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Synthesis of novel pyrano[2,3-*b*]quinolines from simple acetanilides via intramolecular 1,3-dipolar cycloaddition

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Abstract—Some novel isoxazole and pyrazole fused pyrano[2,3-*b*]quinolines were synthesized from simple acetanilides via intramolecular 1,3-dipolar cycloaddition reactions involving nitrones, nitrile oxides and nitrile imines as 1,3-dipoles, in a regioselective manner.
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The importance of quinoline and its annelated derivatives is well recognized by synthetic and biological chemists.[1] Compounds possessing this ring system have wide applications as drugs and pharmaceuticals.[2] Pyranoquinolines are an important class of compounds that constitute the basic frameworks of a number of alkaloids of biological significance, for example, geibalasine, ribalinine, flindersine, etc. (Fig. 1).[3] Therefore, considerable efforts have been directed towards the preparation and synthetic manipulation of these molecules.[4] As a result, a number of compounds have been obtained with diverse biological activities.

Cycloaddition reactions are among the most useful reactions in synthetic and mechanistic organic chemistry.[5] They allow the direct construction of a new ring with a wide variety of substituents by simple addition of two or more reagents. Within this class, inter- and intramolecular 1,3-dipolar cycloaddition reactions have found extensive use as efficient regio- and stereoselective methods for the synthesis of a variety of natural products[6] and other heterocyclic compounds of biological significance.[7] Cycloaddition reactions, particularly hetero Diels–Alder reactions, are effective procedures employed for the preparation of pyranoquinolines.[8]

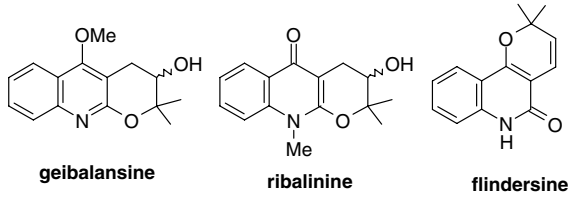

Figure 1.

Isoxazoles and pyrazoles are important classes of biologically active compounds. They have a rich chemistry because of their easy reductive cleavage and susceptibility to ring transformations.[9]

In continuation of our interest[10] in the development of highly expedient methods and syntheses of heterocyclic compounds of biological importance, we report here the synthesis of novel tetrahydroisoxazolo-, dihydroisoxazolo- and dihydropyrazolo-fused pyrano[2,3-*b*]-quinolines from simple acetanilides and via intramolecular 1,3-dipolar cycloaddition reactions involving nitrones, nitrile oxides and nitrile imines as 1,3-dipoles, in a regioselective manner.

Acetanilides **1** were chosen as the parent molecules (Scheme 1). The 2-chloro-3-formyl quinolines **2** were prepared from **1** by modifying the existing method.[11] Thus acetanilide **1a** ($R^1 = H$) on treatment with the Vilsmeier reagent ($DMF + POCl_3$) gave 2-chloro-3-formyl quinoline **2a** in excellent yield.[12] The ether derivative **3a** with an isolated dipolarophile site was prepared from **2a** by treatment with allyl alcohol in the presence of sodium hydroxide (50% aqueous solution) under phase transfer catalytic conditions.[13] Allyl ether **3a**, on treatment with *N*-methylhydroxylamine hydrochloride in

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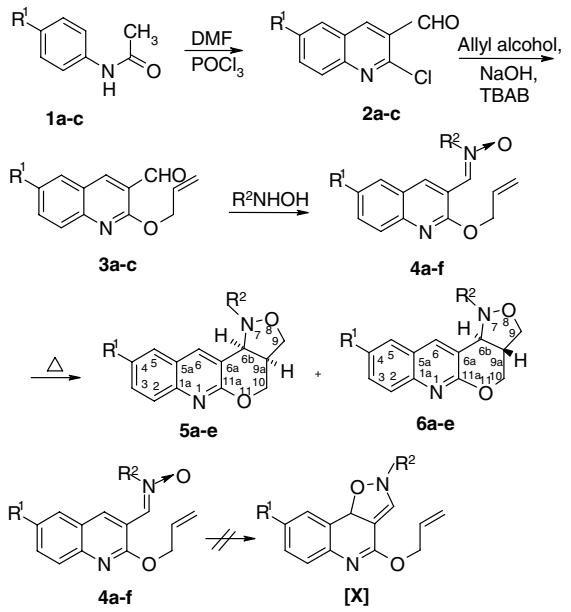


