Synthesis of 4-Arylethynyl-2-methyloxazole Derivatives as mGluR5 Antagonists for Use in the Treatment of Drug Abuse

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Abstract: In structure–activity relationship studies directed toward the use of mGluR5 antagonists in the treatment of drug abuse, we sought a convenient means for gaining access to the oxazole analogues of MTEP. Toward this end, the aldehyde group in 2-methyloxazole-4-carboxaldehyde was successfully converted to a trimethylsilylethynyl group via the preparation of a dibromoolefin, conversion to acetylide using NaHMDS and MeLi, and trapping with TMSCl. The resulting versatile intermediate, 2-methyl-4-[(trimethylsilyl)ethynyl]oxazole, was subjected to a modified Sonogashira coupling reaction involving an in situ desilylation reaction with Bu_4NF and palladium-catalyzed coupling with an aryl or heteroaryl iodide to give the desired oxazole analogues.

Key words: alkynes, cyclizations, lithiation, palladium, cross-coupling

Cocaine abuse and addiction remain a major societal and health problem in the United States and elsewhere. Despite advances in our understanding of the basic psychological and neurobiological mechanisms of reward, addiction, and relapse, the success rate for those in treatment programs for cocaine addiction remains low. To date most programs that have utilized adjunct pharmacological therapies have focused on the biogenic amines. While some modest success with various antidepressants has been reported, it is clear that novel approaches are required.[1] Recent preclinical advances have implicated glutamate as a major player in the actions of acute and chronic cocaine use. Genetic and pharmacological studies now strongly suggest that the type 5 metabotropic glutamate receptor (mGluR5) may be a particularly attractive target for the development of drugs that will blunt the stimulant and reinforcing effects of cocaine.[2] 3-[(2-Methyl-1,3-thiazol-4-yl)ethynyl]pyridine (MTEP)[3] (Figure 1) has been identified to be one of the more potent metabotropic glutamate receptor subtype 5 (mGluR5) non-competitive antagonists, and the structure–activity relationship (SAR) of a broad range of thiazole derivatives based on the MTEP structure has been enthusiastically investigated and reported.[4]

In carrying out our own SAR studies in the mGluR5 field, we were interested to compare the biological activity of isosteres of MTEP, and in particular its oxazole analogues. Although the binding properties of such isosteres are likely to be similar to MTEP, we reasoned that they may exhibit more favorable pharmacokinetic properties.

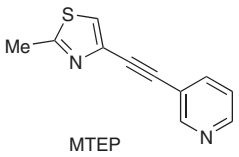
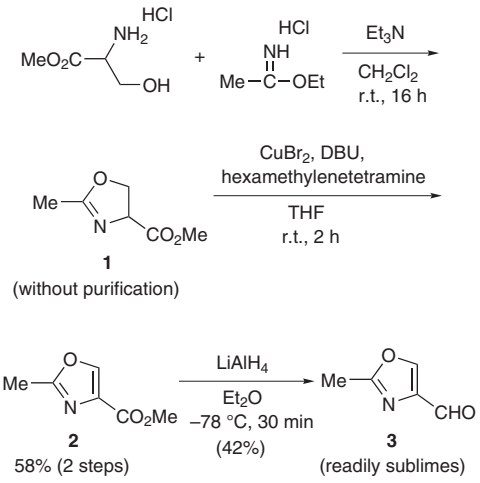


Figure 1

A search of the literature failed to reveal any reports of the preparation of such 2-alkyl-4-ethynyloxazoles, a consequence perhaps of the lack of stability of the required oxazole intermediates.

Herein we wish to report a facile method for gaining rapid access to a host of these oxazoles through the intermediacy of 2-methyl-4-[(trimethylsilyl)ethynyl]oxazole (**7**). This key intermediate was itself derived from the corresponding aldehyde **3** using a modified Corey–Fuchs protocol.[5] Next, by employing a modification of the Sonogashira coupling reaction involving in situ desilylation with Bu_4NF, the building block **7** reacted with both aryl and heteroaryl iodides to afford the required MTEP analogues.

