

SYNTHESIS OF N-SUBSTITUTED-2-STYRYLQUINAZOLIN-4(3H)-ONES UNDER SOLVENT FREE CONDITION

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Abstract: A green approach for the synthesis 2-methyl-3H-quinazoline-4-one (2) from anthranilamide (1) with acetic anhydride by physical grinding in mortar and pestle . Treatment of 2 with benzaldehydes for 5-1 minute, gave 2-styrylquinazolinone-4-ones (3). Treatment of 3 (a-d) either with DMS, DES, or with Ph-CH₂-Cl, individually using K₂CO₃ as a base, followed by simple processing resulted in N-substituted-2-styrylquinazolin-4-ones 5 (a-l). The whole of the reactions were carried out by physical grinding in mortar and pestle

Keywords: Anthranilamide; 2-Methylquinazolinones; 2-Styrylquinazolinones; Physical grinding; Benzaldehydes.

Introduction: The quinazolinone ring system forms an important class of N-heterocyclic compounds as it is present in a large number of compounds with useful biological properties such as anti-cancer^I, anti-inflammatory^{II}, anti-convulsant^{III}, hypotensive^{IV} and anti-malarial^V types. 2-Styrylquinazolinones are associated with inhibitory effects on tubulin polymerization and the growth of L1210 murine leukemia cells^{VI}. Some derivatives are also known to possess anticonvulsant activities^{VII}.

However, many of the protocols for the initial generation of the quinazolines core/or preparation of N-substituted-2-styrylquinazolinones suffer from drawbacks such as requiring multistep procedure, harsh reaction conditions, long reaction times, or low yields^{VIII-XV}. Also there is a need to develop an environmentally-friendly method for the synthesis of quinazolinones. The emerging area of Green chemistry is need in the design and attainment of sustainable development. Chemical Synthesis without the use of solvents has developed into a powerful methodology as it reduces the amount of toxic waste produced and therefore becomes less harmful to the environment.

Results and Discussion

In the first step, condensation of anthranilamide (1) with acetic anhydride grinding in mortar and pestle for 5 minutes gave the previously reported^X 2-methyl-3H-quinazoline-4-one(2). Its IR spectrum in KBr showed the diagnostic absorption at 3200 cm⁻¹ (broad, medium) due to –NH- stretching vibration and another at 1669 cm⁻¹ (strong, sharp) due to –CO- group and the absence of an unequal doublet at 3455, 3483 cm⁻¹ due to asymmetrical &

symmetrical stretching vibrations of -NH₂ group that was there in **1**. Its ¹H NMR (DMSO-d₆/TMS) spectrum showed signals at δ 3.10 (s, 3H, CH₃), 7.45-8.22 (m, 4H, **phenyl ring protons**), 12.32 (s, 1H, br, -NH, D₂O exchangeable). Its APCI mass spectrum showed M⁺-1 ion peak at 159 corresponding to a molecular mass of 160.

In the second step, treatment of **2** with benzaldehydes grinding in mortar and pestle using K₂CO₃ as a base for 5-10 min. at room temperature, gave 2-styrylquinazolinone-4-ones (**3**) in excellent yields. The products showed in their IR spectra (KBr), characteristic peaks at 3460 cm⁻¹ (broad, medium) due to -NH group and at 1665 cm⁻¹ (strong, sharp) due to -CO- group. In their ¹H NMR (DMSO-d₆/TMS) spectra, the products showed signals at δ 6.96-7.06 (d, J=14 Hz, 1H), 7.94-7.97 (d, J=14 Hz, 1H), due to trans disposed **vinyllic protons** and at δ 12.34 (s, 1H, br, D₂O exchangeable), due to the -NH- protons in addition to the signals due to aryl protons. For details, please see the Experimental Section.

