Tetrahedron Letters 50 (2009) 5474–5478

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Synthesis of highly functionalized oxazines by Vilsmeier cyclization of amidoalkyl naphthols

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ARTICLE INFO

Article history:
Received 23 May 2009
Revised 7 July 2009
Accepted 10 July 2009
Available online 15 July 2009

ABSTRACT

The intramolecular cyclization of amidoalkyl naphthols by Vilsmeier reagent produced 1,3-oxazines. The Vilsmeier reagent (chloromethylenedimethylammonium chloride) has been used as an efficient and cheap acid activator for the one-step synthesis of oxazine derivatives. A mechanism involving sequential haloformylation and intramolecular nucleophilic cyclization is proposed.

The synthesis of 1,3-oxazines has attracted attention in the past because of their potential as antibiotics,[1a–d] antitumor agents,[1e–g] analgesics,[1h,i] and anticonvulsants.[1j] 1,3-Oxazines have generated great interest as *anti*-psychotic agents and as possible effectors for serotonin and dopamine receptors.[2] In addition, benzo-1,3-oxazines are known to be biologically active as *anti*-malarial,[3a] *anti*-anginal ,[3b] *anti*-hypertensive [3c] and potent *anti*-rheumatic agents.[3d] Several methods for the preparations of 1,3-oxazine derivatives have previously been reported.[4] The ring-chain tautomeric interconversion of N-unsubstituted 1,3-*N*-*O*-heterocycles and the corresponding hydroxyalkylimines can often be exploited advantageously in different areas of organic synthesis and also in physical, medicinal and peptide chemistry.[5] Hence, the synthesis of these derivatives is of considerable interest.

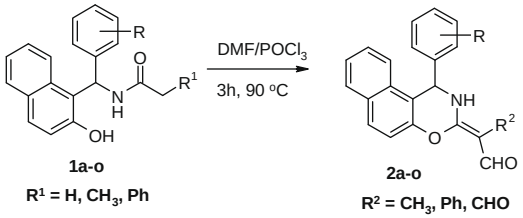
The Vilsmeier–Haack reagent is an efficient, economical and mild reagent for the formylation of reactive aromatic and heteroaromatic substrates.[6] It is now used as a powerful synthetic tool for the construction of many heterocyclic compounds.[7] The classical Vilsmeier–Haack reaction, however, involves electrophilic substitution of an activated aromatic ring with a halomethyleniminium salt to yield the corresponding iminium species, which facilitates easy entry into various nitrogen- and oxygen-based heterocycles.[8,7a,d] Vilsmeier reagent serves not only as a formylating agent,[9] but also as an activating reagent for carboxylic acids to give esters,[10] amides[11] and acid chlorides,[12] and for alcohols to give alkyl chlorides,[13] esters,[14] alkyl aryl sulfides[15] and imides.[16]

In our previous work, we have demonstrated the utility of the Vilsmeier reagent in the synthesis of functionalized heterocycles.[17,6c] In connection with our interest in the synthesis of highly valuable heterocycles,[18] herein we report a convenient and efficient synthesis of highly functionalized oxazines via the Vilsmeier–Haack reactions of amidoalkyl naphthols. To the best of our knowledge, the highly functionalized system (**2**) is unknown in the literature, which provided the impetus to synthesize these novel compounds.

Initially, we synthesized amidoalkyl naphthols based on reported procedure.[19] The synthesized amidoalkyl naphthols were treated with Vilsmeier reagent to give oxazine derivatives.

To begin our study, compound **1b** was treated with Vilsmeier reagent (DMF 12 equiv, $POCl_3$ 8 equiv)[20] at room temperature. The resulting mixture quickly became a viscous liquid, but no product was detected by TLC. When the resulting mixture was heated at 90 °C for about 3 h the reaction proceeded smoothly and the product was formed as indicated by TLC. After complete consumption of the starting materials, the mixture was poured into ice and neutralized with sodium acetate. The crude compound was extracted with chloroform and washed with water. The organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The crude product was purified by column chromatography (Scheme 1, Table 1, entry 2).