Details of these procedures are as follows. 2-Methyloxazole-4-carboxaldehyde (**3**) was prepared according to a literature procedure[6] (Scheme 1). Thus, the oxazoline **1**



Scheme 1 Synthesis of aldehyde **3**

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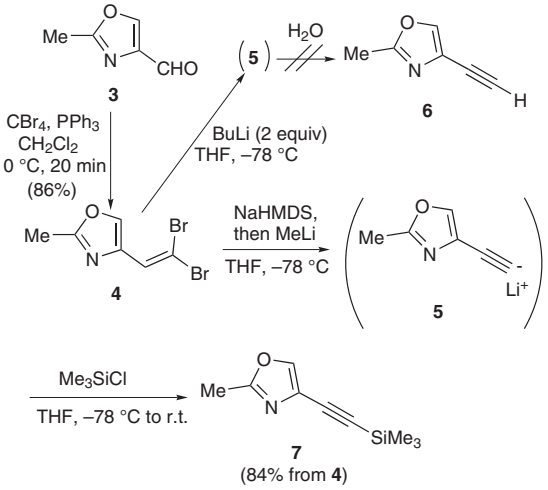
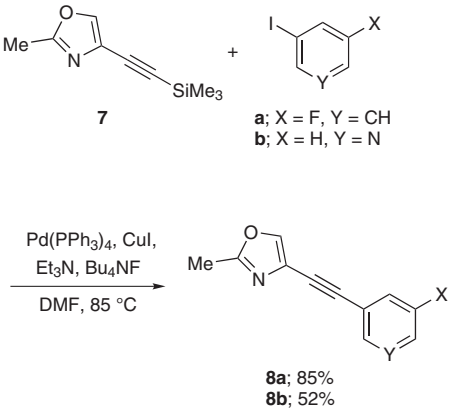
was obtained by reaction of DL-serine methyl ester hydrochloride with ethyl acetimidate hydrochloride, and the intermediate oxazoline **1** was then directly subjected to oxidation using cupric bromide[7] to afford the oxazole **2**. Reduction of **2** to **3** was performed in two steps, which included reduction of **2** to alcohol by $LiBH_4$ and Swern oxidation of this alcohol to **3** as reported.[6] We found that **3** could be obtained directly and more conveniently by shortening the reaction time in this reduction step. Thus, the methyl ester **2** was reduced with $LiAlH_4$ in diethyl ether at –78 °C for 30 minutes to give the aldehyde **3**. As we found that intermediate **3** readily undergoes sublimation, particularly during evaporation after chromatography, it is important that some care be taken at this stage to prevent compound loss.



Scheme 2 Synthesis of key intermediate **7**

Further steps in the synthesis of compound **7** are shown in Scheme 2. The aldehyde **3** was immediately subjected to a Wittig reaction, using CBr_4 and PPh_3 to furnish the dibromoolefin **4** in good yield. This compound **4** was then reacted with two equivalents of *n*-BuLi in THF at –78 °C for one hour and at 25 °C for one hour to generate the lithium acetylide **5**. Following the original Corey–Fuchs procedure[8], acetylide **5** was hydrolyzed by the addition of water. Unfortunately, after several attempts, the expected terminal acetylene **6** could not be obtained. We thus sought to trap the intermediate anion with another electrophile that might lend greater stability to the product. For this purpose, a trimethylsilyl group was selected, as it could later be removed by fluoride-ion treatment. Accordingly, we next explored application of a procedure previously reported by Nicolaou in the synthesis of thiazolyl acetylene derivatives.[5] Dehydrobromination of dibromoolefin **4** was performed by reaction with one equivalent of NaHMDS in THF at –78 °C, and after 45 minutes, lithiation was brought about using one equivalent of MeLi in THF at –78 °C for 85 minutes. TMSCl was then added dropwise to the reaction mixture, the mixture was stirred at –78 °C for three hours, and allowed to slowly warm to room temperature over 1.5 hours. A standard workup procedure was carried out by quenching with aqueous saturated NH_4Cl solution, followed by purification by flash chromatography (hexane–EtOAc 25:1) to afford the intermediate **7** in good yield.



Scheme 3 Synthesis of oxazole analogues (**8a**, **8b**) of MTEP

To test the utility of intermediate **7**, we examined its conversion to the MTEP analogues **8a** and **8b**. Using the one-pot, modified Sonogashira coupling reaction, the in situ desilylation of **7** with Bu_4NF and subsequent palladium-catalyzed cross-coupling reaction with the appropriate aryl or heteroaryl iodide was carried out in a manner similar to that reported for the synthesis of certain thiazole MTEP derivatives (Scheme 3).[3,4] The desired compounds were formed in good yield.

In summary, the chemistry described herein provides a ready means for acquiring the oxazole isosteres of MTEP. The biological activity of these analogues will be reported separately.

