.15, 78.19, 47.36. HRMS (EI) for $C_{11}H_9NO_2$ 188.0712 $[M - H]^+$, found 188.0705.

(E)-2-fluoro-4-((prop-2-yn-1-ylimino)methyl)phenol (**5**). To a solution of 3-fluoro-4-hydroxybenzadehyde (0.200 g, 1.43 mmol) in a 5:1 DCE:THF (6 mL), propargylamine (110 µL, 1.46 mmol, 1.2 eq) was added dropwise and the reaction was magnetically stirred under nitrogen overnight at room temperature. The reaction solvent was then dried with sodium sulfate, filtered, and evaporated in vacuo and the obtained product was dried under high vacuum. Compound **5** was isolated as a solid (0.228 g, 1.28 mmol, 90%). ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 10.39 (br s, 1H), 8.39 (s, 1H), 7.53 (d, *J* = 12.0, 1.9 Hz, 1H), 7.41 (d, *J* = 8.4, 1.9 Hz, 1H), 7.02 (t, *J*= 8.6 Hz, 1H), 4.43 (s, 2H), 3.41 (t, *J* = 2.4 Hz, 1H).^{13}C-NMR (101 MHz, DMSO-d_6) δ: 161.09, 151.6 (d, *J* = 243 Hz), 150.39, 148.31, 128.03, 125.93, 118.12, 115.23 (d, *J* = 19 Hz), 80.57, 77.73, 46.96. HRMS (EI) for $C_{10}H_9FNO$ 178.0668 $[M - H]^+$, found 178.0670.

N-(4-((prop-2-yn-1-ylimino)methyl)phenyl)acetamide (**6**). To a solution of 4-acetamidobenzaldehyde (0.200 g, 1.23 mmol) in 5:1 DCE:THF (6 mL), propargylamine (94 µL, 1.47 mmol, 1.2 eq) was added dropwise and the reaction was magnetically stirred under nitrogen overnight at room temperature. The reaction solvent was then dried with sodium sulfate, filtered then evaporated in vacuo and the obtained product was dried under high vacuum. Compound **6** was isolated as a light yellow solid (0.215 g, 1.07 mmol, 87%). ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 10.16 (s, 1H), 8.45 (t, *J* = 1.8 Hz, 1H), 7.68 (m, 4H), 4.45 (br s, 2H), 3.41 (t, *J* = 2.5 Hz, 1H), 2.08 (s, 3H). ^{13}C-NMR (101 MHz, DMSO-d_6) δ: 169.11, 161.80, 142.22, 130.81, 129.23, 119.14, 80.62, 77.78, 47.15, 24.58. HRMS (EI) for $C_{12}H_{13}N_2O$ 201.1028 $[M - H]^+$, found 201.1030.

Methyl (E)-4-((prop-2-yn-1-ylimino)methyl)benzoate (**7**). To a solution of methyl-4-formyl-benzoate (0.200 g, 1.22 mmol) in 1,2-dichloroethane (6 mL), propargylamine (94 µL, 1.47 mmol, 1.2 eq) was added dropwise and the reaction was magnetically stirred under nitrogen overnight at room temperature. The reaction solvent was then dried with sodium sulfate, filtered, and evaporated in vacuo and the obtained product was dried under high vacuum. Compound **7** was isolated as an off-white solid (0.219 g, 1.08 mmol, 89%). ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 8.63 (s, 1H), 8.04 (d, *J* = 8.2 Hz, 2H), 7.92 (d, *J* = 8.3 Hz, 2H), 4.56 (t, *J* = 2.2 Hz, 2H), 3.88 (s, 3H), 3.49 (t, *J* = 2.5 Hz, 1H). ^{13}C-NMR (101 MHz, DMSO-d_6) δ: 166.26, 161.71, 140.04, 131.91, 130.01, 128.71, 80.08, 78.26, 52.78, 47.39. HRMS (EI) for $C_{12}H_{11}NO_2$ 202.0863 $[M - H]^+$, found 202.0870.

(E)-4-((prop-2-yn-1-ylimino)methyl)phenol (**8**). To a solution of 4-hydroxybenzadehyde (0.200 g, 1.64 mmol) in 1,2-dichloroethane (6 mL), propargylamine (126 µL, 1.97 mmol, 1.2 eq) was added dropwise and the reaction was magnetically stirred under nitrogen overnight at room temperature. The reaction solvent was then dried with sodium sulfate, filtered, and evaporated in vacuo and the obtained product was dried under high vacuum. Compound **8** was isolated as a light red solid (0.232 g, 1.45 mmol, 88%). ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 9.85 (s, 1H), 8.39 (t, *J* = 1.7 Hz, 1H), 7.60 (d, *J* = 8.0 Hz, 2H), 6.83 (d, *J* = 8.0 Hz, 2H), 4.40 (t, *J* = 2.5, 1.7 Hz, 2H), 3.38 (t, *J* = 2.5 Hz, 1H).^{13}C-NMR (126 MHz, DMSO) δ: 161.90, 160.52, 130.27, 127.48, 115.96, 80.87, 77.50, 47.10. HRMS (EI) for $C_{10}H_9NO$ 160.0672 $[M - H]^+$, found 159.9674.