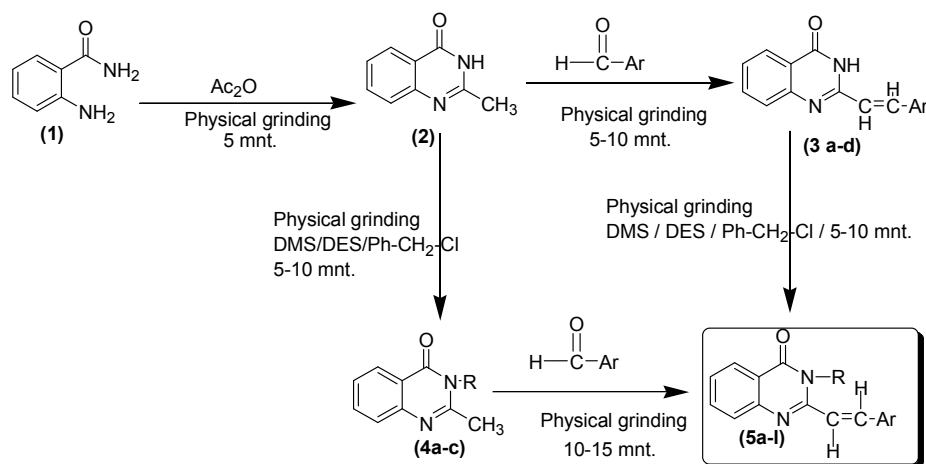
Treatment of **3 (a-d)** either with DMS, DES, or with Ph-CH₂-Cl individually in physical grinding for 5-10 min. using K₂CO₃ mild base, followed by simple processing resulted in **5 (a-l)** in yields of 80-88%. The products showed in their IR spectra (in KBr) characteristic peaks at 1666 cm⁻¹ (strong, sharp) due to -CO- group and absence of any absorption due to -NH grouping. In their ¹H NMR (DMSO-d₆/TMS) spectra, the products showed signals at δ 6.96-7.02 (d, J=14 Hz, 1H), 7.93-7.96 (d, J=14 Hz, 1H), due to trans disposed **vinyllic protons** and at δ 12.37 (s, 1H, br, D₂O exchangeable), due to the -NH- protons in addition to signals due to aryl protons. For details, please see the Experimental Section.

In an alternative approach, **5(a-i)** could be also prepared by treatment of **2** with either DMS, DES, or with Ph-CH₂-Cl, individually, in physical grinding for 5-10 min. using K₂CO₃ mild base, resulted in **4(a-c)** in yields of 80-86% on processing the reaction mixture. The products showed in their IR spectra (in KBr) absorptions at 1665 cm⁻¹ (strong, sharp) due to the -N-CO- group and absence of any absorption in the 3410-3030 cm⁻¹ due to any -NH- grouping which was seen in the spectra of starting compounds **2**. All the products **4 (a-c)** showed in their ¹H NMR spectra signals due to alkyl protons in the aliphatic region in addition to aryl protons in the 7.10-8.00 region and absence of the -NH- proton signal (D₂O exchangeable) that was observed prominently in the spectra of starting compounds **2**.

In an alternative approach, reaction of **4 (a-c)** with benzaldehydes in physical grinding for 5-10 min. using K₂CO₃ mild base, followed by simple processing resulted in **5 (a-l)** in yields of 85-90%, identical in m.p., m.m.p., TLC and IR with that of the same products obtained in the route described above, (ie. **3** → **5**). For details, please see the Experimental Section.

It is obvious from the above results that physical grinding is very efficient method for synthesis in organic chemistry, the above reaction previously reported^{xii} refluxing in PEG-600 energy was required for carried out the reaction, now we prepared the compounds in solvent free method and heating energy is not required for this method.

Scheme – I



Experimental Section

General: Melting points are uncorrected and were determined in open capillary tubes in sulphuric acid bath. TLC was performed on silica gel-G and spotting was done using iodine or UV-light. IR spectra were recorded with Perkin-Elmer 1000 instrument in KBr phase, $^1\text{H-NMR}$ on VARIAN 400MHz instrument and Mass spectra on Agilent-LC-MS instrument giving only M^+ values using Q+1 or Q-1 mode.

Preparation of 2 from 1 (General Procedure): A mixture of **1** (2.74 gm, 20 mM), acetic anhydride (2.5mL, 30 mM) physical grinding in mortar and pestle for 5-10 min. at room temperature. After completion of reaction (as indicated by TLC), water (2×40 mL) was added to the reaction mixture and the separated solid was filtered, washed with water (2×10 mL) and dried. Yield = 2.75 gm. (85%). Pure **2** (EtOH), M.P. = 228-230 °C. (lit.¹⁴ M.P. 230-232 °C).

