Supporting Information

Clicking 3'-azidothymidine into novel potent inhibitors of human immunodeficiency virus

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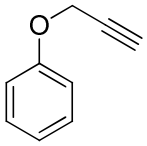
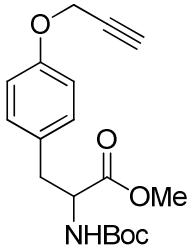
Table of contents

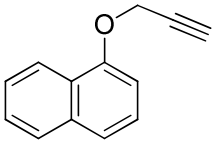
General procedure for the synthesis of propargyl aryl ethers from phenols. To a stirred solution of phenol (1.0 equiv.) in DMF were added K_2CO_3 (2.0 equiv.) and propargyl bromide (1.5 equiv.) in DMF at room temperature. The mixture was stirred at room temperature for 12-15h. Solvent was evaporated and water was added and extracted with ethyl acetate. The combined extracts were dried over Na_2SO_4 and concentrated to get crude product. The crude product was purified by column chromatography, eluted with 10-15% EtOAc in hexane, yielded the desired propargyl aryl ethers.



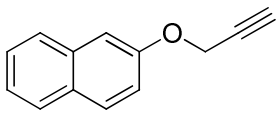
(Prop-2-yn-1-yloxy)benzene (7a). Prepared from phenol, yielded (prop-2-yn-1-yloxy)benzene **7a** (76%) as a oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.28–7.39 (m, 2H), 6.85–6.98 (m, 3H), 4.65 (s, 2H), 2.48 (s, 1H).



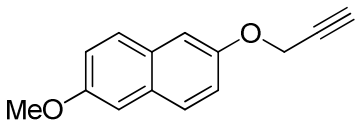
Methyl 2-((*tert*-butoxycarbonyl)amino)-3-(4-(prop-2-yn-1-yloxy)phenyl)propanoate (7b). Prepared from methyl 2-((tert-butoxycarbonyl)amino)-3-(4-hydroxyphenyl)propanoate, yielded methyl 2-((*tert*-butoxycarbonyl)amino)-3-(4-(prop-2-yn-1-yloxy)phenyl)propanoate **7b** (60%) as a oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.04 (d, J = 9.0 Hz, 2H), 6.88 (d, J = 9.0 Hz, 2H), 4.97 (d, J = 8.0 Hz, 1H), 4.65 (d, J = 2.4 Hz, 2H), 4.52-4.57 (m, 1H), 3.72 (s, 3H), 2.98-3.10 (m, 1H), 2.49 (t, J = 2.6 Hz, 1H), 1.41 (s, 9H).



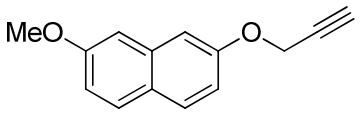
1-(Prop-2-yn-1-yloxy)naphthalene (7c). Prepared from naphthalen-1-ol, yielded 1-(prop-2-yn-1-yloxy)naphthalene **7c** (75%) as a solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.34-8.26 (m, 1H), 7.82 (dt, J = 4.0, J = 3.0 Hz, 1H), 7.50-7.52 (m, 3H), 7.42 (t, J = 7.9 Hz, 1H), 6.96 (d, J = 7.6 Hz, 1H), 4.91 (d, J = 2.4 Hz, 2H), 2.56 (t, J = 2.3 Hz, 1H).



2-(Prop-2-yn-1-yloxy)naphthalene (7d). Prepared from naphthalen-2-ol, yielded 2-(Prop-2-yn-1-yloxy)naphthalene **7d** (70%) as a pale yellow solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.71-7.67 (m, 3H), 7.40-7.36 (m, 1H), 7.29-7.27 (m, 1H), 7.17 (d, J = 2.5 Hz, 1H), 7.11 (dd, J = 2.6 Hz, J = 9.0 Hz, 1H), 4.74 (d, J = 2.4 Hz, 2H), 2.47 (t, J = 2.4 Hz, 1H).



2-Methoxy-6-(prop-2-yn-1-yloxy)naphthalene (7e). Prepared from 6-methoxynaphthalen-2-ol, yielded 2-methoxy-6-(prop-2-yn-1-yloxy)naphthalene **7e** (74%) as a solid, confirmed by NMR.



2-Methoxy-7-(prop-2-yn-1-yloxy)naphthalene (7f). Prepared from 7-methoxynaphthalen-2-ol, yielded 2-methoxy-7-(prop-2-yn-1-yloxy)naphthalene **7f** (72%) as a brown solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.62–7.69 (m, 2H), 7.18 (s, 1H), 6.96–7.12 (m, 3H), 4.78 (s, 2H), 3.94 (s, 3H), 2.56 (s, 1H).

