# α-Cyclisation of Tertiary Amines: Synthesis of Some Novel Annelated Quinolines via a Three-Component Reaction under Solvent-Free Conditions

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**Abstract:** Synthesis of some novel classes of quinolizine-, indolizine- and pyrido-1,4-oxazine-fused quinoline derivatives via a three-component reaction under solvent-free conditions by exploring the 'tertiary amine effect' reaction strategy.

**Key words:** quinolines, pyrimidines, tertiary amine effect, solvent-free reaction, multicomponent reaction

α-Cyclisation of tertiary amines is a mechanistically intriguing and synthetically useful cyclisation which has not received much attention. Certain tertiary anilines or enamines and enamine esters undergo such cyclisation leading to annelated pyrrolidines. Suchitzky and Meth-Cohn[1] have coined the term 'tertiary amine effect' to describe such processes which have been further developed by Reinhoudt and Verboom.[2]

Development of new solid-phase (solvent-free) reactions and transferring solution-phase reactions to the solid phase are subjects of recent interest in the context of generating libraries of molecules for the discovery of biologically active leads and also for the optimisation of potent drug candidates.[3] Multi-component reactions (MCRs) by virtue of their convergence, productivity, facile execution and generally high yield of products have attracted considerable attention from the point of view of combinatorial chemistry.[4] The first MCR was described by Strecker in 1850 for the synthesis of amino acids.[5] However, in the past decade there have been tremendous developments in three- and four-component reactions and great efforts have been and still are being made to find and develop new MCRs.[6]

Quinoline and its annelated derivatives are well known by synthetic as well as biological chemists. Compounds with this ring system have found wide application as drugs and pharmaceuticals.[7] Therefore, large efforts have been directed towards the synthetic manipulation of quinolines to find more useful compounds. As a result, a number of compounds have been obtained with diverse biological activities some of which are used as potent drugs.[8] In this regard the [b]-annelation of quinolines gave access to a huge number of new quinoline derivatives,[9] besides providing novel approaches for the synthesis of alkaloids

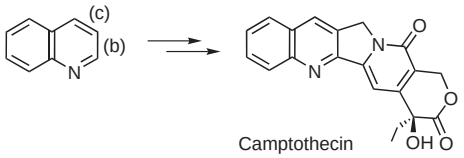
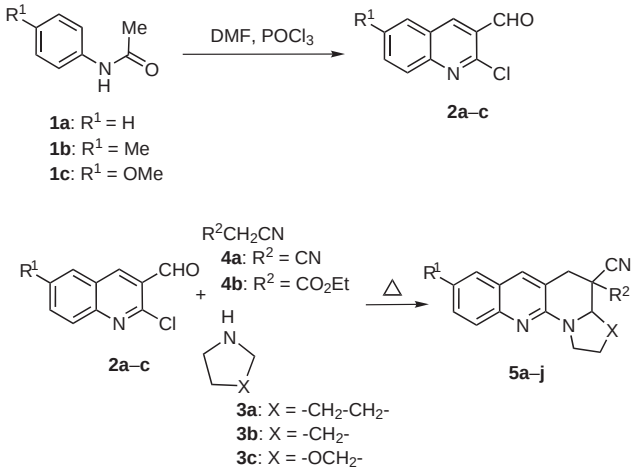


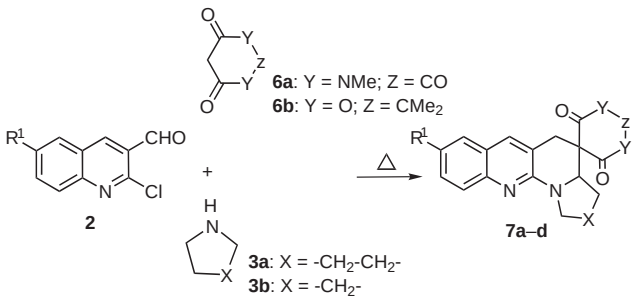

**Figure 1**

such as camptothecin,[10] luotonin A,[11] 22-hydroxyacuminatine[12] or nothapodytine[13] (Figure 1).

As a result of our continued interest[14] in the development of highly expedient methods and syntheses of diverse heterocyclic compounds of biological significance we report here the preparation of some novel classes of quinolizine-, indolizine- and pyrido-1,4-oxazine-fused quinoline derivatives via a three-component reaction under solvent-free conditions by exploring the 'tertiary amine effect' reaction strategy (Schemes 1 and 2).