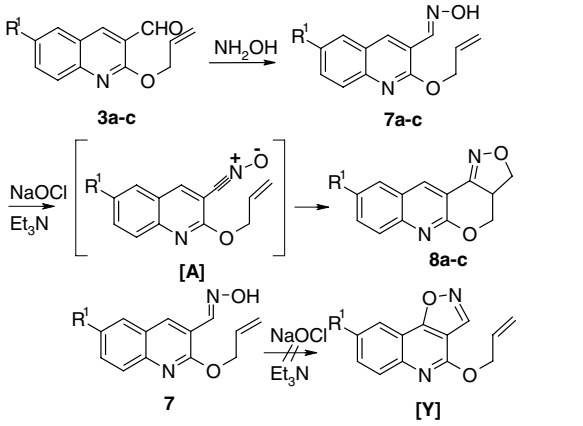
Scheme 1.

the presence of triethylamine afforded the nitrone **4a** as a white solid (mp 102 °C).[14] The structure of **4a** was ascertained from the spectroscopic data. The ^{1}H NMR spectra showed the presence of the *N*-Me protons of the nitrone at δ 3.96 as a singlet. The allylic protons appeared at δ 6.21 (m, 1H), 5.29 (dd, 2H), 5.47 (d, 2H). On refluxing **4a** in toluene at 110 °C, two isomers, **5a** (cis) and 6a (trans) of tetrahydroisoxazolo[3′4′:4,5]pyrano[2,3-*b*]quinolines were obtained in 70% and 7% yields, respectively. The structures of **5a** and **6a** were determined from spectroscopic data and elemental analysis.[15] The stereochemistries were determined from the coupling constant of the H-6b and H-9a protons (for the cis isomer $J = 3.0$ Hz and for the trans isomer $J = 9.0$ Hz). The chemical shifts of the *N*-Me protons at δ 2.90 and δ 2.85, respectively, as singlets further confirmed the involvement of the nitrone in the cycloaddition process. Both stereoisomers **5a** and **6a** exhibited strong molecular ion peaks $(M+H)^+$ at 243 (using positive ionization technique). Similarly, tetrahydroisoxazolo[3′,4′:4,5]pyrano[2,3-*b*]quinoline derivatives **5a–e** and **6a–e** were synthesized by *N*-methyl- and *N*-phenylhydroxylamine with compound **4** (Table 1). It is noteworthy that although the nitrones form easily, the cycloaddition required forcing conditions (110 °C, refluxing toluene). The reaction is totally regioselective and there was no evidence of the formation of any 1,5-electrocyclized product **[X]**.

In order to prepare the dihydroisoxazolo[3′,4′:4,5]pyrano[2,3-*b*]quinolines, we first prepared oximes **7** from **3** by treatment with hydroxylamine hydrochloride in the presence of aqueous sodium hydroxide (Scheme 2).[16] The oximes on treatment with NaOCl in the presence of Et_3N at 0–20 °C afforded the desired dihydroisoxazolo[3′,4′:4,5]pyrano[2,3-*b*]quinolines **8** in excellent yields via the formation of the nitrile oxides **[A]**.[17] The structures of **8a–c** were determined from spectroscopic

Table 1. Synthesis of novel pyrano[2,3-*b*]quinoline derivatives **5**, **6**, **8** and **11** via intramolecular 1,3-dipolar cycloaddition

