# Nitrile Oxide Cycloaddition of Non-activated Alkynes: A Novel Approach to the Synthesis of Neuroactive Isoxazoles

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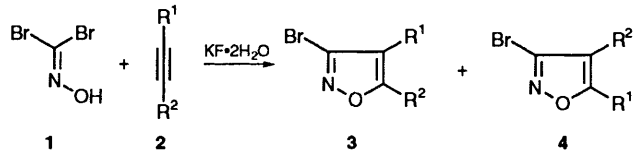
A general method for the unprecedented 1,3-dipolar cycloaddition of bromonitrile oxide to disubstituted non-activated alkynes provides a useful alternative route to the neuropharmacological tools AMPA and 4-methylhomoibotenic acid.

Isoxazoles are common substructures in medicinal and natural product chemistry.[1] In particular, the 3-hydroxyisoxazole functionality has gained popularity as an effective bioisosteric substitute for the carboxylic group.[2,3] In this view, a series of GABA (γ-aminobutyric acid) and excitatory amino acid (EAA) receptor ligands have been introduced in the past decade, Krogsgaard-Larsen's group being the most active in this field.[3] Trisubstituted isoxazoles are key intermediates in the synthesis of such important pharmacological tools. Until now, their synthesis has been accomplished by condensation of hydroxylamine and β-keto-esters; the 4,5-disubstituted 3-hydroxyisoxazoles so obtained were then transformed into the final products in low yields and under conditions unsuitable for large scale preparations.[4] On the other hand, a 1,3-dipolar cycloaddition approach to the synthesis of neuroactive isoxazole compounds has been hampered by the lack of methods for the cycloaddition of a nitrile-oxide onto a non-activated disubstituted alkyne. In fact, whereas the presence of an electron withdrawing group in the starting alkyne provides 4-substituted isoxazoles in good yields,[5] simple dialkyl-substituted acetylenes are known to be virtually unreactive.[5,6] This very low reactivity was once more observed during the recent synthesis of one of the most potent AMPA [2-amino-3-(3-hydroxy-5-methylisoxazol-4-yl)propionic acid]-receptor agonists.[7]

We report here a new methodology for the 1,3-dipolar cycloaddition of bromonitrile oxide to non-activated 1,2-disubstituted alkynes **2** in acceptable yields (Scheme 1).

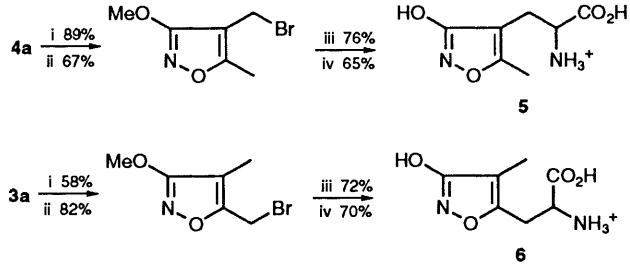



**1** **2** **3** **4**

| | $R^1$ | $R^2$ | Yield (%)[b] | Ratio[c] 3 : 4 |
|---|---|---|---|---|
| **a** | Me | $CH_2OH$ | 57 | 1 : 1.4[d, e, g] |
| **b** | Me | $CH_2CH_2OH$ | 33 | 1 : 1.1[d, e, f, g] |
| **c**[a] | Me | $(CH_2)_4Me$ | 22 | 1 : 1[d, e] |
| **d**[a] | $CH_2OH$ | $CH_2OH$ | 60 | — |
| **e** | $CH_2Cl$ | $CH_2Cl$ | 31 | — |

**Scheme 1** [a] 3:1 Excess of the dipolarophile. [b] Non-optimised yields of isolated products. [c] Ratios determined by: [d] $^1H$ NMR (4-Me *vs.* 5-Me); [e] GC–MS (DB-5, 30 m, film thickness 0.25 μm; 140 °C isotherm); [f] HPLC [Merck LiChrocart 250–4 RP 8 endcapped; mobile phase $H_2O$–MeCN (6:4); 0.5 ml $min^{-1}$; $l$ = 225 nm]; [g] isolation of the products

The synthesis entails the use of potassium fluoride dihydrate as a hydrohalide scavenger. Potassium fluoride has been employed in 1,3-dipolar cycloadditions of nitrile oxides[8] in the past, but apparently its usefulness has not yet been fully recognized. A distinguishing feature of the KF-mediated nitrile oxide cycloaddition is that the pH remains acidic throughout the reaction (in the pH range 2–5), presumably due to formation of $KHF_2$ (*e.g.* KF·HF).[9] The acidic conditions seem to be necessary for reaction: only traces of the products were observed by addition of dibromoformaldehyde oxime to a preformed mixture of alkyne **2b** and KF dihydrate or when KF-basic alumina was used as an acid scavenger, that is when the medium was maintained at pH > 5 throughout the reaction.




**Scheme 2** *Reagents and conditions:* i, KOH, MeOH–$H_2O$, 12 h, reflux; ii, *N*-bromosuccinimide, $PPh_3$, $CH_2Cl_2$, room temp., 30 min; iii, $(Ph)_2C{=}NCH_2CO_2Et$, KOH, tetrabutylammonium iodide, $CH_2Cl_2$, 16 h, room temp.; iv. 48% HBr, reflux, 30 min

Using this methodology we were able to develop an alternative and more efficient synthesis of AMPA **5** and its regioisomer 4-methylhomoibotenic acid **6** (Scheme 2).†

The process outlined here seems to be general and, due to the abundance of commercially available 1,2-alkyl disubstituted alkynes,‡ provides a general entry to other precursors of neuroactive isoxazoles.