All solvents and reagents were used as obtained from commercial sources, unless otherwise indicated. All starting materials were also obtained from commercial sources. All reactions were carried out under a positive pressure of nitrogen. Glassware for water-sensitive reactions was dried in an oven at 120 °C overnight. ^1H and ^{13}C NMR spectra were measured in deuterated chloroform (99.8% D) solution and recorded on a Bruker Avance 300 spectrometer, operating at 300 MHz for ^1H and 75 MHz for ^{13}C. Chemical shift values (δ), from TMS as internal standard, are expressed in ppm and coupling constants (*J*) in hertz. The exact masses were determined on a Micromass Q-TOF time-of-flight mass spectrometer, using positive mode electrospray ionization. Anhydrous solvents were purchased from Aldrich Chemical Co., and organic solutions were dried over $MgSO_4$. Flash chromatography was performed on silica gel Fluka Art. No. 60738. Analytical thin layer chromatography (TLC) was performed on Merck TLC glass plates, precoated with F254 silica gel 60 (UV, 254 nm, and iodine). Analytical HPLC was performed using a Shimadzu LC-10AD system, equipped with a SPD-10A valuable wavelength detector set at 254 nm. An ACE 5 AQ column (250 mm × 4.6 mm; 5 μm) was used. A linear gradient mobile phase starting with 50% H_2O with 0.05% TFA, 50% CH_3CN with 0.05% TFA up to 17 min, then 100% CH_3CN with 0.05% TFA thereafter was used. Flow rate = 1.3 mL/min.

2-Methyloxazole-4-carboxylic Acid Methyl Ester (2)

To a stirred suspension of ethyl acetimidate hydrochloride (6.18 g, 50.0 mmol) and DL-serine methyl ester hydrochloride (7.78 g, 50.0 mmol) in CH_2Cl_2 (100 mL) was added dropwise over 25 min a soln of Et_3N (15.0 ml, 108 mmol) in CH_2Cl_2 (35 mL). After 16 h the solids were removed by filtration and washed with Et_2O. The filtrate was concentrated, and the resulting solid residue was washed several times with Et_2O. The combined organic extracts were concentrated to give crude 4,5-dihydro-2-methyl-oxazole-4-carboxylic acid methyl ester (**1**) as a yellow oil. Hexamethylenetetramine (17.5 g, 125 mmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (18.7 mL, 125 mmol) were added to a stirred suspension of $CuBr_2$ (27.9 g, 125 mmol) at 0 °C. After 20 min, the above crude compound **1** was added, and the reaction mixture was stirred at r.t. for 2 h. The solvent was removed in vacuo, and the residue was partitioned between EtOAc (150 mL) and sat. aq NH_4Cl soln–sat. aq NH_4OH soln 1:1 (100 mL). The aq layer was extracted with EtOAc (150 mL), and the combined organic layers were washed with sat. aq NH_4Cl soln–sat. aq NH_4OH soln 1:1 (100 mL), 10% citric acid soln (100 mL), sat. aq. $NaHCO_3$ soln (100 mL), and brine (100 mL), then dried over $MgSO_4$ and evaporated in vacuo. The residue was chromatographed on silica gel, eluting with hexane–EtOAc (3:2) to give **2** (4.09 g, 58%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.54 (s, 3 H), 3.93 (s, 3 H), 8.16 (s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.07, 52.47, 133.69, 144.62, 162.04, 162.78.

ESI-MS: *m/z* = 142.3 $[M + H]^+$.

HRMS-FAB: *m/z* $[M + H]^+$ calcd for $C_6H_8NO_3$: 142.0504; found: 142.0501.

2-Methyloxazole-4-carboxaldehyde (3)

$LiAlH_4$ soln (1.0 M in THF) (31.9 mL, 31.9 mmol) was added to a soln of **2** in Et_2O (200 mL) at –78 °C. After 30 min, a sat. aq soln of NaOAc (100 mL) was added, and the mixture was extracted with Et_2O (2 × 100 mL). The combined organic layers were dried over $MgSO_4$ and evaporated carefully under slightly reduced pressure (caution: compound **3** readily sublimes). The residue was chromatographed on silica gel, eluting with hexane–EtOAc (2:1) to give **3** (994 mg, 42%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.56 (s, 3 H), 8.19 (s, 1 H), 9.92 (s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.04, 141.22, 145.57, 163.38, 183.97.

ESI-MS: *m/z* = 112.2 $[M + H]^+$.

HRMS-FAB: *m/z* $[M + H]^+$ calcd for $C_5H_6NO_2$: 112.0399; found: 112.0394.