The structures of compounds **2a–i** were confirmed by IR, ^1H and ^{13}C NMR spectroscopy, mass spectrometry and elemental analysis. The mass spectrum of **2b** displayed the molecular ion (M+1) peak



1a-o

R^1 = H, CH_3, Ph

2a-o

R^2 = CH_3, Ph, CHO

Scheme 1.

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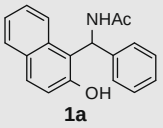
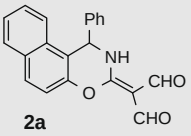
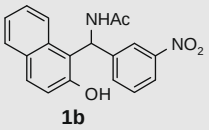
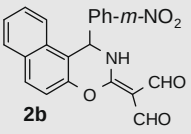
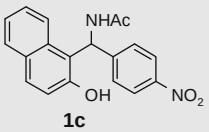
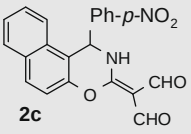
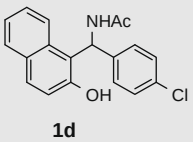
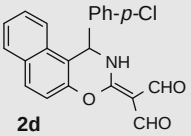
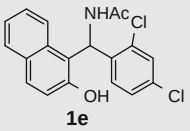
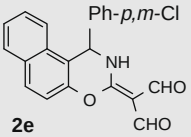
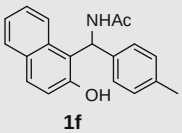
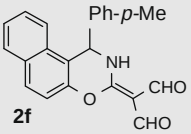
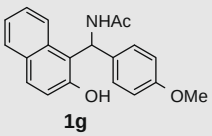
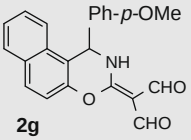
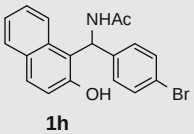
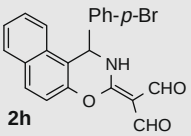
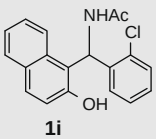
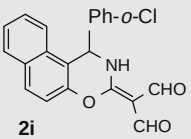
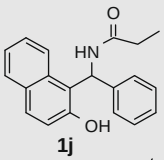
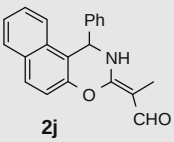
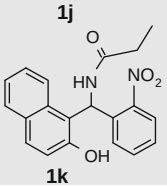
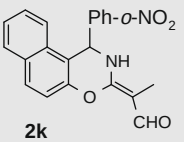
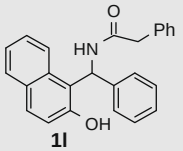
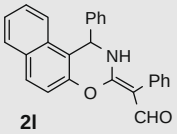
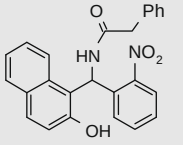
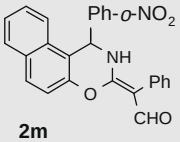
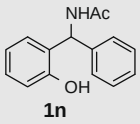
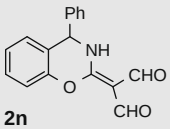
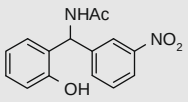
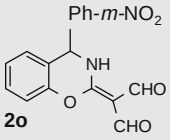
doi:10.1016/j.tetlet.2009.07.051

Table 1
Synthesis of oxazine derivatives using Vilsmeier reagent

Entry	Amidoalkyl naphthols	Product[a] (2)	Time (h)	Yield[b] (%)
1	 **1a**	 **2a**	3	86
2	 **1b**	 **2b**	3	90
3	 **1c**	 **2c**	3	90
4	 **1d**	 **2d**	3	85
5	 **1e**	 **2e**	3	78
6	 **1f**	 **2f**	3	76
7	 **1g**	 **2g**	3	75
8	 **1h**	 **2h**	3	82
9	 **1i**	 **2i**	3	74
10	 **1j**	 **2j**	3	75
11	 **1k**	 **2k**	3	85

(*continued on next page*)

Table 1 (*continued*)

