Synthesis of 12-ethoxy-3-oxo-4-phenylquino[3,2-c][1,3]diazocines via Vilsmeier-Haack reaction

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Application of Vilsmeier condition on 4-hydroxyquinaldines give potentially useful intermediates 4-chloro-3-formyl-2-(2-hydroxyethene-1-yl)quinolines, which are utilized to prepare quino[3,2-c][1,3]diazocine on treatment with N-phenyluracil.

In recent past there has been a widespread interest on the application of Vilsmeier reagent in organic syntheses. Earlier reports reveal the reagent to be a mild and efficient formylating agent for reactive aromatic and heteroaromatic substrates. The versatility of the reaction has been further extended as an activating agent for acylhalo addition and ring annihilation. Moreover, a wide variety of alkene derivatives, carbonyl compounds, activated methyl and methylene groups as well as oxygen and nitrogen nucleophiles efficiently react with Vilsmeier-Haack reagent to yield the corresponding iminium salts. The intramolecular cyclization potential of halomethyleniminium salts formed under Vilsmeier condition and microwave induced Vilsmeier conditions have been reported. The classical Vilsmeier-Haack reaction involves electrophilic substitution of an activated aromatic ring with a halomethyleniminium salt to yield the corresponding iminium species, which facilitates easy entry into large number of novel heterocyclic systems.

The capability of the reagent to generate a broad spectrum of iminium species has been explored further for the construction of [c]annelated nitrogen and oxygen heterocycles via 4-chloro-3-formylquinoidalines obtainable from 4-hydroxyquinaldines by Vilsmeier-Haack reaction.

Results and discussion

It was presumed that the Vilsmeier-Haack reaction on 4-hydroxyquinaldines (1) (previously prepared from corresponding aniline and ethyl acetoacetate followed by subsequent cyclization of the β-anilinocrotonates) could provide a utility intermediate for the preparation of several substituted [c]annelated heterocyclic compounds. The reaction was carried out at 100° for 15–20 h, using the Vilsmeier-Haack reagent derived from phosphorus oxychloride-dimethylformamide in situ. The reaction yielded a mixture of products, which were separated by using silica gel column chromatography. The analytical and spectroscopic data confirmed the products as 4-chloro-3-formyl-2-(2-hydroxyethene-1-yl)quinoline (2), 4-hydroxy-3-formylquinoline (3) and 4-chloroquinoline (4) in good yields (Scheme 1).

![Scheme 1](image-url)

The reaction of Vilsmeier reagent on 4-hydroxyquinaldines (1) at 100° resulted in the formation of 4-chloro-3-formyl-2-(2-hydroxyethene-1-yl)quinolines (2a–e), which could be further utilized for the construction of a novel nitrogen heterocyclic ring system.

The Vilsmeier-Haack reagents are usually applied for the formylation of aromatic and heteroaromatic compounds. These are the chloromethyleniminium species responsible for the formylation (Scheme 2). As in our reaction, the chloromethyleniminium species obtained in situ...
from phosphorus oxychloride-dimethylformamide react with the active methyl group of 4-hydroxyquinaldine (1) to yield 6. Another formylation occurs at the aromatic C of the quinaldine leading to the iminium compound 8. Since these iminium salts have the special ability to replace the hydroxyl group at aromatic C by the nucleophiles like chlorine, bromine etc., they have led to the formation of 4-chloroquinaldine (4) in minor yields and also to the replacement of hydroxy group by the chloro group forming 4-quinolines. The vinyl derivative was treated with N-phenylurea in alcoholic potassium hydroxide solution and refluxed for two hours. After the solvent was removed under reduced pressure, the residue was poured onto crushed ice and extracted with ethyl acetate. The silica gel column chromatography of the extract afforded the desired compounds 12a-e using petroleum ether-ethyl acetate as the eluents (Scheme 3).

The reaction proceeded via the corresponding N-phenylhydrazone. Subsequent cyclization yielded the diazocine. The yields, reaction time and the temperature at which the reaction was carried out are shown in Table 1.