3,4-Dihydroxy-N-(prop-2-yn-1-yl)benzamide (**10**). To a stirred solution of 3,4-dihydroxybenzoic acid (**8**, $R_1 = R_2 = OH$) (0.200 g, 1.30 mmol, 1.0 eq) in acetonitrile (10 mL), propargylamine (**2**) (165 µL, 2.55 mmol, 2.0 eq) was added dropwise, resulting in a white precipitate. Subsequently, 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide (0.240 g, 1.55 mmol, 1.2 eq) was added slowly and the reaction mixture was refluxed overnight with magnetic stirring. Following the removal of the reaction solvent in vacuo, the product was extracted with ethyl acetate (3 × 20 mL) from water (10 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and the solvent was removed in vacuo. The crude product was purified by column chromatography on silica gel (3:4 EtOAc/Hex) to obtain compound **10** as a tan-colored solid (0.209 g, 1.09 mmol, 69%): ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 9.31 (br s, 2H), 8.56 (s, 1H), 7.29 (s, 1H), 7.20 (d, *J* = 8.3 Hz, 1H), 6.76 (d, *J* = 8.3 Hz, 1H), 3.99 (m, 2H), 3.06 (t, *J* = 2.5 Hz, 1H). ^{13}C-NMR (400 MHz, DMSO-d_6) δ: 166.25, 149.02, 145.32, 125.52, 119.51, 115.60, 115.33, 82.20, 72.94, 28.82. HRMS (ESI-TOF) for $C_{10}H_9NO_3$ 192.0661 $[M + H]^+$, found 192.0663.

4-hydroxy-N-(prop-2-yn-1-yl)benzamide (**11**). This compound has been prepared previously by an alternate procedure [13]. To a stirred solution of 4-hydroxybenzoic acid (**8**, $R_1 = OH$, $R_2 = H$) (0.200 g, 1.45 mmol, 1.0 eq) in acetonitrile (10 mL), propargylamine (111 µL, 1.74 mmol, 1.2 eq) was added dropwise, resulting in a white precipitate. Subsequently, 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide (0.270 g, 1.74 mmol, 1.2 eq) was added slowly and the reaction mixture was refluxed overnight with magnetic stirring. Following the removal of the reaction solvent in vacuo, the product was extracted with ethyl acetate (3 × 20 mL) from water (10 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and the solvent was removed in vacuo. The crude product was purified by column chromatography on silica gel (1:1 EtOAc/Hex) to obtain compound **11** as a tan-colored solid (0.185 g, 1.06 mmol, 73%) ^{1}H-NMR (400 MHz, DMSO-d_6) *δ*: 10.00 (s, 1H), 8.64 (t, *J* = 5.5 Hz, 1H), 7.72 (d, *J* = 8.0 Hz, 2H), 6.80 (d, *J* = 8.0, 2H), 4.01 (dd, *J* = 5.6, 2.5 Hz, 2H), 3.08 (t, *J* = 2.5 Hz, 1H). ^{13}C-NMR (101 MHz, DMSO-d_6) δ: 166.05, 160.75, 129.67, 124.96, 115.29, 82.13, 73.05, 28.80.

2,2-Dimethylbenzo[d][1,3]dioxole-5-carbaldehyde (**12**). A mixture of 3,4-dihydroxybenzaldehyde (**1**) (0.276 g, 2 mmol) and P_2O_5 (0.141 g, 1 mmol) was stirred in toluene (dry) (100 mL). Acetone (0.74 mL, 10 mmol) was added and the mixture stirred at 75 °C for 3 h. Four portions of P_2O_5 (4 × 0.100 g) were added every 30 min during heating. The reaction was quenched with 25% NaOH (aq) (25 mL) and the toluene solvent removed under vacuum after separation. The crude solid obtained was purified by column chromatography (DCM:Hexane, 2:1) to obtain a light brown solid (**12**) (0.300 g, 1.6 mmol, 80%) identical by NMR comparison to previously reported material [10,11]: ^{1}H-NMR (400 MHz, DMSO-d_6) δ 9.79 (s, 1H), 7.51 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.26 (d, *J* = 1.6 Hz, 1H), 7.06 (d, *J* = 8.0 Hz, 1H), 1.69 (s, 6H).