Preparation of 3 from 2 (General Procedure): A mixture of **2** (2.74 gm, 15 mM), aromatic aldehyde (15 mM) and grinding in mortar and pestle using K_2CO_3 as a base for 5-10 min. at room temperature. After completion of reaction (as indicated by TLC), water (2×40 mL) was added to the reaction mixture and the separated solid was filtered, washed with water (2×10 mL) and dried. The crude product was recrystallized from ethanol to obtain pure **3**.

3a: Yield = 3.40 gm. (80 %), as a white solid: m.p. 251 °C (Lit.^{XVI} M.P. 252 °C); IR (KBr): 3400 cm^{-1} (broad, medium -NH-), 1664 cm^{-1} (strong, sharp, -CO-). $^1\text{H-NMR}$ (400 MHz, DMSO/ d_6 /TMS): δ 6.98-7.02 (d, **1H**, $J = 14$ Hz, **vinyllic proton**), 7.40-7.4 (m, **4H**, aromatic ring protons), 7.64-8.11 (m, **6H**, four quinazolinone ring protons + one aromatic benzene ring proton + one vinyllic proton). 12.33 (s, 1H, br, -NH, D_2O exchangeable). MS: m/z 249 ($\text{M}^+ + 1$).

3b: Yield = 3.90 gm. (82 %), as a white solid: m.p. 259 °C (Lit.^{XV} M.P. 260 °C); IR (KBr): 3400 cm^{-1} (broad, medium -NH-), 1667 cm^{-1} (strong, sharp, -CO-). $^1\text{H NMR}$ (400 MHz, DMSO/ d_6 /TMS): δ 3.80 (s, **3H**, OCH_3), 6.98-7.02 (d, **1H**, $J = 14$ Hz, **vinyllic proton**), 7.00-8.21 (m, **9H**, four quinazolinone ring protons + four aromatic benzene ring + one vinyllic proton), 12.33 (s, 1H, br, -NH, D_2O exchangeable). MS m/z 279 ($\text{M}^+ + 1$).

3c: Yield = 4.50 gm. (81 %), as a white solid: m.p. 253 °C (Lit.^X M.P. 255 °C); IR (KBr): 3400 cm^{-1} (broad, medium -NH-), 1670 cm^{-1} (strong, sharp, -CO-). $^1\text{H-NMR}$ (400 MHz, DMSO/ d_6 /TMS): δ 3.80 (s, **3H**, OCH_3), 4.20 (t, **3H**, - CH_3), 4.50 (m, **2H**, - CH_2 -), 6.98-7.02

(d, **1H**, $J = 14$ Hz, **vinyllic proton**), 7.00-8.21 (m, **8H**, four quinazolinone ring protons + three aromatic benzene ring proton + one vinyllic proton), 12.33 (s, 1H, br, -NH, D₂O exchangeable). MS m/z 323 ($M^+ + 1$).

3d: Yield = 3.60 gm. (80 %), as a white solid: m.p. 255 °C (Lit.^X M.P. 258 °C); IR (KBr): 3400 cm^{-1} (broad, medium -NH-), 1668 cm^{-1} (strong, sharp, -CO-). ¹H-NMR (400 MHz, DMSO-*d*₆/TMS): δ 6.98-7.02 (d, **1H**, $J = 14$ Hz, **vinyllic proton**), 6.87-8.21 (m, **9H**, four quinazolinone ring protons + four aromatic benzene ring proton + one vinyllic proton), 10.22 (s, 1H, br, -OH, D₂O exchangeable), 12.33 (s, 1H, br, -NH, D₂O exchangeable). MS m/z 265 ($M^+ + 1$).

Preparation of 4 from 2 (General Procedure): A mixture of **2** (2.74 gm, 15 mM), DMS/DES/ Ph-CH₂-Cl (15 mM) and PEG-600 (40 mL), was heated at 100 °C for 1-2 hr. After completion of reaction (as indicated by TLC), water (2×40 mL) was added to the reaction mixture and the separated solid was filtered, washed (2×10 mL) with water and dried. The crude product was recrystallized from ethanol to obtain pure **4**.

4a: Yield = 2.50 gm. (84%), as a white solid: m.p. 63 °C (Lit.^X M.P. 65 °C); IR (KBr): 1666 cm^{-1} (strong, sharp, -CO-). ¹H-NMR (400 MHz, DMSO-*d*₆/TMS): δ 2.5 (s, **3H**, -CH₃), 3.50 (s, **3H**, -CH₃), 7.5-8 (m, **4H**, aromatic benzene ring proton). MS m/z 175 ($M^+ + 1$).