Entry	Product	R^1	R^2	Mp (°C)	Yield (%)
1	**5a**	H	CH_3	153	75
2	**6a**	H	CH_3	109	7
3	**5b**	H	C_6H_5	167	67
4	**6b**	H	C_6H_5	162	5
5	**5c**	CH_3	CH_3	142	73
6	**6c**	CH_3	CH_3	104	76
7	**5d**	CH_3	C_6H_5	139	75
8	**6d**	CH_3	C_6H_5	127	6
9	**5e**	OCH_3	CH_3	149	78
10	**6e**	OCH_3	CH_3	106	7
11	**8a**	H	—	203	87
12	**8b**	CH_3	—	216	85
13	**8c**	OCH_3	—	224	78
14	**11a**	H	—	232	85
15	**11b**	CH_3	—	214	83
16	**11c**	OCH_3	—	197	80

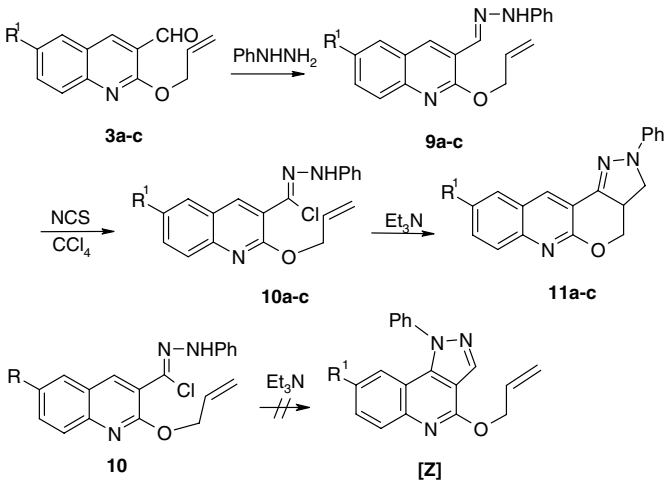


Scheme 2.

data and elemental analysis (Table 1). The 1,5-electrocyclization product **[Y]** was not formed.

For the preparation of pyrazolo[3′,4′:4,5]pyrano[2,3-*b*]quinolines, we first synthesized hydrazone **9a** via reaction of aldehyde **3a** with phenylhydrazine (Scheme 3).[18] Chlorination of **9a** with *N*-chlorosuccinimide in carbon tetrachloride at 50 °C afforded chloride **10a** in very good yield.[19] This intermediate could not be purified due to decomposition. Hence, the nitrile imine was generated in situ from the reaction of **10a** with triethylamine at 80 °C which underwent intramolecular cyclization to give exclusively, the desired dihydropyrazolo-[3′,4′:4,5]-pyrano[2,3-*b*]quinoline **11a** without the formation of any of the 1,5-electrocyclization product **[Z]**.[20] The structure of **11a** was ascertained from the spectroscopic data and elemental analysis. Similarly, compounds **11b–c** were synthesized and characterized (Table 1). Unlike the nitrones, the nitrile oxides and nitrile imines were found to be highly reactive and gave the desired compounds in high yields.

In conclusion, we have reported the synthesis of several novel tetrahydroisoxazolo-, dihydroisoxazolo- and dihydropyrazolo-fused pyrano[2,3-*b*]quinolines from



Scheme 3.

simple acetanilides via intramolecular 1,3-dipolar cycloaddition reactions involving nitrones, nitrile oxides and nitrile imines as 1,3-dipoles, in a regioselective manner. The present intramolecular 1,3-dipolar cycloaddition reaction strategy, which is the first example in quinoline chemistry can be further explored for the synthesis of various heterocycle-fused quinoline derivatives.

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12. $POCl_3$ (9 ml, 98.28 mmol) was added dropwise to DMF (2.7 ml, 34.65 mmol) whilst maintaining the temperature at 0–5 °C. The mixture was allowed to stir for about 5 min. Acetanilide **1a** (10.37 mmol) was then added and the resulting solution heated for 8 h at 75–80 °C. The reaction mixture was cooled to room temperature and then poured into crushed ice with stirring. A pale yellow precipitate appeared immediately and was filtered and washed with water and then dried. The crude compound was recrystallized from ethyl acetate. Aldehydes **2b** (74%) and **2c** (67%) were prepared similarly.

