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A Novel Three-Component Reaction: Synthesis of Some Complex Annelated Quinolines from Simple Acetanilides and via Intramolecular 1,3-Dipolar Cycloaddition of Azide to Nitrile

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Abstract: Synthesis of a novel class of tetrazolo[4′,5′:1,6]pyrido[2,3-*d*]quinolines from simple acetanilides and via intramolecular 1,3-dipolar cycloaddition of azides to nitriles using a three-component one-pot protocol is reported.

Key words: quinolines, acetanilides, multicomponent reaction, cyano-stabilised carbanion, intramolecular 1,3-dipolar cycloaddition reactions

Quinoline and its annelated derivatives have wide applications as drugs and pharmaceuticals.[1] Therefore, considerable efforts have been directed towards the preparation and synthetic manipulation of quinolines and a number of compounds have been obtained with diverse biological activities some of which are used as potent drugs.[2] In this regard the [*b*]-annelation of quinolines gives access to a range of derivatives besides providing novel approaches to the synthesis of alkaloids such as camptothecin,[3] luotonin A,[4] 22-hydroxyacuminatine,[5] or nothapodytine[6] (Figure 1).

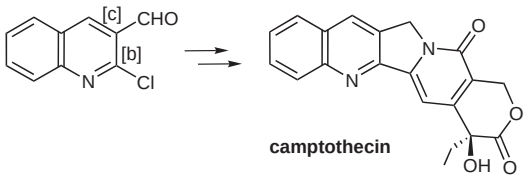
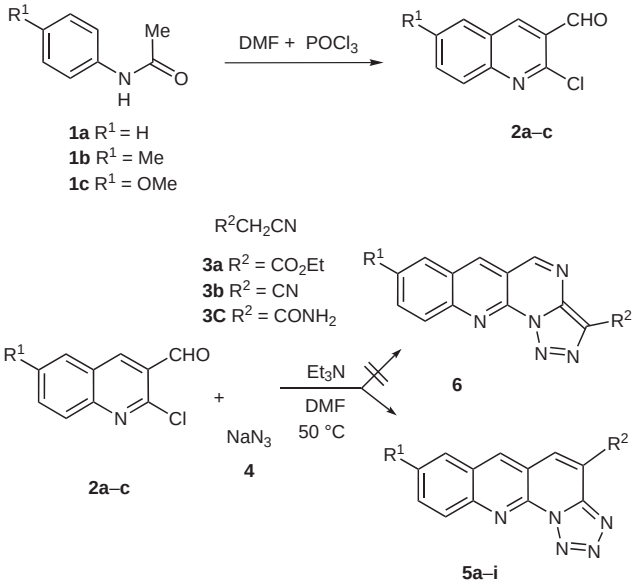


Figure 1

The attack of cyanide-stabilised carbanions on azide functions leading to 1,2,3-triazoles is a well-established conversion in organic synthesis.[7] In an extensive study,[8] the carbanion derived from diethyl acetonedicarboxylate can also be employed in this reaction process, and the triazoles resulting from the reaction undergo base-catalysed intramolecular condensation at the *ortho* substituent to give well-funtionalised triazolo[1,5-*a*]quinolines.

One-pot multicomponent reactions (MCRs), by virtue of their convergence, ease of execution and generally high yields of products have attracted considerable attention.[9] In the past decade there have been tremendous developments in three- and four-component reactions and great efforts have been and continue being made to find and develop new MCRs.[10]

As part of our continued interest on quinolines[11] and development of highly expedient methods for the synthesis of diverse heterocyclic compounds of biological importance, we report herein the synthesis of a novel class of tetrazolo[4′,5′:1,6]pyrido[2,3-*d*]quinolines from simple acetanilides by intramolecular 1,3-dipolar cycloaddition of azides to nitriles using a three-component one-pot protocol under mild conditions (Scheme 1).



Scheme 1

Acetanilides **1** were chosen as the parent molecules in our reaction strategy (Scheme 1). The 2-chloro-3-formyl quinolines **2** were prepared from acetanilides **1** by our own reported method.[11b] Thus acetanilide (**1a**) on treatment with Vilsmeier reagent gave 2-chloro-3-formyl quinoline (**2a**) in excellent yield. In the three-component reaction[12] equimolar amounts of **2a**, ethyl cyanoacetate (**3a**), and sodium azide (**4**) were treated at 50 °C in the presence of a catalytic amount of triethylamine for four hours using DMF as solvent. The solid compound obtained on pouring the reaction mixture into water and workup afforded the product **5a** in good yield. The structure of the compound was ascertained from the

