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Synthesis of substituted quinazolines

Yadagiri Bathini,[a,*] Inderjit Sidhu,[a] Rajeshwar Singh,[a] Ronald G. Micetich[a] and Peter L. Toogood[b]

[a]*NAEJA Pharmaceutical Inc., #2, 4290-91A Street, Edmonton, Alberta, Canada T6E 5V2*
[b]*Pfizer Global Research and Development, Ann Arbor Laboratories, 2800 Plymouth Road, Ann Arbor, MI 48105, USA*

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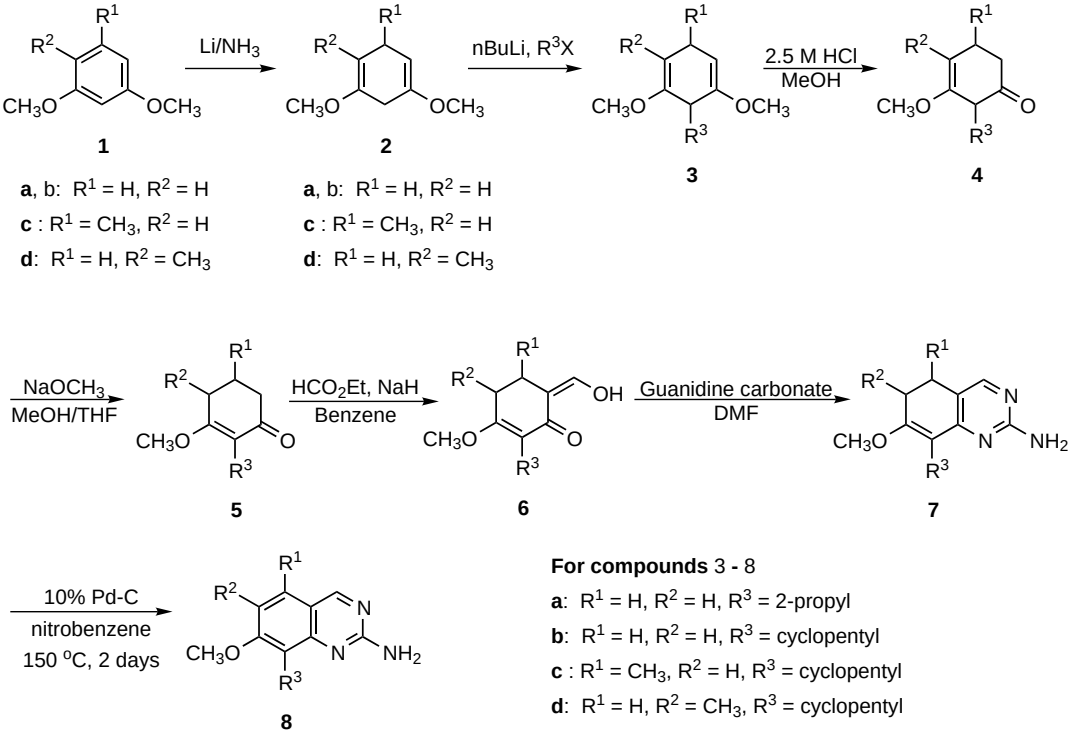
Abstract—A novel and flexible synthetic route is described for the synthesis of 5,6,8-alkyl-7-methoxy-2-aminoquinazolines using dihydrobenzenes as key intermediates. © 2002 Elsevier Science Ltd. All rights reserved.

The many and varied biological properties of quinazolines have engendered widespread interest in their synthesis.[1,2] This group of compounds exhibits numerous pharmacological activities such as sedative, analgesic, diuretic, antihypertensive, antibiotic and antitumoral properties and many quinazolines have been demonstrated to inhibit kinases by competing with ATP for the kinase active site.[3,4] During a project directed at the discovery of new quinazoline-based kinase inhibitors, we required a synthetic route that would facilitate the introduction of substituents at the 2, 5, 6, 7, and 8 positions of the quinazoline core. Frequently, quinazolines are synthesized starting from 2-aminobenzoic acid or its derivatives.[5] Alternatively, the fused phenyl ring may be assembled via a cycloaddition strategy.[6]



Scheme 1.