13. To a solution of 2-chloro-3-formyl quinoline **2a** (8 mmol) in dichloromethane (10 ml) were added allyl alcohol (0.4 ml, 10 mmol) and a catalytic amount of tetrabutylammonium bromide. To this was added, 10 ml of 50% aqueous KOH solution and the mixture was allowed to stir for 8 h. The organic layer was separated and washed 2–3 times with water. The solvent was evaporated and the crude product was purified by column chromatography using 5% ethyl acetate in hexane as eluent. Compound **3a**, yield 78%, mp 56 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.30 (dd, $J = 9.7$, 6.8 Hz, 2H), 5.40 (d, $J = 6.00$ Hz, 2H), 6.29 (m, 1H), 6.95–7.80 (m, 4H), 8.20 (s, 1H), 9.80 (s, 1H). Compound **3b** (75%) and **3c** (70%) were prepared as above.
14. To a solution of 2-allyloxy 3-formylquinoline **3a** (2 mmol) in 5 ml toluene was added MeNHOH·HCl (2 mmol), and the reaction stirred at room temperature. $NaHCO_3$ (168 mg, 2 mmol) was added portionwise over a period of 5 min ($NaHCO_3$ was not required in the case of PhNHOH) and stirring was continued for 2 h. The solvent was removed under reduced pressure and the product **4a** was purified by preparative TLC using $CHCl_3$ as eluent. Compound **4a**, yield 90%, mp 102 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.96 (s, 3H), 5.29 (dd, $J = 9.8$, 6.2 Hz, 2H), 5.47 (d, $J = 6.0$ Hz, 2H), 6.21 (m, 1H), 7.20–7.90 (m, 4H), 8.34 (s, 1H), 8.60 (s, 1H).
15. Compound **4a** (1 mmol) was refluxed in toluene (5 ml) for 10 h. The solvent was removed under reduced pressure. The residue was purified by preparative TLC using ethyl acetate/hexane (4:6) as eluent to give **5a** and **6a**. Compound **5a**: yield 75%, mp 153–154 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.90 (s, 3H), 3.22 (m, 1H), 4.30 (m, 2H), 4.43 (m, 2H), 3.86 (d, $J = 3.0$ Hz, 1H), 7.20–7.90 (m, 4H), 8.10 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 152.96 (C-1a), 149.1 (C-11a), 147.89 (C-5a), 130.45 (C-6a), 127.36 (C-6), 127.22 (C-3), 123.92 (C-2), 123.84 (C-4), 112.51 (C-5), 66.8 (C-10), 65.5 (C-9), 30.5 (*N*-CH_3), 29.5 (C-9a), 28.3 (C-6b). *m*/*z* $[M+H]^+$ 243. CHN analysis (calcd%) C, 69.43; H, 5.78; N, 11.57; $C_{14}H_{14}N_2O_2$ (found%) C, 69.40; H, 5.72; N, 11.52. Compound **6a**: yield 7%, mp 109 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.85 (s, 3H), 3.22 (m, 1H), 4.30 (m, 2H), 4.45 (m, 2H), 3.90 (d, $J = 9.0$ Hz, 1H), 7.2–8.0 (m, 4H), 8.15 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 152.80 (C-1a), 149.01 (C-11a), 147.00 (C-5a), 131.15 (C-6a), 126.86 (C-6), 126.20 (C-3), 124.00 (C-2), 123.70 (C-4), 113.00 (C-5), 67.5 (C-10), 65.5 (C-9), 31.0 (*N*-CH_3), 29.5 (C-9a), 28.3 (C-6b). *m*/*z* $[M+H]^+$ 243. CHN analysis (calcd%) C, 69.43; H, 5.78; N, 11.57; $C_{14}H_{14}N_2O_2$ (found%) C, 69.50; H, 5.91; N, 11.48.
16. Compound **3a** (2 mmol) in 6 ml of EtOH/H_2O mixture (1:1) was reacted with an aqueous solution of hydroxylamine prepared by adding NaOH (175 mg in 4 ml H_2O) to a solution of NH_2OH·HCl (166.7 mg, 2 mmol in 3 ml water), with stirring at room temperature. After 10 min, the solution was clear. The reaction mixture was allowed to stir at room temperature for 1 h after which the EtOH was evaporated and the compound was separated by extraction with dichloromethane. The organic extract was dried over anhydrous sodium sulfate and then evaporated under reduced pressure to obtain **7a**. Yield 98%, mp 156–158 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.12 (dd, $J = 9.6$, 5.8 Hz, 2H), 5.46 (d, $J = 6.4$ Hz, 2H), 6.10 (m, 1H), 7.20–7.60 (m, 4H), 8.15 (s, 1H), 8.46 (s, 1H). Compounds **7b** (94%) and **7c** (88%) were prepared similarly.