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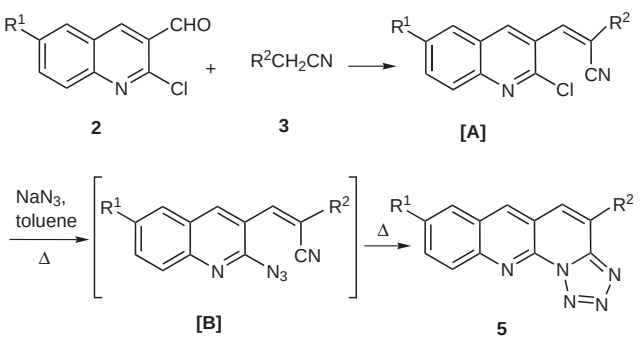
Table 1 Synthesis of Compound **5** via the Three-Component Reaction

Product	R^1	R^2	Temp (°C)	Time (h)	Mp (°C)	Yield (%)
5a	H	CO_2Et	60	4	205	80
5b	Me	CO_2Et	60	4	210	83
5c	OMe	CO_2Et	60	4	196	86
5d	H	$CONH_2$	60	4	167	74
5e	Me	$CONH_2$	60	4	173	76
5f	OMe	$CONH_2$	60	4	187	78
5g	H	CN	50	2	182	56
5h	Me	CN	50	2	179	57
5i	OMe	CN	50	2	175	60

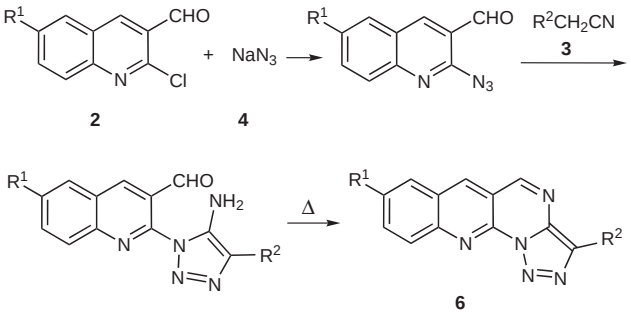
spectroscopic data and elemental analysis. The ^{1}H NMR spectrum showed the absence of the aldehyde proton and the presence of the ethyl group of the ester and a proton at $\delta = 7.26$ ppm. The IR spectrum showed the absence of the cyanide group, which evidenced its involvement in the cycloaddition reaction. The mass spectrum revealed a strong peak at 316 [M^+ + Na]. Although there was the possibility of the formation of compound **6** via a reaction route as shown in Scheme 3, no such compound was formed. With suitable conditions established for the three-component reaction a series of compounds **5a**–**i** was synthesised by utilizing various 2-chloro-3-formyl quinolines **2a**–**c** with alkyl nitriles **3a**–**c** and sodium azide (**4**). The structures of the compounds were determined from their spectroscopic data and elemental analysis (Table 1). Electron-donating groups at the 4-position of the acetanilides **1** (or the 6-position of the quinoline **2**) were found to enhance the formation of the product **5**.

A reasonable mechanism for the reaction is outlined in Scheme 2. The reaction occurs via initial Knoevenagel condensation of **2** and **3** in the presence of triethylamine to give intermediate **[A]** which then reacts with sodium azide to give the intermediate **[B]**. This undergoes an intramolecular 1,3-dipolar cycloaddition to the pendant cyano group of the sterically favoured quinoline derivative to afford the desired product **5** (Scheme 2).



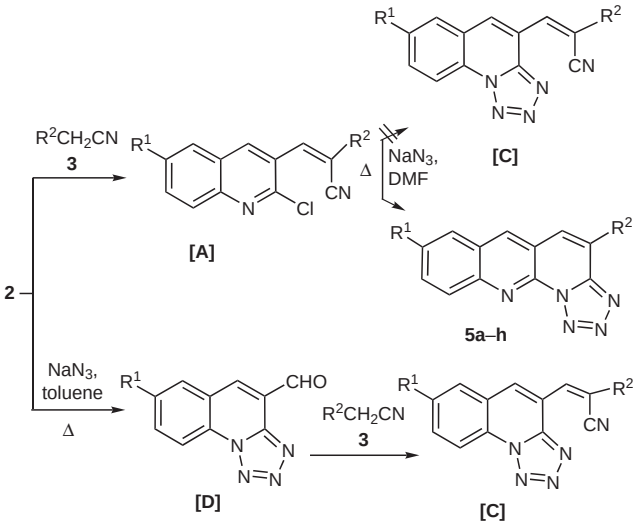
Scheme 2

The absence of compound **6** rules out the other possible reaction path as shown in Scheme 3.



