

Synthesis of 6,7-dimethoxy-3,4-diphenyl-2(1H)-quinazolinone from 1-(3,4-dimethoxyphenyl)-urea and benzoic acid in polyphosphoric acid

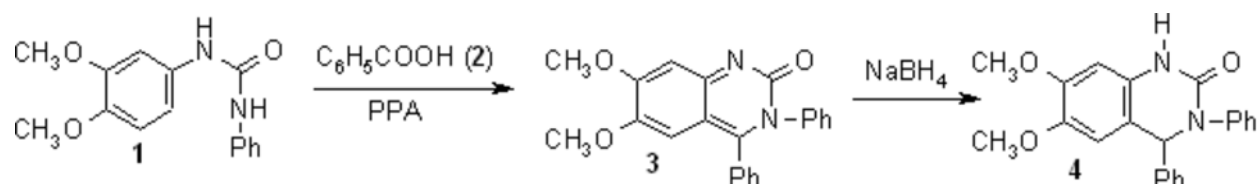
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The quinazoline skeleton, when selectively functionalized, is a building block for the preparation of numerous alkaloids and substances capable of exhibiting a wide variety of biological activity [1]. The quinazolinones were investigated in several research laboratories, as potent antagonists of platelet activating factor [2]. They were also used as α -1-adrenergic receptor antagonists [3] and as agonists on human ORL1 (nociceptin) receptor [4]. There have been few reports about the synthesis of quinazolinones. R. Conley et al. [5] were used direct metalation starting with 3,4-dimethoxyanilin with n-butillithium, then treating with potassium cyanate and followed cyclization in PPA [5,6]. Recently, J. Vicente et al. reports the first ortho-palladated arylurea complexes, obtained by oxidative addition reactions, and has studied their reactivity toward different reagents to prepare quinazolinone derivatives [7]. The Friedel-Crafts acylation of activated benzene rings in the presence of polyphosphoric acid is a very convenient method for direct synthesis of aromatic ketones [8]. The newly synthesized compound 6,7-dimethoxy-3,4-diphenyl-2(1H)-quinazolinone was obtained from 1-(3,4-dimethoxy-phenyl)-3-phenyl-urea.



1-(3,4-dimethoxyphenyl)-3-phenylurea (**1**) (0.544 g, 2 mmol) and benzoic acid (**2**) (0.366 g, 3 mmol) were dissolved in CH₂Cl₂ (3-5 mL) in an open flask and polyphosphoric acid (10 g) was added. The mixture was stirred at 80°C for 6 h, then poured on crushed ice. The solution was alkalinized with 25% ammonia, then extracted with CH₂Cl₂ (3 x 20 mL) and the combined extracts were dried (Na₂SO₄) and concentrated. To crude product 6,7-dimethoxy-3,4-diphenyl-3H-quinazolinone **3** in 15 mL methanol, NaBH₄ (4 mmol, 0.18 g) was added portionwise. The solution was stirred 30 min at room temperature, then the solvent was removed under vacuum. Water (30 mL) was added to the residue and the solution was extracted with CH₂Cl₂ (3 x 20 mL), then the combined extracts were dried (Na₂SO₄) and filtered. The products were filtered through a short column with neutral Al₂O₃ and then were purified by recrystallization from ether or n-hexane/ether=1:1 (yield 59%).

Melting Point: 210-211°C

IR (KBr, cm⁻¹): ν 3334(NH); ν 1674(CO).

¹H-NMR (CDCl₃, 250 MHz): δ = 3.73 (3H, s, OCH₃), 3.75 (3H, s, OCH₃), 5.71 (1H, s, C-4), 6.38-7.28 (12H, m, Ar), 8.87 (1H, s, NH).

^{13}C -NMR (CDCl_3 , 67.5 MHz): δ = 55.9, 56.4, 66.9, 98.8, 109.6, 113.1, 126.6, 126.7, 127.4, 127.9, 128.8, 129.5, 141.5, 142.2, 144.5, 149.3, 154.0.

Elemental Analysis: Calculated for $\text{C}_{22}\text{H}_{20}\text{N}_2\text{O}_3$: C 73.32, H 5.59, N 7.77. Found: C 73.45, H 5.71, N 7.90.

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