17. To a mixture of oxime **7a** (2 mmol) and Et_3N (202 mg, 2 mmol) in dichloromethane (8 ml), 10% aqueous NaOCl solution (3.5 ml) was added dropwise at −10 °C. The reaction mixture was allowed to stir for 1 h at room temperature. The organic phase was separated and the solvent was removed under reduced pressure. Product **8a** was purified by preparative TLC using dichloromethane and hexane (7:3) as eluent. Yield 87%, mp 203 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.07 (m, 2H), 4.35 (m, 1H), 4.86 (m, 2H), 7.20–7.75 (m, 4H), 7.95 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 152.2 (C-11a), 153.96 (C-1a), 147.80 (C-5a), 132.10 (C-6b), 130.55 (C-6a), 127.00 (C-6), 126.15 (C-3), 124.20 (C-2), 123.95 (C-4), 112.00 (C-5), 66.85 (C-10), 65.50 (C-9), 30.5 (C-9a). *m*/*z* $[M+H]^+$ 227. CHN analysis (calcd%) C, 69.02; H, 4.43; N, 12.39; $C_{13}H_{10}N_2O_2$ (found%) C, 68.98; H, 4.38; N, 12.34. Compounds **8b–c** were prepared similarly.
18. Compound **3a** (2 mmol) and phenylhydrazine (2.5 mmol) in 15 ml of ethanol were reacted at room temperature for half an hour and then warmed for 10 min. The reaction mixture was filtered hot. The solution was evaporated and the solid compound obtained was recrystallized from ethanol. Compound **9a**, yield 87%, mp 161–162 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.05 (dd, $J = 9.8$, 6.7 Hz, 2H), 5.32 (d, $J = 6.2$ Hz, 2H), 5.95 (m, 1H), 6.90–7.40 (m, 9H), 8.00 (s, 1H), 8.32 (s, 1H). Compounds **9b** (82%) and **9c** (77%) were prepared similarly.
19. To a suspension of phenylhydrazone **9a** (2 mmol) in carbon tetrachloride (10 ml) was added a solution of *N*-chlorosuccinimide (2.5 mmol) in 10 ml of carbon tetrachloride. The reaction mixture was heated at 50 °C for 1 h, then cooled and filtered. The filtrate was concentrated in vacuo to afford the hydrazonyl chloride **10a**. Chlorides **10b–c** were prepared in a similar way and used in the next step without further purification.
20. A mixture of compound **10a** (2 mmol) and triethylamine (2 mmol) was refluxed in toluene (15 ml) for 2 h. The solvent was removed under reduced pressure and the residue was purified by preparative TLC using chloroform and hexane (1:2) as eluent to give **11a**, yield 85%, mp 189 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.12 (m, 1H), 4.21 (m, 2H), 4.69 (m, 2H), 6.95–7.72 (m, 9H), 7.82 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 154.05 (C-1a), 151.25 (C-11a), 148.00 (C-5a), 128.20 (C-6b), 129.55 (C-6a), 127.00 (C-6), 126.85, 126.20, 125.10, 124.30, 123.53 (two C), 122.19 (two C), 121.00 [all Ar], 67.25 (C-10), 65.00 (C-9), 31.15 (C-9a). *m*/*z* $[M+H]^+$ 302. CHN analysis (calcd%) C, 75.75; H, 4.98; N, 13.95; $C_{19}H_{15}N_3O$ (found%) C, 75.65; H, 4.94; N, 13.90. Compounds **11b–c** were synthesized similarly.