Scheme 3

The path of the reaction and hence the proposed mechanism was established by performing the reaction stepwise (Scheme 4). First we reacted the 2-chloro-3-formyl quinoline (**2a**) with ethyl cyanoacetate (**3a**) in the presence of piperidine at room temperature, which gave the Knoevenagel product **[A]** in quantitative yield.[13] In order to introduce the azido group at the 2-position of the quinoline molecules, the compound **[A]** was treated with NaN_3 in DMF at 50 °C with stirring.[14] However, the intermediate **[B]** (Scheme 2) could not be isolated but spontaneously underwent intramolecular cycloaddition to the cyanide group to produce the product **5a**. The compound was comparable in all respects to the compound obtained from the three-component reaction. Although there was the possibility of the formation of compound **[C]** no such compound was found in the reaction mixture. However, when we tried to introduce the azide group before the Knoevenagel condensation the azide group underwent intramolecular cycloaddition to the imine bond in the first step to give the product **[D]**. Hence in the next step we obtained simply the Knoevenagel condensation product **[C]** instead of **5**.



Scheme 4

In conclusion we have reported the synthesis of a novel class of complex quinoline derivatives from simple acetanilides by exploiting the intramolecular 1,3-dipolar cycloaddition of azides to nitriles using a three-component one-pot protocol under mild conditions. The pathway for formation of the products in the three-component process was established by performing the reaction stepwise. This very simple protocol for the synthesis of tetracyclic angularly annelated quinolines from readily available starting materials is a valuable addition to quinoline chemistry. This is the first example of this type of reaction, which can be explored for the synthesis of various complex heterocyclic compounds. Further study of the reaction is in progress.

Acknowledgment

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(12) **Three-Component Reaction**
To a mixture of 2-chloro-3-formylquinoline (**2a**, 192 mg, 1 mmol), ethyl cyanoacetate (**3a**, 140 mg, 1.24 mmol) and NaN_3 (**4**, 80 mg, 1.24 mmol) in DMF (10 mL) were added two drops of water. A catalytic amount (1–2 drops) of Et_3N was then added to the reaction mixture and it was allowed to stir for 4 h at 50–60 °C. After completion of the reaction, the mixture was cooled to r.t. and poured into H_2O under continuous stirring. A brown solid precipitated that was shown to be almost totally pure **5a**. However, it was further purified by preparative TLC using EtOAc–hexane (3:7); mp 205 °C, yield 234 mg (80%). ^1H NMR ($CDCl_3$): δ = 1.43 (t, 3 H), 4.32 (q, 2 H), 7.26 (s, 1 H), 7.60–8.05 (m, 4 H), 8.63 (s, 1 H). ^{13}C NMR ($CDCl_3$): δ = 14.50 (CH_3), 61.20 (CH_2C=O), 112.55 (C-5), 123.75 (C-4), 124.00 (C-2), 126.20 (C-7), 127.45 (C-3), 127.70 (C-6), 131.00 (C-6a), 136.20 (C-11b), 138.36 (C-8), 145.12 (C-8a), 146.67 (C-5a), 151.25 (C-1a), 171.75 (C=O). MS: *m/z* = 316 $[M + Na]^+$. IR ($CHCl_3$): 2923.70, 2852.60, 1742.80 cm^{-1}. Anal. Calcd for $C_{15}N_5O_2H_{11}$: C, 61.43; H, 3.75; N, 23.89. Found: C, 61.43; H, 3.82; N, 23.95.

(13) 2-Chloro-3-formyl quinoline (**2a**, 384 mg, 2 mmol) was mixed with ethyl cyanoacetate (**3a**, 260 mg, 2.17 mml) in toluene (10 mL). One drop of piperidine was added and the reaction mixture was allowed to stir at r.t. for 1 h. The solvent was evaporated and the yellow solid obtained was purified by recrystallisation from EtOH.
Compound [**Aa**] (R^1 = H, R^2 = CO_2Et): mp 110 °C, yield 516 mg (98%). ^{1}H NMR ($CDCl_3$): δ = 1.43 (t, 3 H), 4.43 (q, 2 H), 7.46–815 (m, 4 H), 8.74 (s, 1 H), 9.05 (s, 1 H). IR ($CHCl_3$): 2226.70, 1730.90 cm^{-1}.

(14) The condensed product [**Aa**] (286 mg, 1 mmol) was mixed with NaN_3 (**4**, 80 mg, 1.24 mmol) in DMF (10 mL) and 2 drops of H_2O were added. The reaction mixture was allowed to stir for 4 h at 50–60 °C. After completion of the reaction the mixture was cooled to r.t. and poured into H_2O under continuous stirring. A brown coloured solid which appeared was filtered and purified by preparative TLC using EtOAc–hexane (3:7) to furnish **5a** (176 mg, 60%).