* Corresponding author. Tel.: (780) 462 4044; fax: (780) 461 0196; e-mail: ybathini@naeja.com

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Recently, the reaction of 2-fluoroacetophenones with guanidine carbonate was used for the synthesis of 2-amino-4-alkylsubstituted quinazolines.[7] Separately, regioselective metallation at the peri position of quinazolines has been reported using LTMP.[8] Surprisingly, quinazolines bearing substitution at positions 2, 7, and 8 as we needed were not previously known in the literature and none of the previously reported approaches to quinazolines were generally useful for the synthesis of our target compounds. Here we describe the synthesis of various substituted quinazolines using dihydrobenzenes as key intermediates. Dihydrobenzenes are readily available from Li/NH_3 reduction of benzenoid precursors. This approach also allows for the introduction of alkyl groups at what will become position C-8 in the final quinazoline target (Scheme 1).

1,3-Dimethoxybenzenes **1a–d** were reduced to cyclohexa-1,4-dienes **2a–d** using lithium metal in liquid ammonia. Compounds **2a–d** then were alkylated with either 2-iodopropane or cyclopentyl bromide to give compounds **3a–d** using *n*-BuLi as the base. The alkylated products were obtained in 80–95% yield. With some care, partial hydrolysis of dienolethers **3a–d** could be achieved with 2.5% HCl in methanol at 0°C to give β, γ, unsaturated ketones **4a–d** in high yield. It should be noted that only the trisubstituted enolether in **3d** was hydrolyzed to give **4d** exclusively. The non-conjugated double bond in compounds **4a–d** was isomerized using NaOMe in methanol at room temperature to give α,β-unsaturated ketones **5a–d**. Compounds **5a–d** then were formylated with ethyl formate in the presence of sodium hydride in benzene to give compounds **6a–d** in moderate yield. The condensation of **6a–d** with guanidine carbonate at 140°C in DMF provided 5,6-dihydroquinazolines **7a–d** as the major products. ^1H NMR analysis indicated that the 5,6-dihydroquinazoline products were isolated with a small amount (~10%) of the corresponding 5,8-dihydroquinazolines. These dihydroquinazoline mixtures could be aromatized without separation to cleanly produce compounds **8a–d** by heating them in nitrobenzene at 150°C in the presence of 10% Pd–C.[9] The overall yields of **8** from **6** ranged from 40 to 50%.[†] It is noteworthy that the guanidine amino group was stable under the aromatising conditions.

In conclusion, we report here a convenient synthesis of 2, 5/6, 7, 8-tetrasubstituted quinazolines that employs dihydrobenzenes as key intermediates. This route offers flexibility to introduce a variety of alkyl groups at the C-5, C-6 and C-8 positions either by choosing the appropriate starting material or through the choice of alkylating agent. The intermediate **6** is a 1,3-dicarbonyl compound that may have utility in the synthesis of various heterocyclic compounds. To our knowledge this is the first application of dihydroaromatic compounds in the synthesis of 2-aminoquinazolines.

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[†] All new compounds showed satisfactory spectral and analytical data, e.g. **8a**: Off-white solid; mp 112–113°C, ^1H NMR ($CDCl_3$) δ: 1.38 (d, 6H, 2×CH_3), 3.95 (s, 3H, OCH_3), 4.24 (m, 1H, CH), 5.0 (s, 2H, NH_2), 7.02 (d, 1H, Ar-H, $J=9$ Hz), 7.55 (d, 1H, Ar-H, $J=9$ Hz), 8.87 (s, 1H, Ar-H); MS: m/z 218.05 (MH^+). **8b**: Off-white solid; mp 181–183°C, ^1H NMR ($CDCl_3$) δ: 1.6–2.2 (complex, 8H, 4×CH_2), 3.9 (s, 3H, OCH_3), 4.27 (m, 1H, CH), 5.02 (s, 2H, NH_2), 7.02 (d, 1H, Ar-H, $J=9$ Hz), 7.54 (d, 1H, Ar-H, $J=9$ Hz), 8.87 (s, 1H, Ar-H); MS: m/z 244.07 (MH^+). **8c**: Off-white solid; mp 200–201°C, ^1H NMR ($CDCl_3$) δ: 1.6–2.1 (complex, 8H, 4×CH_2), 2.63 (s, 3H, CH_3), 3.93 (s, 3H, OCH_3), 4.24 (m, 1H, CH), 5.02 (s, 2H, NH_2), 6.81 (s, 1H, Ar-H), 9.06 (s, 1H, Ar-H); MS: m/z 258.17 (MH^+). **8d**: Off-white solid; mp 144–145°C, ^1H NMR ($CDCl_3$) δ: 1.6–2.3 (complex, 8H, 4×CH_2), 2.36 (s, 3H, CH_3), 3.8 (s, 3H, OCH_3), 3.87 (m, 1H, CH), 4.99 (s, 2H, NH_2), 7.34 (s, 1H, Ar-H), 8.85 (s, 1H, Ar-H); MS: m/z 258.06 (MH^+).