## Experimental

*3-Bromo-4-hydroxymethyl-5-methylisoxazole* **4a** *and 3-Bromo-5-hydroxymethyl-4-methylisoxazole* **3a**.—But-2-yn-1-ol **2a** (0.5 g, 7.13 mmol) was dissolved in ethylene glycol dimethyl ether (50 $cm^3$) and heated to reflux. Dibromoformaldehyde oxime **1**[10] (3.61 g, 17.82 mmol) and KF·$2H_2O$ (2.01 g, 21.35 mmol) were added in five portions at 1 h intervals and the mixture was then refluxed for 8 h. After evaporation, water (10 $cm^3$) was added and the mixture extracted with ethyl acetate (3 × 15 $cm^3$). After drying and evaporation, the crude residue

† Earlier syntheses of AMPA and 4-methylhomoibotenic acid, starting from β-keto esters and hydroxylamine, gave total yields ranging between 1 and 5% *vs.* 5–10% in our procedure, see ref. 4.

‡ More than 150 compounds in the Fine Chemicals Directory of REACCS™.

was purified by flash chromatography (silica gel 60; eluent: cyclohexane–ethyl acetate, 90:10 then 80:20) to give isoxazoles **3a** (0.32 g; 23%) and **4a** (0.46 g; 34%).*

* All new compounds gave satisfactory elemental analyses. Physical and spectroscopic data for compounds **3**/**4a–e**, **5** and **6** (*J* values are given in Hz). **3a**: $^1$H NMR ($CDCl_3$) $\delta$ 4.66 (s, 2 H, $CH_2OH$), 1.99 (s, 3 H, $CH_3$); MS (*m/z*, 70 eV) 191 (10.5, $M^+$), 173 (7.5), 160 (39.6), 132 (12.2), 31 (100); $\eta_D^{22}$ 1.5215. **3b**: $^1$H NMR ($CDCl_3$) $\delta$ 3.97 (t, 2 H, $CH_2CH_2OH$, *J* 7), 3.01 (t, 2 H, $CH_2CH_2OH$, *J* 7), 2.00 (s, 3 H, $CH_3$); MS (*m/z*, 70 eV) 191 ($M^{+\cdot}$), 173 (7.5), 160 (39.6), 132 (12.2), 31 (100); $\eta_D^{22}$ 1.5179. **4a**: $^1$H NMR ($CDCl_3$) $\delta$ 4.42 (s, 2 H, $CH_2OH$), 2.48 (s, 3 H, $CH_3$); MS (*m/z*, 70 eV) 205 (9.8, $M^{+\cdot}$), 175 (24), 133 (18.9), 96 (34.4), 43 (100), 31 (96.2); m.p. 63.5–65.5 °C. **4b**: $^1$H NMR ($CDCl_3$) $\delta$ 3.76 (t, 2 H, $CH_2CH_2OH$, *J* 7), 2.60 (t, 2 H, $CH_2CH_2OH$, *J* 7), 2.41 (s, 3 H, $CH_3$); MS (*m/z*, 70 eV) 205 (2.8, $M^{+\cdot}$), 187 (2.8), 174 (4.5), 96 (29.2), 43 (100), 31 (34.5), $\eta_D^{22}$ 1.5171. **3c** + **4c**: $^1$H NMR ($CDCl_3$) $\delta$ 2.71 (t, 2 H, $CH_2$Bu-**3c**), 2.39 (s, 3 H, 5-$CH_3$, **4c**), 2.33 (t, 2 H, $CH_2$Bu-**4c**), 1.98 (s, 3 H, 4-$CH_3$-**3c**), 1.2–1.7 [m, 12 H, $(CH_2)_3$-**3c**/**4c**), 0.88 (m, 6 H, side-chain terminal $CH_3$-**3c**/**4c**); MS (*m/z*, 70 eV) **3c**: 231 (14.6, $M^{+\cdot}$), 214 (4.2), 188 (23.8), 175 (40.3), 55 (81), 43 (79), 41 (100); **4c**: 231 (7.6, $M^{+\cdot}$), 216 (1), 188 (1.2), 174 (40.8), 43 (100). **3d**: $^1$H NMR ($CDCl_3$) $\delta$ 4.63 (s, 2 H, 5-$CH_2OH$), 4.38 (s, 2 H, 4 $CH_2OH$); MS (*m/z*, 70 eV) 207 (3.2, $M^{+\cdot}$), 189 (31.5), 176 (6.5), 146 (5), 110 (20.8), 31 (100), $n_D^{22}$ 1.5402. **3e**: $^1$H NMR ($CDCl_3$) $\delta$ 4.71 (s, 2 H, 5-$CH_2Cl$), 4.49 (s, 2 H, 4-$CH_2Cl$); MS (*m/z*, 70 eV) 243 (12, $M^{+\cdot}$), 208 (100), 194 (7.6), 77 (94); $\eta_D^{22}$ 1.5603. **5**: $^1$H NMR (DMSO) ~11 (br, 1 H, OH), 8.1 (br s, 3 H, $NH_3^+$), 3.94 (t, 1 H, $CH_2CH$, *J* 6), 2.73 (d, 2 H, $CH_2CH$, *J* 6), 2.20 (s, 3 H, $CH_3$); FAB(−)-MS (*m/z*) 185 (100, $M - H^+$); m.p. 200 °C (decomp.). **6**: $^1$H NMR (DMSO) 11.1 (br s, 1 H, OH), 8.3 (br s, 3 H, $NH_3^+$), 4.21 (t, 1 H, $CH_2CH$, *J*, 6), 3.09 (d, 2 H, $CH_2CH$, *J* 6), 1.75 (s, 3 H, $CH_3$). FD-MS (*m/z*) 186 (100, $M - H^{+\cdot}$), 141 (15.4); m.p. 190 °C (decomp.).

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