**Table 1. Vilsmeier-Haack reaction on 4-hydroxyquinaldines (1a-e) and synthesis of quino[3,2-c][1,3]diazocines (12a-e)**

| Compd no | Reaction time (h) | Yields (%) |
|----------|-------------------|------------|
|          | 2     | 3     | 4     | 12    |
| 1a       | 15    | 70    | 15    | 10    | –     |
| 1b       | 12.5  | 73.5  | 18    | 5     | –     |
| 1c       | 16    | 55    | 12    | 17    | –     |
| 1d       | 17.5  | 78    | 12    | 5     | –     |
| 1e       | 20    | 65    | 10    | 15    | –     |
| 2a       | 1.5   | –     | –     | –     | 68    |
| 2b       | 2     | –     | –     | –     | 72    |
| 2c       | 2.5   | –     | –     | –     | 65    |
| 2d       | 2     | –     | –     | –     | 55    |
| 2e       | 3     | –     | –     | –     | 75    |

**Experimental**

Thin layer chromatography was used to monitor the reactions and the purity of products. M.ps. were determined on a Boetius Microheating table (Japan) and are uncorrected. IR spectra (KBr) were recorded on a Shimadzu 8201 FT spectrophotometer. $^1$H and $^{13}$C NMR spectra (CDCl$_3$) on a Bruker AMX-400 MHz spectrometer with TMS as internal standard and mass spectra on a Jeol D-300 spectrometer (70 eV). C, H, N analyses were carried out on a Perkin-Elmer 240 analyser.

**General procedure**

**Vilsmeier-Haack reaction on 4-hydroxyquinaldine** The Vilsmeier reagent was prepared by taking N,N-dimethylformamide (3.86 ml, 0.05 mol) at 0–5°. Phosphorus oxychloride (13.04 ml, 0.014 mol) was added to it dropwise over a period of 30 min with constant stirring and the resultant mixture was stirred for another 1 h. The appropriate 4-hydroxyquinaldine (1a-e) was added to the Vilsmeier reagent. The mixture was stirred for 30 min at RT and was then kept on a water-bath at 100° for the period of time stated in Table 1. After the reaction was over (monitored through TLC), the reaction mixture was poured onto crushed ice (500 g) with constant stirring and set aside.
overnight. The precipitate obtained on neutralization with 4 N NaOH was washed with water and extracted using ethyl acetate. The silica gel chromatography of ethyl acetate soluble product afforded three compounds 4, 3 and 2 using petroleum ether. Petroleum ether-ethyl acetate (94: 6) and petroleum ether-ethyl acetate (85: 15), respectively. The products were recrystallized with methanol and were identified by the analytical and spectroscopic data.

12-Ethoxy-3-oxo-4-phenylquinone[3,2-c][1,3]diazocines: To an alcoholic solution of KOH (15%; 50 ml), N-phenylurea (0.002 mol) and appropriate 4-chloro-3-formyl-2-(2-hydroxyethene-1-yl)quinoline (0.002 mol) were added and the mixture was refluxed on a steam bath for 2 h. The excess ethanol was then removed under reduced pressure, cooled and poured onto crushed ice. Precipitate obtained was extracted with ethyl acetate and the silica gel column chromatography of the extract yielded the desired products:

2a m.p. 155°. C12H12O2NCI (Found : C, 61.62; H, 3.38; N, 5.92. calcd. for : C, 61.69; H, 3.45; N, 5.99%); δH 7.7 (1H, d, J 8.1 Hz, C5-H), 7.6 (1H, t, J 8.3 Hz, C7-H), 7.9 (1H, t, J 7.3 Hz, C6-H), 8.2 (1H, d, J 8.3 Hz, C5-H) 9.2 (1H, s, C4-CHO), 9.4, 9.6 (2H, s, vinylic protons), 16.5 (vinylic-OH, bs, D2O exchangeable); δC 140.7, 189.33, 189.08, 146.24, 137.50, 135.50, 133.32, 126.93, 125.21, 122.61, 119.32, 118.99; m/z (M+) 233, (M+2) 235; νmax 3438, 1664, 1595 cm⁻¹. 3a m.p. 140°. C11H10O2N (Found : C, 70.54; H, 4.81; N, 7.43. calcd. for : C, 70.58; H, 4.85; N, 7.48%); δH 2.4 (3H, s, CH3), 7.3 (1H, d, J 7.8 Hz, C5-H), 7.5 (1H, t, J 7.5 Hz, C5-H), 7.7 (1H, t, J 7.6 Hz, C6-H), 8.2 (1H, d, J 8.28 Hz, C5-H), 9.4 (1H, s, CHO), 14.1 (1H, bs, OH); m/z (M+) 187; νmax 3520, 1695, 1610 cm⁻¹. 4a m.p. 65°. δH 2.5 (3H, s, CH3), 7.3 (1H, s, C1-H), 8.1 (1H, d, J 8.2 Hz, C5-H), 7.7 (1H, t, J 7.54 Hz, C6-H), 7.9 (1H, t, J 7.82 Hz, C7-H), 7.5 (1H, d, J 8.14 Hz, C8-H); νmax 1590 cm⁻¹. 2b m.p. 214°. C12H11N2O2 (Found : C, 73.32; H, 4.82; N, 12.31. calcd. for : C, 73.45; H, 4.99; N, 12.24%); δH 1.35 (3H, t, J 7.24 Hz, OCH2CH3), 4.2 (2H, q, J 7.10 Hz, OCH2CH3), 6.8-8.2 (11H, m, Ar-H), 9.1 (1H, s, C1-H); m/z (M+) 343; νmax 1550, 1585, 1620 cm⁻¹.