4-(2,2-Dibromovinyl)-2-methyloxazole (4)

To a soln of CBr_4 (2.88 g, 8.68 mmol) in CH_2Cl_2 (10 mL), cooled in an ice bath, a soln of PPh_3 (4.53 g, 17.4 mmol) in CH_2Cl_2 (10 mL) was added dropwise, and the reaction mixture was stirred for 10 min at the same temperature. A soln of **3** (241 mg, 2.17 mmol) in CH_2Cl_2 (10 mL) was added dropwise to the reaction mixture with continued ice-cooling, and the mixture was stirred for 20 min at the same temperature. After addition of H_2O (20 mL), the mixture was extracted with CH_2Cl_2 (40 mL), and the organic layer was washed with sat. aq $NaHCO_3$ soln (20 mL) and saturated aq NH_4Cl soln (20 mL), dried over $MgSO_4$, and evaporated in vacuo. The residue was chromatographed on silica gel, eluting with hexane–EtOAc (6:1) to give **4** (500 mg, 86%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.45 (s, 3 H), 7.35 (s, 1 H), 8.13 (s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.06, 90.75, 129.34, 136.98, 137.84, 161.19.

ESI-MS: *m/z* (%) = 265.3 $[M + H^+]$.

HRMS–FAB: *m/z* $[M + H]^+$ calcd for $C_6H_6Br_2NO$: 265.8816; found: 265.8819.

2-Methyl-4-[(trimethylsilyl)ethynyl]oxazole (7)

To a soln of **4** (258 mg, 0.970 mmol) in THF (10 mL), cooled at –78 °C was added NaHMDS soln (1.0 M in THF) (0.97 mL, 0.97 mmol) dropwise over 3 min. The mixture was stirred for 45 min at –78 °C, then MeLi soln (1.6 M in Et_2O) (1.21 mL, 1.94 mmol) was added dropwise over 6 min. After further 75 min, TMSCl (0.62 mL, 4.9 mmol) was added dropwise, and the reaction mixture was stirred at –78 °C for 3 h. Then the mixture was allowed to slowly warm to r.t. over 100 min. After quenching by addition of sat. aq NH_4Cl soln (20 mL), the mixture was extracted with Et_2O (2 × 30 mL), and the combined organic layers were dried over $MgSO_4$ and evaporated in vacuo. The residue was chromatographed on silica gel, eluting with hexane–EtOAc (25:1) to give **7** (146 mg, 84%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.25 (s, 9 H), 2.46 (s, 3 H), 7.68 (s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 0.08, 14.17, 94.68, 98.87, 124.05, 141.79, 161.81.

ESI-MS: *m/z* (%) = 180.2 $[M + H^+]$.

HRMS–FAB: *m/z* $[M + H]^+$ calcd for $C_9H_{14}NOSi$: 180.0845; found: 180.0850.

4-[(3-Fluorophenyl)ethynyl]-2-methyloxazole (8a)

2-Methyl-4-[(trimethylsilyl)ethynyl]oxazole (**7**) (43 mg, 0.24 mmol) and 1-fluoro-3-iodobenzene (0.031 mL, 0.26 mmol) were combined in a flask containing deoxygenated DMF (5 mL). To this were added $Pd(PPh_3)_4$ (14 mg, 0.012 mmol), CuI (4.6 mg, 0.024 mmol) and Et_3N (0.040 mL, 0.29 mmol). The mixture was warmed to 85 °C, and Bu_4NF (63 mg, 0.24 mmol) was then added dropwise over 15 min. The reaction mixture was allowed to stir for 13 h at 85 °C, filtered through celite, then partitioned between EtOAc (40 mL) and 0.1 N HCl soln (15 mL). The organic layer was washed with H_2O (2 × 15 mL), dried over $MgSO_4$, and evaporated in vacuo. The residue was chromatographed on silica gel, eluting with hexane–EtOAc (7:1) to give **8a** (41 mg, 85%). Purity (HPLC): 96%.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.50 (s, 3 H), 7.03–7.12 (m, 1 H), 7.22 (d, *J* = 8.8 Hz, 1 H), 7.29–7.35 (m, 1 H), 7.31 (s, 1 H), 7.77 (s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.24, 80.54, 91.36, 116.45 (d, $^2J_{CF}$ = 21.2 Hz), 118.72 (d, $^2J_{CF}$ = 22.9 Hz), 123.82, 124.65 (d, $^3J_{CF}$ = 9.4 Hz), 127.87 (d, $^4J_{CF}$ = 3.1 Hz), 130.38 (d, $^3J_{CF}$ = 8.6 Hz), 141.61, 162.20, 162.72 (d, $^1J_{CF}$ = 246.8 Hz).

