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.

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, geibalansine, 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 products6 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

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 interest10 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 (R1 = H) on treatment with the Wilsmeier reagent (DMF + POC13) 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

Figure 1.
the presence of triethylamine afforded the nitrone 4a as a white solid (mp 102 °C). 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 \(\delta 3.96\) as a singlet. The allylic protons appeared at \(\delta 6.21\) (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′: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. 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 \(\delta 2.90\) and \(\delta 2.85\), 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′:5]pyrano[2,3-b]quinoline derivatives 5a–e and 6a–e were synthesized by \(N\)-methyl- and \(N\)-phenyl-hydroxylamine with compound 4 (Table 1). It is noteworthy that although the nitrone 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′: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). The oximes on treatment with NaOCl in the presence of Et\(_3\)N at 0–20 °C afforded the desired dihydroisoxazolo[3′,4′:5]pyrano[2,3-b]quinolines 8 in excellent yields via the formation of the nitrile oxides [A]. The structures of 8a–c were determined from spectroscopic data and elemental analysis (Table 1). The 1,5-electrocyclization product [Y] was not formed.

For the preparation of pyrazolo[3′,4′:5]pyrano[2,3-b]-quinolines, we first synthesized hydrozone 9a via reaction of aldehyde 3a with phenylhydrazine (Scheme 3). Chlorination of 9a with \(N\)-chlorosuccinimide in carbon tetrachloride at 50 °C afforded chlorine 10a in very good yield. 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′:5]pyrano[2,3-b]quinoline 11a without the formation of any of the 1,5-electrocyclization product [Z]. 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 nitrone, 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...
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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References and notes


12. POCl3 (9 ml, 98.28 mmol) was added dropwise to DMF (2.7 ml, 34.65 mmol) whilst maintaining the temperature at about 0–5 °C. The mixture was allowed to stir for about 3–5 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 2e (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. 1H NMR (300 MHz, CDCl3) 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 4a (2 mmol) in 5 ml toluene was added MeNH2HCl (168 mg, 2 mmol) and the reaction stirred at room temperature. NaHCO3 (8 mmol) was added portionwise over a period of 5 min (NaHCO3 was not required in the case of PhNH2OH) and stirring was continued for 2 h. The solvent was removed under reduced pressure and the product 4a was purified by preparative TLC using CHCl3 as eluent. Compound 4a, yield 90%, mp 102°C. 1H NMR (300 MHz, CDCl3) δ 3.96 (s, 3H), 5.29 (dd, J = 9.8, 6.7 Hz, 2H), 4.30 (m, 2H), 4.43 (m, 2H), 3.86 (d, J = 3.0 Hz, 1H), 7.20–7.90 (m, 4H), 8.34 (m, 2H), 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 purifed by preparative TLC using ethyl acetate/hexane (4:6) as eluent to give 5a and 6a. Compound 5a: yield 75%, mp 153–154°C. 1H NMR (300 MHz, CDCl3): δ 2.90 (s, 3H), 3.22 (m, 1H), 4.30 (m, 2H), 4.43 (m, 2H), 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). 13C NMR (75 MHz, CDCl3): 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), 66.85 (C-10), 65.50 (C-9), 30.5 (C-9a). Compounds 10a and 11a were prepared similarly.

16. Compound 3a (2 mmol) in 6 ml of EtOH/H2O mixture (1:1) was reacted with an aqueous solution of hydroxylamine prepared by adding NaOH (175 mg in 4 ml H2O) to a solution of NH2OH.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. 1H NMR (300 MHz, CDCl3): 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 Et3N (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. 1H NMR (300 MHz, CDCl3): δ 4.07 (m, 2H), 4.35 (m, 1H), 4.86 (m, 2H), 7.20–7.75 (m, 4H), 7.95 (s, 1H). 13C NMR (75 MHz, CDCl3): 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+]243. CHN analysis (calcd%) C, 69.02; H, 4.43; N, 12.39; C13H10N2O2 (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. 1H NMR (300 MHz, CDCl3): 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 phenylhydrazine 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. 1H NMR (300 MHz, CDCl3): δ 4.12 (m, 1H), 4.21 (m, 2H), 4.69 (m, 2H), 6.95–7.72 (m, 9H), 7.82 (s, 1H). 13C NMR (75 MHz, CDCl3): 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), 66.05 (C-9), 31.15 (C-9a), m/z [M+H+]302. CHN analysis (calcd%) C, 75.75; H, 4.98; N, 13.95; C14H12N3O2 (found%) C, 75.65; H, 4.94; N, 13.90. Compounds 11b–c were synthesized similarly.