Entry	Amidoalkyl naphthols	Product[a] (2)	Time (h)	Yield[b] (%)
12	 **1l**	 **2l**	3	70
13	 **1m**	 **2m**	3	80
14	 **1n**	 **2n**	3	75
15	 **1o**	 **2o**	3	81

[a] All compounds were characterized by ^{1}H NMR, ^{13}C NMR, IR, mass spectrometry and elemental analysis.
[b] Isolated yield.

at *m/z* 375. The ^{1}H NMR spectrum of **2b** exhibited two singlets due to –CHO and –NH protons at δ 9.78 and δ 11.84 (D_2O exchangeable). Signals at δ 50.3 (benzylic carbon) and δ 186.7 (–C=O) in the ^{13}C NMR spectrum confirmed the formation of the product. Finally, the structure **2b** was confirmed by single-crystal X-ray diffraction data (Fig. 1).[21] To investigate the scope of this reaction, a series of oxazine derivatives were synthesized and characterized (Table 1, entries 1–9). All the prepared compounds gave good to excellent yields (75–90%).

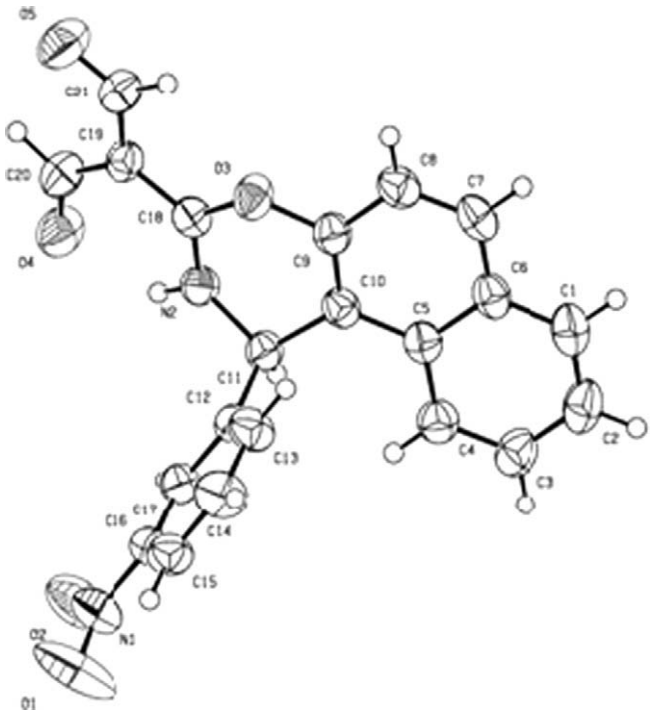
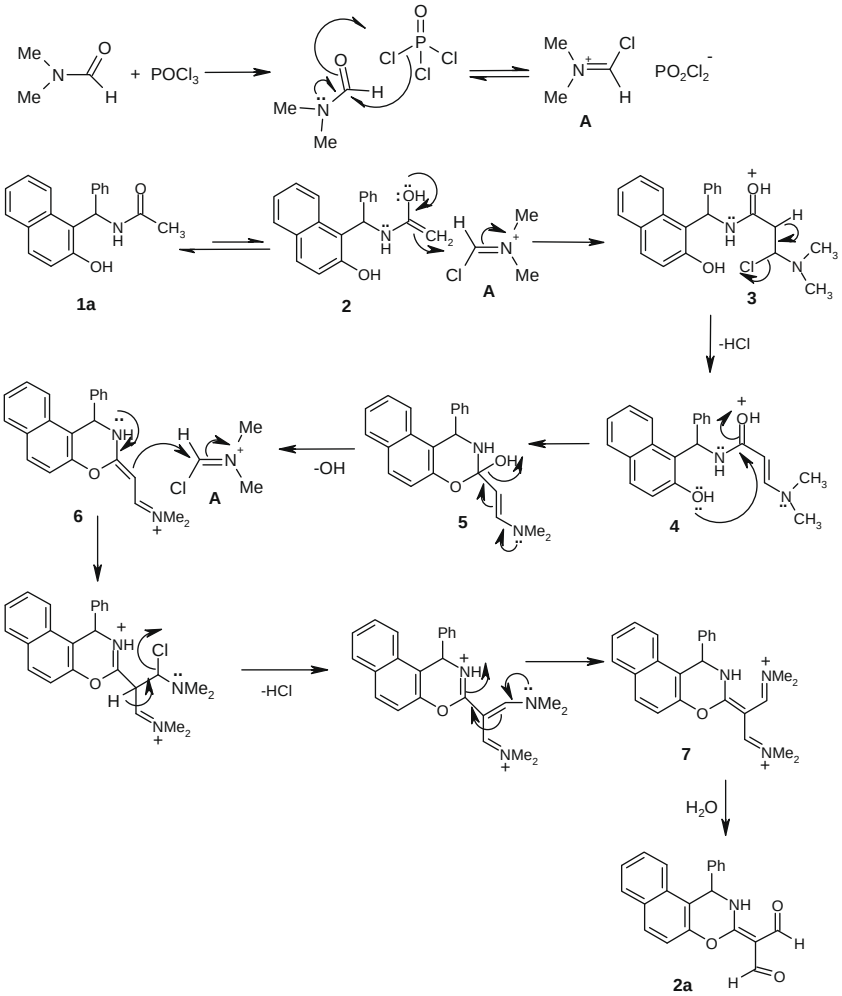