**Scheme 1**




**Scheme 2**

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Simple acetanilides **1** were taken as starting materials in our reaction strategy. 2-Chloro-3-formyl quinolines **2** were prepared from acetanilides **1** by modifying the existing method (Scheme 2).[15] Thus acetanilide **1a** on treatment with the Vilsmeier reagent ($DMF/POCl_3$) gave 2-chloro-3-formyl quinoline (**2a**) in excellent yields.[16] In a simple three-component reaction[17] equimolar amounts of 2-chloro-3-formyl quinoline (**2a**), piperidine (**3a**) and malononitrile (**4a**) were treated at 110–120 °C in the absence of solvent for five hours. The solid material obtained on cooling the reaction mixture and after work-up afforded compound **5a** in good yield. The structure of the compound was determined from the spectroscopic data and elemental analysis. The IR spectrum exhibited a sharp band at 2217 $cm^{-1}$ confirming the presence of the CN functionality. The $^1H$ NMR spectra showed the absence of the aldehyde proton and the presence of a methylene group at $\delta$ = 5.30 ppm as a singlet. The mass spectrum revealed a strong molecular ion peak at 289 $(M + H)^+$. With suitable conditions established for the three-component reaction, compounds **5b**–**j** were synthesised by utilising **2a**–**c** with various secondary amines **3a**–**c** and alkyl nitriles **4a** and **4b** (Table 1). The use of less reactive ethyl cyanoacetate requires a longer reaction time to give comparatively a lower yield of the cyclised product. The structures of the compounds were ascertained from their spectroscopic data and elemental analysis.

We then studied the reactivity pattern of **2** and **3** with highly active cyclic β-diamide (Barbituric acids) or cyclic β-dilactone (Meldrum's acid) **6** under solvent-free conditions (Scheme 2). As expected the dimethyl barbituric acid and Meldrum's acid **6** underwent ring closure in shorter reaction times to afford the product **7** with the spirocyclic ring system in excellent yields (Table 2).

A reasonable mechanism for the reaction is outlined in Scheme 3. The base **3** initially catalyses the condensation of **2** and **4**, and then substitutes the chloro group to give compound [**A**]. Then compound [**A**] undergoes a 1,5-hydride shift under thermolytic conditions to generate a 1,6-dipole [**B**], which subsequently underwent intramolecular cyclisation to give the product **5**.

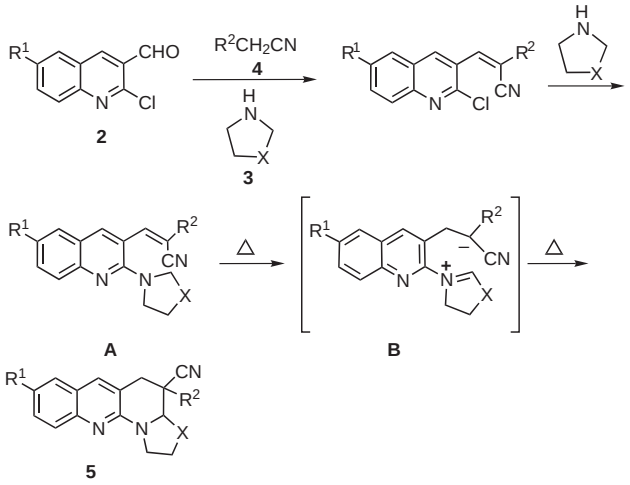
The formation of compound **5** was established by performing the reaction stepwise (Scheme 4). In a simple experimental procedure equimolar amounts of 2-chloro-3-formyl quinoline (**2a**), piperidine (**3a**) and potassium carbonate were reacted in DMF under refluxing conditions, which after work-up afforded the product **8a** in high yield.[18] The structure of the compound was ascertained by spectroscopy. Then compound **8a** was treated with malononitrile (**4a**) in the presence of a catalytic amount of **3a** to afford the Knoevenagel product **9** in excellent yields,[19] which under thermolytic conditions in the absence of solvent afforded the cyclised product **5a** in excellent yield.[20]