ESI-MS: *m/z* (%) = 202.3 $[M + H^+]$.

HRMS–FAB: *m/z* $[M + H]^+$ calcd for $C_{12}H_9FNO$: 202.0668; found: 202.0661.

3-[(2-Methyloxazol-4-yl)ethynyl]pyridine (8b)

2-Methyl-4-[(trimethylsilyl)ethynyl]oxazole (**7**) (43 mg, 0.24 mmol) and 3-iodopyridine (42 mg, 0.26 mmol) were combined in a flask containing deoxygenated DMF (5 mL). To this mixture were added $Pd(PPh_3)_4$ (14 mg, 0.012 mmol), CuI (4.6 mg, 0.024 mmol) and Et_3N (0.040 mL, 0.29 mmol). The mixture was warmed to 85 °C, and Bu_4NF (63 mg, 0.24 mmol) was then added dropwise over 15 min. The reaction mixture was allowed to stir for 13 h at 85 °C, filtered through celite, and partitioned between EtOAc (40 mL) and 0.1 N HCl soln (15 mL). The organic layer was washed with H_2O (2 × 15 mL), dried over $MgSO_4$, and evaporated in vacuo.

The residue was chromatographed on silica gel, eluting with hexane–EtOAc (1:2) to give **8b** (23 mg, 52%). Purity (HPLC): 95%.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.51 (s, 3 H), 7.31 (t, *J* = 9.0 Hz, 1 H), 7.80 (s, 1 H), 7.81 (d, *J* = 9.0 Hz, 1 H), 8.58 (br s, 1 H), 8.78 (br s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.25, 82.98, 89.36, 123.22, 123.47, 123.67, 138.82, 141.79, 149.34, 152.56, 162.30.

ESI-MS: *m*/*z* (%) = 185.2 [M + H$^+$].

HRMS–FAB: *m*/*z* [M + H]$^+$ calcd for $C_{11}H_9N_2O$: 185.0715; found: 185.0709.

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References

(1) Lima, M. S.; Oliveira, M. G.; Soares, B. G.; Reisser, A. A. P.; Farrell, M. *Addiction* **2002**, *97*, 931.
(2) Chiamulera, C.; Epping-Jordan, M. P.; Zocchi, A.; Marcon, C.; Cottiny, C.; Tacconi, S.; Corsi, M.; Orzi, F.; Conquet, F. *Nat. Neurosci.* **2001**, *4*, 873.
(3) Cosford, N. D. P.; Tehrani, L.; Roppe, J.; Schweiger, E.; Smith, N. D.; Anderson, J.; Bristow, L.; Brodkin, J.; Jiang, X.; McDonald, I.; Rao, S.; Washburn, M.; Varney, M. A. *J. Med. Chem.* **2003**, *46*, 204.
(4) (a) Alagille, D.; Baldwin, R. M.; Roth, B. L.; Wroblewski, J. T.; Grajkowska, E.; Tamagnan, G. D. *Bioorg. Med. Chem.* **2005**, *13*, 197. (b) Alagille, D.; Baldwin, R. M.; Roth, B. L.; Wroblewski, J. T.; Grajkowska, E.; Tamagnan, G. D. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 945.
(5) (a) Nicolaou, K. C.; Namoto, K.; Ritzen, A.; Ulven, T.; Shoji, M.; Li, J.; D'Amico, G.; Liotta, D.; French, C. T.; Wartmann, M.; Altmann, K.; Giannakakou, P. *J. Am. Chem. Soc.* **2001**, *123*, 9313. (b) Grandjean, D.; Pale, P.; Chuche, J. *Tetrahedron Lett.* **1994**, *35*, 3529.
(6) Lafontaine, J. A.; Provencal, D. P.; Gardelli, C.; Leahy, J. W. *J. Org. Chem.* **2003**, *68*, 4215.
(7) Barrish, J. C.; Singh, J.; Spergel, S. H.; Han, W. C.; Kissick, T. P.; Kronenthal, D. R.; Mueller, R. H. *J. Org. Chem.* **1993**, *58*, 4494.
(8) Corey, E. J.; Fuchs, P. L. *Tetrahedron Lett.* **1972**, *13*, 3769.