4b: Yield = 2.60 gm. (81%), as a white solid: m.p. 85 °C (Lit.^X M.P. 87 °C); IR (KBr): 1664 cm^{-1} (strong, sharp, -CO-). ¹H-NMR: (400 MHz, DMSO-*d*₆/TMS): δ 2.5 (s, **3H**, -CH₃), 4.20 (t, **3H**, -CH₃), 4.50 (m, **2H**, -CH₂-), 7.5-8 (m, **4H**, aromatic benzene ring). MS m/z 189 ($M^+ + 1$).

4c: Yield = 3.50 gm. (81%), as a white solid: m.p. 95 °C (Lit.^{XI} M.P. 97 °C); IR (KBr): 1668 cm^{-1} (strong, sharp, -CO-). ¹H-NMR: (400 MHz, DMSO-*d*₆/TMS): δ 2.5 (s, **3H**, -CH₃), 4.50 (s, **2H**, -CH₂-), 7-7.5 (m, **5H**, aromatic benzene ring protons), 7.5-8 (m, **4H**, quinazolinone ring protons). MS: m/z 251 ($M^+ + 1$).

Preparation of 5 from 3 (General Procedure): A mixture of **3** (2.48 gm, 10 mM), DMS/DES/ Ph-CH₂-Cl (10 mM) and grinding in mortar and pestle using K₂CO₃ as a base for 5-10 min. at room temperature After completion of reaction (as indicated by TLC), water (2×40 mL) was added to the reaction mixture and the separated solid was filtered, washed with water (2×10 mL) and dried. The crude product was recrystallized from ethanol to obtain pure **5**.

5a: Yield = 2.27 gm. (87 %), as a maroon solid: m.p. 120-22 °C; IR (KBr): 1666 cm^{-1} (strong, sharp, -CO-). ¹H-NMR (400 MHz, DMSO-*d*₆/TMS): δ 3.50 (s, **3H**, -CH₃), 6.98-7.02 (d, **1H**, $J = 14$ Hz, **vinyllic proton**), 7.40-7.4 (m, **4H**, aromatic benzene ring), 7.64-8.11 (m, **6H**, four quinazolinone ring protons + one aromatic benzene ring + one vinyllic proton). MS: m/z 263 ($M^+ + 1$). [Found: C: 77.83, H: 5.36, N: 10.68, C₁₇H₁₄N₂O requires C: 77.84, H: 5.38, N: 10.68 %].

5b: Yield = 2.62 gm. (90 %), as a light yellow solid: m.p. 125-26 °C; IR (KBr): 1668 cm^{-1} (strong, sharp, -CO-). ¹H-NMR (400 MHz, DMSO-*d*₆/TMS): δ 3.70 (s, **3H**, -CH₃), 3.80 (s, **3H**, OCH₃), 6.98-7.02 (d, **2H**, $J = 16$ Hz, **vinyllic protons**), 7.28-8.11 (m, **8H**, four quinazolinone ring protons + four aryl protons). MS m/z 293 ($M^+ + 1$). [Found: C: 73.85, H: 5.50, N: 9.55, C₁₈H₁₆N₂O₂ requires C: 73.95, H: 5.52, N: 9.58 %].

5c: Yield = 2.95 gm. (88 %), as a light yellow solid: m.p. 120-22 °C; IR (KBr): 1665 cm^{-1} (strong, sharp, -CO-); ¹H-NMR (400 MHz, DMSO-*d*₆/TMS): δ 3.70 (s, **3H**, -CH₃), 3.80 (s, **3H**, OCH₃), 4.20 (t, **3H**, -CH₃), 4.50 (m, **2H**, -CH₂-), 6.98-7.02 (d, **1H**, $J = 14$ Hz, **vinyllic proton**), 7.00-8.21 (m, **8H**, four quinazolinone ring protons + three aromatic benzene ring + one vinyllic proton). MS m/z 337 ($M^+ + 1$). [Found: C: 71.39, H: 5.95, N: 8.30, C₂₀H₂₀N₂O₃ requires C: 71.41, H: 5.99, N: 8.33 %].