N-((2,2-Dimethylbenzo[d][1,3]dioxol-5-yl)methyl)prop-2-yn-1-amine (**13**). Compound **12** (0.250 g, 1.4 mmol) was dissolved in methanol (dry) (25 mL) and propargylamine (**3**) (0.13 mL, 2.0 mmol) was added dropwise. The solution was allowed to stir for 1 h and sodium borohydride (3 × 0.100 g, 8.0 mmol) was added in portions over 30 min. The reaction was stirred overnight under nitrogen atmosphere and quenched with brine (15 mL). The

aqueous was extracted using ethyl acetate (25 mL) and solvent dried (Na_2SO_4), and evaporated in vacuo to obtain a viscous liquid (**13**) (0.197 g, 0.91 mmol, 65%): ^{1}H-NMR (400 MHz, DMSO-d_6) δ 6.78 (dd, *J* = 1.4, 0.7 Hz, 1H), 6.72 (dd, *J* = 2.9, 1.0 Hz, 2H), 3.62 (s, 2H), 3.24 (d, *J* = 2.4 Hz, 2H), 3.06 (t, *J* = 2.4 Hz, 1H), 1.62 (s, 6H). ^{13}C-NMR (101 MHz, DMSO-d_6) δ: δ 147.31, 146.09, 133.86, 121.01, 118.01, 108.70, 108.02, 83.33, 74.13, 51.57, 36.90, 26.00. HRMS (ESI-TOF) for $C_{13}H_{16}NO_2$ 218.1181 $[M + H]^+$, found 218.1171.

N-(3,4-Dihydroxybenzyl)prop-2-yn-1-ammonium chloride (**14**). Compound **13** (0.180 g, 0.82 mmol) was dissolved in anhydrous methanol (20 mL) and purged with dry HCl for 5 min. The solution was refluxed overnight. The solvents were evaporated and the solid triturated with diethyl ether (3 × 5 mL) to obtain blue-black solid (**14**) (0.165 g, 0.77 mmol, 94%): ^{1}H-NMR (400 MHz, DMSO-d_6) δ 9.67 (s, 2H), 7.08–6.66 (m, 3H), 3.96 (brs, 2H), 3.78 (brs, 2H), 3.73 (brs, 1H), 3.17 (brs, 1H). ^{13}C-NMR (101 MHz, DMSO-d_6) δ: 146.68, 145.76, 122.25, 121.87, 118.11, 116.12, 80.06, 75.46, 49.32, 35.20. HRMS (ESI-TOF) for $C_{10}H_{12}NO_2$ 178.0868 $[M + H]^+$, found 178.0862.

4-((Prop-2-yn-1-ylamino)methyl)benzene-1,2-diol (**15**). Compound **14** (0.150 g, 0.7 mmol) was dissolved in methanol (anhydrous) (20 mL) and sodium methoxide (0.040 g, 0.74 mmol) was added. The mixture was stirred for 2 h at room temperature and quenched with DI water 1 mL). The mixture was then filtered through celite and the solvent was removed in vacuo to yield a brown solid (**15**) (0.105 g, 0.593 mmol, 85%): ^{1}H-NMR (400 MHz, DMSO-d_6) δ 6.71 (d, *J* = 2.1 Hz, 1H), 6.65 (d, *J* = 7.9 Hz, 1H), 6.52 (dd, *J* = 8.0, 2.1 Hz, 1H), 3.54 (s, 2H), 3.22 (d, *J* = 2.5 Hz, 2H), 3.05 (t, *J* = 2.4 Hz, 1H). ^{13}C-NMR (101 MHz, DMSO-d_6) δ: 145.03, 144.06, 130.74, 118.84, 115.78, 115.32, 82.97, 73.55, 50.93, 36.35. HRMS (ESI-TOF) for $C_{10}H_{12}NO_2$ 178.0868 $[M + H]^+$, found 178.0868.

4. Conclusions

We successfully prepared a number of new polar aromatic substituted terminal alkynes from propargyl amine and we hope scientists working with thiolated hydrogels will incorporate them into their hydrogels and that they will also be used in pharmaceutical chemistry, with the anticipation that those modified molecules will have interesting new properties.

Supplementary Materials: The following data are available online: ^{1}H and ^{13}C-NMR spectra for compounds **3**–**15**.

Author Contributions: K.M.Y. prepared compounds **3**–**11**; S.R.B. prepared compounds **12**–**15**; K.M.Y., S.R.B. and M.E.W. analyzed the spectral data and wrote the manuscript. All authors have read and agreed to the published version of the manuscript.

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