**Table 1** Synthesis of Novel Annelated Quinoline Derivatives **5**

| Product | $R^1$ | $R^2$ | X | Time (h) | Temp (°C) | Mp (°C) | Yield (%) |
|---|---|---|---|---|---|---|---|
| **5a** | H | Me | $(CH_2)_2$ | 5 | 110–120 | 169–170 | 54 |
| **5b** | Me | CN | $CH_2$ | 5 | 110–120 | 174–175 | 57 |
| **5c** | OMe | CN | $CH_2$ | 6 | 110–120 | 164–165 | 52 |
| **5d** | H | $CO_2Et$ | $(CH_2)_2$ | 6 | 110–120 | 147–148 | 45 |
| **5e** | H | CN | $CH_2$ | 5 | 110–120 | 191–192 | 58 |
| **5f** | Me | CN | $CH_2$ | 6 | 110–120 | 203–204 | 60 |
| **5g** | OMe | CN | $CH_2$ | 6 | 110–120 | 183–184 | 55 |
| **5h** | H | $CO_2Et$ | $CH_2$ | 5 | 110–120 | 161–162 | 45 |
| **5i** | H | CN | $OCH_2$ | 5 | 110–120 | 210–211 | 51 |
| **5j** | Me | CN | $OCH_2$ | 5 | 110–120 | 218–219 | 58 |

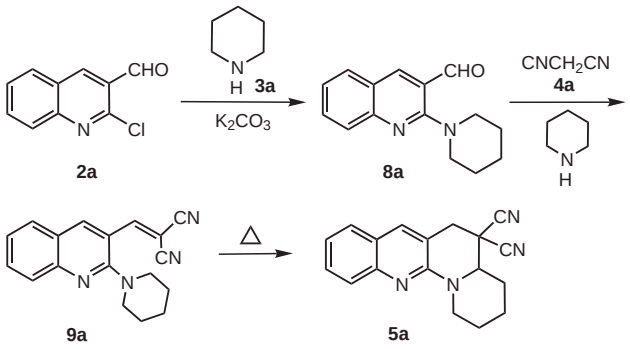
**Table 2** Synthesis of Novel Annelated Quinoline Derivatives **7**

| Product | $R^1$ | X | Y | Z | Time (h) | Temp (°C) | Mp (°C) | Yield (%) |
|---|---|---|---|---|---|---|---|---|
| **7a** | H | $(CH_2)_2$ | $NMe_2$ | C=O | 4 | 110–120 | 148–149 | 62 |
| **7b** | Me | $(CH_2)_2$ | $NMe_2$ | C=O | 4 | 110–120 | 175–176 | 59 |
| **7c** | OMe | $(CH_2)_2$ | $NMe_2$ | C=O | 4 | 110–120 | 139–140 | 57 |
| **7d** | H | $CH_2$ | $NMe_2$ | C=O | 5 | 110–120 | 170–171 | 54 |
| **7e** | Me | $CH_2$ | $NMe_2$ | C=O | 5 | 110–120 | 185–186 | 52 |
| **7f** | H | $CH_2$ | O | $CMe_2$ | 4 | 110–120 | 165–166 | 55 |



**Scheme 3**

The structure of the compound was determined from the physical and spectroscopic data. Similarly compounds **5e**, **5i** and **7a** were prepared by the stepwise reaction and then characterised.



**Scheme 4**

In conclusion we have reported the synthesis of some novel classes of quinolizine-, indolizine- and pyrido-1,4-oxazine-fused complex quinoline derivatives via a novel three-component reaction under solvent-free conditions by exploring the 'tertiary amine effect' reaction strategy. Product formation in the three-component reactions was established by performing the reactions stepwise. Spirocyclic compounds such as the cyclic β-diamide (uracil derivative) possess a wide range of biological activity and the β-dilactone (Meldrum's acid) is transformable to other functionality and hence there is further scope for molecular manipulation of these products. This cost-efficient, environment-friendly and operationally very simple procedure for the synthesis of tetracyclic angularly annelated quinolines from easily available starting materials render this method a valuable addition to quinoline chemistry.

## Acknowledgment

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(16) Compound **2a**: $POCl_3$ (9 mL, 98.28 mmol) was added dropwise via dropping funnel to DMF (2.7 mL, 34.65 mmol) at 0–5 °C. The mixture was stirred for about 5 min. Acetanilide (**1a**; 1.42 g, 10.37 mmol) was then added to the reaction mixture and the resulting solution was heated for 8 h (75–80 °C). The reaction mixture was cooled to r.t. and then poured into crushed ice with stirring. A pale-yellow precipitate appeared at once, which was filtered, washed with $H_2O$ and dried. The crude compound was then recrystallised from EtOAc. Yield: 80% (1.62 g); mp 142–143 °C. Similarly compounds **2b**–**d** were synthesised and characterised.