5d: Yield = 2.50 gm. (90 %), as an orange solid: m.p. 121-23 °C; IR (KBr): 1668 cm⁻¹ (strong, sharp, -CO-); ¹H-NMR: (400 MHz, DMSO/d₆/TMS) δ 3.70 (s, 3H, -CH₃), 6.98-7.02 (d, 1H, *J* = 14 Hz, vinylic proton), 6.87-8.21 (m, 9H, four quinazolinone ring protons + four aromatic benzene ring + one vinylic proton), 10.22 (s, 1H, br, OH, D₂O exchangeable). MS m/z 279 (M⁺+1). [Found: C: 73.35, H: 5.04, N: 10.04, C₁₇H₁₄N₂O₂ requires C: 73.37, H: 5.07, N: 10.07 %].

5e: Yield = 2.34 gm. (85 %), as a maroon solid: m.p. 121-23 °C; IR (KBr): 1665 cm⁻¹ (strong, sharp, -CO-); ¹H NMR (400 MHz, DMSO/d₆/TMS, δ): 1.60 (t, 3H, -CH₃) 4.50 (t, 2H, -CH₂-) 6.98-7.02 (d, 1H, *J* = 14 Hz, vinylic proton), 7.40-7.4 (m, 4H, aromatic benzene ring) 7.64-8.11 (m, 6H, four quinazolinone ring protons + one aromatic benzene ring + one vinylic proton); MS m/z 277 (M⁺+1). [Found: C: 78.20, H: 5.80, N: 10.10, C₁₈H₁₆N₂O requires C: 78.24, H: 5.84, N: 10.14 %].

5f: Yield = 2.69 gm. (88 %), as a light yellow solid: m.p. 120-22 °C; IR (KBr): 1665 cm⁻¹ (strong, sharp, -CO-); ¹H-NMR (400 MHz, DMSO/d₆/TMS): δ 1.60 (t, 3H, -CH₃), 4.50 (t, 2H, -CH₂-), 3.80 (s, 3H, OCH₃), 6.98-7.02 (d, 2H, *J* = 16 Hz, vinylic protons), 7.28-8.11 (m, 8H, four quinazolinone ring protons + four aromatic benzene ring). MS m/z 307 (M⁺+1). [Found: C: 74.45, H: 5.92, N: 9.14, C₁₉H₁₈N₂O₂ requires C: 74.49, H: 5.92, N: 9.14 %].

5g: Yield = 2.80 gm. (80 %), as a light yellow solid: m.p. 119-21 °C; IR (KBr): 1669 cm⁻¹ (strong, sharp, -CO-); ¹H-NMR (400 MHz, DMSO/d₆/TMS): δ 1.60 (t, 3H, -CH₃), 4.50 (t, 2H, -CH₂-), 3.80 (s, 3H, OCH₃), 4.20 (t, 3H, -CH₃), 4.50 (m, 2H, -CH₂-), 6.98-7.02 (d, 1H, *J* = 14 Hz, vinylic proton), 7.00-8.21 (m, 8H, four quinazolinone ring protons + three aromatic benzene ring protons + one vinylic proton). MS m/z 351 (M⁺+1). [Found: C: 71.95, H: 6.30, N: 7.95, C₂₁H₂₂N₂O₃ requires C: 71.98, H: 6.33, N: 7.99 %].

5h: Yield = 2.56 gm. (88 %), as an orange solid: m.p. 121-23 °C; IR (KBr): 1664 cm⁻¹ (strong, sharp, -CO-); ¹H-NMR (400 MHz, DMSO/d₆/TMS): δ 1.60 (t, 3H, -CH₃), 4.50 (t, 2H, -CH₂-), 6.98-7.02 (d, 1H, *J* = 14 Hz, vinylic protons), 6.87-8.21 (m, 9H, four quinazolinone ring protons + four aromatic benzene ring + one vinylic proton), 10.22 (s, 1H, br, OH, D₂O exchangeable). MS m/z 293 (M⁺+1). [Found: C: 73.90, H: 5.50, N: 9.54, C₁₈H₁₆N₂O₂ requires C: 73.95, H: 5.52, N: 9.58 %].

