Improved Synthesis of 4-(2-Substituted ethyl)-2-(4-Methylpiperazino)Quinazolines

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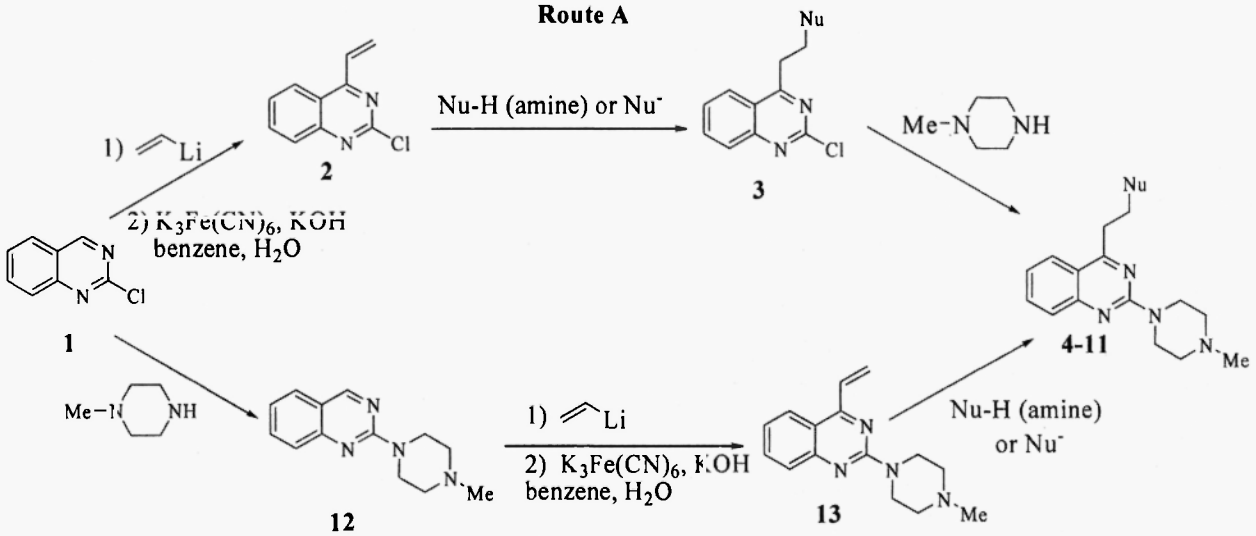
ABSTRACT

An improved synthesis of the title compounds is reported.

Quinazoline derivatives show a wide variety of biological activities.[1-3] In particular, 2-amino substituted quinazolines exhibit activity as anti-inflammatory agents through the interaction with the histamine H_4 receptor,[4] function as CCR4 antagonists,[5] and are selective ligands for the 5-HT_{2A} receptor.[6,7]

An improved procedure for the preparation of 4-(2-substituted ethyl)-2-(4-methylpiperazino)quinazolines **4-11** is the subject of this report.



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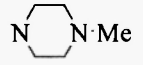
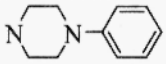
Route B

#	Nu	Yield (%) A	Yield (%) B
4	NMe_2	27	50
5	HN-Bu^n	31	55
6	$NHCH_2Ph$	50	62
7		40	53
8		23	50
9	OMe	27	52
10	SEt	35	54
11	SPh	50	63

The low-yield synthesis of quinazolines **4-11** (route A) was previously published.[8,9] We now report an improved preparation of these products by simply reversing the order of the steps (route B). Thus, the first step of the more efficient synthesis involves nucleophilic displacement of chloride in 2-chloroquinazoline (**1**, 1.2 g, 7.2 mmol) with *N*-methylpiperazine (2.4 mL, 21.8 mmol) in toluene (10.0 mL) by heating the mixture at 80 °C for 4 h. The resulting compound **12** was purified by silica gel chromatography eluting with hexanes/ether (4:1). The subsequent treatment of **12** (0.77 mg, 3.4 mmol) with vinyllithium[10] (3.7 mmol in THF) followed by aromatization of the intermediate dihydroquinazoline (structure not shown) by potassium ferricyanide (2.6 g, 8.1 mmol) in saturated aqueous potassium hydroxide[8] (1.5 mL) furnished compound **13**. Heating of **13** (0.16 g, 0.61 mmol) with a nucleophile (1.8 mmol) in toluene (5.0 mL) at 90 °C overnight gave the desired product **4-11** that, after purification (silica gel chromatography, hexanes/ether, 4:1) was identical in all respects with the corresponding products obtained by route A.[8]

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