(17) Three-Component Synthesis: 2-Chloro-3-formyl quinoline (**2a**) (1.92 g, 10 mmol) was mixed thoroughly with freshly distilled piperidine (**3a**; 0.991 g, 11.66 mmol) and malononitrile (**4a**; 0.660 g, 10 mmol) in a round-bottom flask. The reaction mixture was allowed to fuse at 110–120 °C for 5 h. The progress of the reaction was monitored by TLC and after its completion the product was separated and purified by preparative TLC ($CHCl_3$–hexane, 2:1) to give **5a**. Yield: 540 mg (54%); brown solid; mp 169–170 °C. IR ($CHCl_3$): 2945, 2854, 2225 $cm^{-1}$. $^1H$ NMR (300 MHz, $CDCl_3$): δ = 1.25–1.79 (m, 4 H, $CH_2$), 2.10–2.33 (m, 2 H, $CH_2$), 2.79–2.84 (t, 1 H, CH), 3.54–3.73 (m, 2 H, $CH_2$), 5.3 (s, 2 H, $CH_2$), 7.26–7.75 (m, 5 H, Ar). $^{13}C$ NMR ($CDCl_3$): δ = 23.79 (C-10), 24.68 (C-11), 30.12 (C-7), 36.74 (C-9), 37.11 (C-12), 45.55 (C-8), 60.06 (C-8a), 112.51 (C-5), 113.63 (CN), 114.75 (CN), 123.84 (C-4), 123.92 (C-2), 127.22 (C-3), 127.36 (C-6), 130.45 (C-6a), 137.03 (C-12b), 147.89 (C-5a), 152.96 (C-1a). MS: *m*/*z* = 289 $(M + H)^+$. Similarly compounds **5b**–**j** and **7a**–**f** were synthesised and characterised.

(18) Compound **8a**: 2-Chloro-3-formyl quinoline (**2a**; 1.92 g, 10 mmol) was mixed thoroughly with freshly distilled piperidine (**3a**; 0.991 g, 11.66 mmol) and $K_2CO_3$ (1.469 g, 11.66 mmol) in DMF (50 mL). The resulting mixture was allowed to reflux for 7 h. After completion of the reaction (monitored by TLC), the mixture was cooled to r.t. and poured into crushed ice under continuous stirring. A light-yellow solid appeared, which was allowed to settle for 2 h under ice cooling. The precipitate was filtered under reduced pressure, dried in a hot-air oven and finally purified by column chromatography ($CHCl_3$–hexane). Yield: 87.5% (2.1 g); light yellow crystals; mp 84–85 °C. IR: 2935.1, 2851.2, 1690.7 $cm^{-1}$. $^1H$ NMR (60 MHz, $CDCl_3$): δ = 1.5–1.7 ($CH_2$, 6 H), 3.1–3.3 ($CH_2$, 4 H), 6.9–7.6 (Ph, 5 H), 8.2 (CH, 1 H), 9.8 (CHO, 1 H).

(19) Compound **9a**: Compound **8a** (1.2 g, 5 mmol) and malononitrile (**4a**; 0.33 g, 5 mmol) were added to hexane (5 mL) and the resulting solution was stirred at r.t. To this solution piperidine (1 drop) was added and stirring was continued for 90 min. After completion of the reaction (monitored by TLC) the solvent was evaporated to dryness. The orange solid was further purified by column chromatography using ($CHCl_3$–hexane). Yield: 88.5% (1.24 g); orange crystals; mp 127–129 °C. IR: 2938, 2851, 2229 $cm^{-1}$. $^1H$ NMR (60 MHz, $CDCl_3$): δ = 1.5–1.8 ($CH_2$, 4 H), 3.1–3.3 ($CH_2$, 4 H), 7.0–7.8 (Ph, 5 H), 8.5 (CH, 1 H). Yield: 1.24 g (88.5%). Similarly compounds **9b** and **9c** were synthesised and characterised.

(20) Compound **5a**: Compound **9a** (1 g, 3.47 mmol) was allowed to fuse at 110–120 °C for 5 h. The conversion was monitored by TLC. The new compound was separated by preparative TLC ($CHCl_3$–hexane, 2:1) to give a brown solid. Similarly compounds **5e**, **5i** and **7a** were synthesised and characterised.