Figure 1. ORTEP diagram of compound **2b**.

To further investigate the scope and generality of this methodology, a variety of amidoalkyl naphthols **1j–m** and amidoalkyl phenols **1n–o** were employed (Table 1, **2j–o**). It was observed that under optimized reaction conditions,[20] various amidoalkyl naphthols and amidoalkyl phenols reacted with Vilsmeier reagent to afford a series of substituted oxazines in good yields. The reaction was amenable to a wide range of amidoalkyl naphthols and amidoalkyl phenols. The results are summarized in Table 1 (entries 10–15). The structures of compounds **2j–o** were confirmed by IR, ^{1}H and ^{13}C NMR spectroscopy, mass spectrometry and elemental analysis.

A plausible mechanism for the synthesis of substituted oxazines **2a** is presented in Scheme 2. The in situ formation of the chloromethyleniminium intermediate **A** (derived from $POCl_3$–DMF) is responsible for the formylation. The enolizable ketone moiety of amidoalkyl naphthol derivative **1a** readily reacts with chloromethylenedimethylammonium chloride intermediate at the active methylene position of **2** to yield the intermediate **3**, which undergoes dehydrochlorination to form intermediate **4**. The latter undergoes cyclization to intermediate **5,** which spontaneously undergoes dehydroxylation to form the intermediate **6**. Attack of another Vilsmeier intermediate to **6** leads to the formation of intermediate **7**. Hydrolysis of 7 gives the product **2a**.

In conclusion, we have reported the first example of the use of the Vilsmeier reagent for the synthesis of oxazine derivatives from amidoalkyl naphthols. The results shown above demonstrated the efficiency and synthetic interests of the cyclization reaction with respect to amidoalkyl naphthols **1** bearing various amide groups. Furthermore, the scope of this reaction was explored with different substrates and the reactivity of its heterocyclic products was investigated via further diversification.



Scheme 2. Mechanism for the formation of 1,3-oxazine derivatives by Vilsmeier cyclization of amidoalkyl naphthols.

Acknowledgements

One of the authors, M.D. thanks UGC and CSIR (New Delhi) for the award of Senior Research Fellowship. The authors are thankful to SAIF-IIT Madras for single-crystal X-ray diffraction analysis.