2d m.p. 180°. C12H10O2NCl (Found : C, 53.71; H, 2.65; N, 5.22. calcd. for : C, 53.76; H, 2.63; N, 5.26%); δH 7.3 (1H, d, J 7.68 Hz, C7-H), 7.5 (1H, d, J 7.96 Hz, C6-H), 8.1 (1H, s, C3-H), 9.2 (1H, s, C1-CHO), 9.3, 9.5 (2H, s, vinylic protons), 16.5 (vinylic-OH, bs, D2O exchangeable); δC 192.27, 189.26, 189.08, 133.90, 133.21, 129.80, 129.04, 124.41, 121.13, 120.86. 118.87, 118.34; m/z (M+) 267, (M+2) 269, (M+4) 271; νmax 3470, 1670, 1590 cm⁻¹. 3d m.p. 230°. C12H10O2NCI (Found : C, 59.52; H, 3.57; N, 6.27. calcd. for : C, 59.61; H, 3.64; N, 6.32%); δH 2.5 (3H, s, CH3), 7.4 (1H, d, J 8.76 Hz, C7-H), 7.7 (1H, d, J 7.64 Hz, C6-H), 8.2 (1H, s, C5-H), 9.4 (1H, s, CHO), 14.2 (1H, s, CH2); m/z (M+) 271; νmax 3480, 1715, 1595 cm⁻¹. 4d m.p. 74°. δH 2.4 (3H, s, CH3), 7.4 (1H, s, C1-H), 7.7-8.0 (3H, m, Ar-H); νmax 1575 cm⁻¹. 2d m.p. 180°. C21H16N4O2Cl
Note

(Found : C, 66.71; H, 4.18; N, 11.23. calcd. for : C, 66.76; H, 4.27; N, 11.23%. calcd. for : C, 64.25; H, 4.62; N, 5.35%).

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References

1. O. Meth-Cohn and A. B. Narine, Tetrahedron Lett., 1978, 23, 2045; A. K. Khan and A. Shoeb, Indian J. Chem., Sect. B, 1985, 24, 62; H. L. Bell, M. McGuire and G. A. Freeman, J. Heterocyclic Chem., 1983, 20, 41.

2. T. Fujisawa, S. Iida and T. Sato, Chem. Lett., (B), 1984, 27, 1173.

3. M. Venugopal and P. T. Perumal, Synth. Commun., 1991, 21, 515; D. R. Adams, J. N. Dominguez and J. A. Perez, Tetrahedron Lett., 1983, 24, 517; M. S. C. Rao and G. S. K. Rao, Indian J. Chem., Sect. B, 1998, 27, 213.

4. S. Selvi and P. T. Perumal, Indian J. Chem., Sect. B, 2000, 39, 163.

5. K. Dinakaran and P. T. Perumal, Indian J. Chem., Sect. B, 2000, 39, 135.

6. M. P. Reddy and G. S. K. Rao, J. Org. Chem., 1981, 46, 5371.

7. R. A. Katritzky, M. Charles and M. Marson, J. Am. Chem. Soc., 1983, 105, 3279.

8. S. B. Barnela and S. Seshadri, Indian J. Chem., Sect. B, 1986, 25, 709; A. Horvath, I. Herneicz, B. Podanyi and Z. Meszaros, J. Heterocyclic Chem., 1985, 22, 593; A. Nohara, T. Umetani and A. Sanno, Tetrahedron, 1974, 30, 3553; R. S. Ram Singh and M. R. Singh, Indian J. Chem., Sect. B, 2000, 39, 688; M. M. A. Tassene, K. C. Rajanna and K. S. Prakash, Synlett, 2001, 2, 251; J. Vattoly, V. J. Majo and P. T. Perumal, J. Org. Chem., 1998, 63, 7136; S. Akila, V. J. Majo and K. Balasubramanian, Indian J. Chem., Sect. B, 2002, 41, 647.

9. S. T. Selvi and P. S. Mohan, Z. Naturforsch., Teil B, 1999, 54, 1337.

10. R. N. Kumar, T. Suresh and P. S. Mohan, Spec. Lett., 2002, 35, 741; R. N. Kumar, T. Suresh and P. S. Mohan, Acta Pharm., 2003, 53, 1.