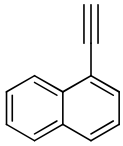
Dimethyl 2-Oxopropylphosphonate (11) To a stirred suspension of KI (82.0 g, 490 mmol) in acetone (100 mL) and MeCN (125 mL) was added chloroacetone **10** (45.0 g, 490 mmol). Stirring was continued for 1 h at room temperature. Trimethyl phosphite (58.0 mL, 490 mmol) was slowly added. After 12 h at room temperature, the mixture was heated to 50 °C to ensure complete conversion. Filtration through a pad of celite and evaporation of the solvents under reduced pressure yielded the crude product. The crude product was further purified by flash column chromatography (EtOAc/hexane 1:1) furnished the product **11 (**41.0 g, 353 mmol, 72%) as a colorless liquid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.78 (d, J = 11.0 Hz, 6H), 3.07 (d, J = 22.8 Hz, 2H), 2.29 (s, 3H).

Tosyl azide (13) Tosylchloride (5.72 g, 26.0 mmol) was dissolved in acetone (85 mL) and water (85 mL). The solution was cooled in ice-bath and NaN_3 (1.71 g, 26.0 mmol) was added. The reaction was stirred for 2 h at the same temperature, then 12 h at room temperature. The acetone was removed under vacuum and the remaining water layer was extracted with EtOAc (2 x 50 mL). The EtOAc layer was dried over Na_2SO_4, filtered and concentrated. The intermediate tosyl azide was obtained as a white solid **13** (4.8 g, 24.3 mmol, 94%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.83 (d, J = 8.4 Hz, 2H), 7.39 (d, J = 8.4 Hz, 2H), 2.46 (s, 3H).

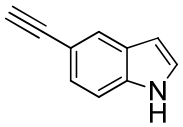
Dimethyl 1-Diazo-2-oxopropylphosphonate (14) To a stirred suspension of NaH (0.56 g, 60 % w/w, 23.2 mmol) in THF/ benzene (1:4, 70 mL) was added a solution of dimethyl (2-oxopropyl)-phosphonate (3.5 g, 21.1 mmol) in dry benzene (15 mL) at 0 °C. A white solid was formed and the stirring was continued for 1 h. A solution of tosylazide (4.3 g, 21.8 mmol) in dry benzene (10 mL) was added. The mixture was stirred overnight at room temperature, and then filtered through a pad of celite and evaporation of the solvents under reduced pressure yielded the crude product. The crude product was further purified by flash column chromatography

(EtOAc/hexane 1:1) furnished the product 1**4 (**2.6 g, 13.3 mmol, 65%) as a colorless liquid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.85 (d, J = 11.8 Hz, 6H), 2.28 (s, 3H).

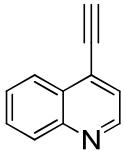
General procedure for the synthesis of aromatic alkyne from aldehyde. To a stirred solution of aldehyde (1.0 equiv.) in MeOH were added Bestmann reagent (1.1 equiv.) in MeOH and K_2CO_3 (3.0 equiv.) at room temperature. The mixture was stirred at room temperature for 12 h. Solvent was evaporated and saturated aqueous NH_4Cl solution was added and extracted with ethyl acetate. The combined extracts were dried over $MgSO_4$ and concentrated to get crude product. The crude product was purified by column chromatography, eluted with 10-20% EtOAc in hexane, yielded the desired aromatic alkyne.



1-Ethynylnaphthalene (16a). Prepared from 1-naphthaldehyde, yielded 1-ethynylnaphthalene **16a** (90%) as a brown oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.36-8.38 (m, 1H), 7.86 (d, J = 7.7 Hz, 2H), 7.75-7.53 (m, 1H), 7.60–7.51 (m, 2H), 7.44-7.41 (m, 1H), 3.48 (s, 1H).



5-Ethynyl-1*H*-indole (16b). Prepared from 1*H*-indole-5-carbaldehyde, yielded 5-ethynyl-1*H*-indole **16b** (81%) as a solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.20 (s, 1H), 7.82 (s, 1H), 7.30-7.34 (m, 2H), 7.21 (dd, J = 2.6, J = 3.2 Hz, 1H), 6.52 (dd, J = 2.1, J = 3.0 Hz, 1H), 2.98 (s, 1H).



4-Ethynylquinoline (16c). Prepared from quinoline-4-carbaldehyde, yielded 4-ethynylquinoline **16c** (45%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.87 (d, J = 4.6 Hz, 1H), 8.27 (dd, J = 8.6 Hz, J = 1.6 Hz, 1H), 8.11 (dd, J = 8.3 Hz, J = 1.6 Hz, 1H), 7.74 (ddd, J = 8.6 Hz, J = 6.7 Hz, J = 1.6 Hz, 1H), 7.60-7.63 (m, 1H), 7.53 (d, J = 4.5 Hz, 1H), 3.67 (s, 1H).