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20. *Representative procedure for the synthesis of [1-(3-nitrophenyl)-1,2-dihydro-3H-naphtho[1,2-e][1,3]oxazine-3-ylidine]-malonaldehyde* **2b** (Table 1, entry 2): To the solution containing acetamidonaphthol **1b** (10 mmol) dissolved in DMF (12 equiv), $POCl_3$ (8 eqiuv) was added slowly dropwise (15 min) at 0 °C and the reaction mixture was allowed to reach room temperature. Then the reaction mixture was stirred at 90 °C for 3 h. After completion of the reaction, it was allowed to cool to room temperature. The reaction mixture was poured into crushed ice and refrigerated overnight. The solution was neutralized with sodium acetate and the crude compound was extracted with chloroform (3 × 50 mL) and washed with water (3 × 25 mL). Organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The crude product was purified through column chromatography using ethyl acetate:pet. ether (1:1) as eluent. Colourless solid. Isolated Yield: 90%, mp: 264–266 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ: 6.75 (s, 1H), 7.50 (m, 2H), 7.58 (t, 1H, J = 7.7 Hz), 7.67 (m, 2H), 7.70 (t, 1H, J = 8.4 Hz), 8.00 (d, 1H, J = 7.7 Hz), 8.12 (d, 2H, J = 9.2 Hz), 8.40 (s, 1H), 9.78 (br s, 2H, C*H*O), 11.84 (s, 1H, D_2O exchangeable). ^{13}C NMR (125 MHz, DMSO-d_6) δ: 50.3, 101.3 (O–C=*C*(CHO)$_2$), 113.4, 117.2, 123.1, 124.3, 126.8, 128.8, 128.9, 129.6, 131.7, 131.8, 131.9, 134.5, 143.0, 144.8, 148.6, 162.1 (C=*C*–O), 186.7 (–*C*HO). IR ν_{max} (KBr): 3429, 1621, 1579, 1449, 1222, 806 cm^{-1}. Mass (ESI): 375 (M+1). Anal. Calcd for $C_{21}H_{14}N_2O_5$: C, 67.38, H, 3.77; N, 7.48. Found: C, 67.69; H, 3.83; N, 7.43. *Spectral data for compound* **2k**: Yellow solid. Isolated yield: 85%, mp: 170–172 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.93 (s, 3H), 6.67 (s, 1H), 6.87 (dd, 1H, J = 1.5, 7.6 Hz), 7.22 (d, 1H, J = 8.5 Hz), 7.34–7.44 (m, 5H), 7.85 (d, 1H, J = 7.6 Hz), 7.92 (d, 1H, J = 9.2 Hz), 8.06 (dd, 1H, J = 1.5, 8.5 Hz), 8.76 (s, 1H, C*H*O), 12.40 (s, 1H, D_2O exchangeable). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 10.5, 47.0 89.5 (O–C=*C*(CHO)$_2$), 112.2, 116.8, 122.2, 125.6 (2), 128.1, 129.0, 129.4, 129.5, 131.0, 134.3, 146.6, 148.3, 159.2, 163.2 (C=*C*–O), 184.7 (–CHO). IR ν_{max} (KBr): 3434, 1651, 1561, 1434, 1220, cm^{-1}. Mass (ESI): 361 (M+1). Anal. Calcd for $C_{21}H_{16}N_2O_4$: C, 69.99, H, 4.48; N, 7.77. Found: C, 70.12; H, 3.93; N, 7.71. *Spectral data for compound* **2o**: mp: 176–178 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 6.77 (s, 1H), 7.42–7.51 (m, 2H), 7.60–7.63 (m, 2H), 7.81 (m, 1H), 8.07 (d, 2H, J = 7.6 Hz), 8.28 (d, 1H, J = 8.4 Hz), 8.51 (s, 2H), 9.95 (s, 1H, D_2O exchangeable). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 48.5, 101.9 (C=*C*(CHO)$_2$), 112.9, 122.9, 124.0, 125.2, 128.4, 130.2, 130.5, 130.6, 133.8, 134.9, 137.3, 149.4, 162.8, (C=*C*–O), 190.1 (–CHO). IR ν_{max} (KBr): 3440, 1632, 1559, 1428, 1218, 812 cm^{-1}. Mass (ESI): 325 (M+1). Anal. Calcd for $C_{17}H_{12}N_2O_5$: C, 62.96, H, 3.73; N, 8.68. Found: C, 63.18, H, 3.78; N, 8.61.
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