5i: Yield = 3.04 gm. (90 %), as a maroon solid; m.p. 118-20 °C; IR (KBr): 1666 cm⁻¹ (strong, sharp, -CO-); ¹H-NMR (400 MHz, DMSO/d₆/TMS): δ 4.50 (s, 2H, -CH₂-), 6.98-7.02 (d, 1H, *J* = 14 Hz, vinylic proton), 7-7.5 (m, 5H, phenyl ring protons), 7.40-7.4 (m, 4H, aromatic benzene ring), 7.64-8.11 (m, 6H, four quinazolinone ring protons + one aromatic benzene ring proton + one vinylic proton). MS m/z 339 (M⁺+1). [Found: C: 81.60, H: 5.30, N: 8.24, C₂₃H₁₈N₂O requires C: 81.63, H: 5.36, N: 8.28 %].

5j: Yield = 2.85 gm. (87 %), as a light yellow solid: m.p. 120-22 °C; IR (KBr): 1665 cm⁻¹ (strong, sharp, -CO-); ¹H-NMR (400 MHz, DMSO/d₆/TMS): δ 3.80 (s, 3H, -OCH₃), 4.50 (s, 2H, -CH₂-), 6.98-7.02 (d, 2H, *J* = 16 Hz, vinylic protons), 7-7.5 (m, 5H, phenyl ring protons), 7.28-8.11 (m, 8H, four quinazolinone ring protons + four aromatic benzene ring protons). MS m/z 369 (M⁺+1). [Found: C: 76.20, H: 5.40, N: 7.55, C₂₄H₂₀N₂O₂ requires C: 78.24, H: 5.47, N: 7.60 %].

5k: Yield = 3.51 gm. (85 %), as a light yellow solid: m.p. 120-22 °C; IR (KBr): 1666 cm⁻¹ (strong, sharp, -CO-); ¹H-NMR (400 MHz, DMSO/d₆/TMS): δ 3.80 (s, 3H, -OCH₃), 4.20 (t, 3H, -CH₃), 4.40 (s, 2H, -CH₂-), 4.50 (m, 2H, -CH₂-), 6.98-7.02 (d, 2H, *J* = 16 Hz, vinylic protons), 7-7.5 (m, 5H, phenyl ring protons), 7.00-8.21 (m, 7H, four quinazolinone ring protons + three aromatic benzene ring protons). MS m/z 413 (M⁺+1). [Found: C: 75.65, H: 5.80, N: 6.70, C₂₆H₂₄N₂O₃ requires C: 75.71, H: 5.86, N: 6.79 %].

5l: Yield = 2.93 gm. (83 %), as an orange solid m.p. 118-20 °C; IR (KBr): 1665 cm⁻¹ (strong, sharp, -CO-); ¹H-NMR (400 MHz, DMSO/d₆/TMS): δ 4.50 (s, 2H, -CH₂-), 6.98-7.02 (d, 1H, *J* = 14 Hz, vinylic proton), 7-7.5 (m, 5H, phenyl ring protons), 6.87-8.21 (m, 9H, four quinazolinone ring protons + four aromatic benzene ring + one vinylic proton), 10.22 (s, 1H, br, OH, D₂O exchangeable). MS m/z 355 (M⁺+1). [Found: C: 77.90, H: 5.05, N: 7.80, C₂₃H₁₈N₂O₂ requires C: 77.95, H: 5.12, N: 7.90 %].

Preparation of 5 from 4 (General Procedure): A mixture of 4 (1.74 gm, 10 mM), aromatic aldehydes (10 mM) grinding in mortar and pestle using K₂CO₃ as a base for 5-10 min. at room temperature. After completion of reaction (as indicated by TLC), water (2×40 mL) was added to the reaction mixture and the separated solid was filtered, washed (2×10 mL) with water and dried. The crude product was recrystallized from ethanol to obtain pure 5.

5a: Yield = 2.35 gm. (90 %).

5b: Yield = 2.65 gm. (91 %).

5c: Yield = 3.05 gm. (91 %).

5d: Yield = 2.50 gm. (90 %).

5e: Yield = 2.40 gm. (87 %).

5f: Yield = 2.75 gm. (90 %).

5g: Yield = 3.08 gm. (88 %).

5h: Yield = 2.62 gm. (90 %).

5i: Yield = 2.90 gm. (86 %).

5j: Yield = 3.12 gm. (85 %).

5k: Yield = 3.62 gm. (88 %).

5l: Yield = 2.93 gm. (83 %).

Conclusion

In conclusion, the use of solvents like DMF / CH₃CN are not green and hence we have developed a green approach for the synthesis of 3-alkyl 2-styrylquinazolin-3(4H)-one under physical grinding method.

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