A novel method for the synthesis of α-oximino-6-acylmethylphenanthridines under neutral conditions

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A novel method is described for the synthesis of α-oximino-6-acylmethylphenanthridine derivatives (**2a–g**)**B** in good to excellent yields based on treatment of 6-acylmethylphenanthridines with isoamyl nitrite (IAN) in DMF without any added acid.

Keywords: nitrosation, 6-acylmethylphenanthridines, enaminone, isoamyl nitrite (IAN)

The α-oximinoketones are known to be important intermediates for the synthesis of, for example, aminoacids,[1] nitrosopyrazoles,[2] 2-vinylimidazoles.[3] Although nitrous acid or one of its esters,[4] alkyl thionitrite or thionitrate,[5] nitrosyl halides[6] and sodium nitrite in acetic acid[7] are all used for the synthesis of α-oximinoketones, the yields and selectivity for mono oximination and chemoselectivity on the methylene carbon where there are two possible sites of nitrosation are low.[5] It is clear on the basis of the above facts that there is a need for more regioselective control of the nitrosation of enaminone compounds. It has been shown that, isoamyl nitrite under neutral conditions can be applied for selective C-nitrosation of aminopyrimidine derivatives.[8] Therefore, we decided to use the same procedure for our systems where there are two possible sites of nitrosation (N,C-nitrosation).

In our previous work, we have proved that all the primary compounds (*viz* **1a–g**) in the present study exist predominantly in the enaminone form.[9] In continuation, 6-acylmethylphenanthridines (**1a–g**) in the presence of a slight excess of isoamyl nitrite (IAN) (1.2 mmol equivalents/mmol substrate) in DMF at room temperature produced α-nitroso-ketones (**2a–g**)**A** and the initial nitroso compounds were rapidly converted into the corresponding α-oximinoketones (**2a–g**)**B** (see Scheme 1 and Table 1).

The structures of compounds (**2a-g**)**B** were confirmed by their spectra (^{1}H NMR, ^{13}C NMR, Elemental analysis, IR and MS). In all the ^{1}H NMR spectra the OH group of the α-oximinoacylmethylphenanthridines appeared around δ = 12.01–13.03 ppm as a broad singlet and in the IR spectra the C=O/C=N groups were observed around 1630–1655 cm^{-1}.

The actual nitrosating species operating under the conditions described here remains unclear. Traces of water, difficult to remove from the highly hygroscopic DMF or readily incorporated into the medium during solvent transfers or sampling for TLC monitoring, seem to play an important role in these reactions. This statement is based on the very long reaction times and the fact that the reactions only go to completion after several days when mixtures of anhydrous DMF and IAN were used. Therefore, we think the actual nitrosating species in wet DMF could be nitrous acid (HNO_2), produced *in situ* in small concentration by reaction between IAN and the traces of water present in the medium.

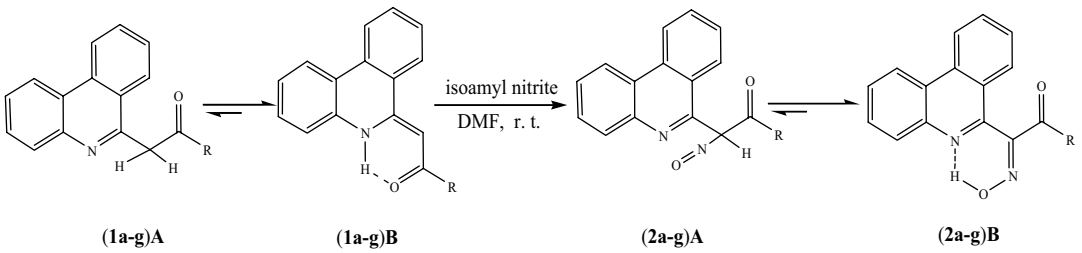
The main reason for the production of the oximino products (**2a–g**)**B** is the intramolecular hydrogen bonding. The remarkabe strengthening of the hydrogen bond as observed for the current systems and other similar systems[10] is related to the presence of a π-conjugated chain. This strong interaction is called a RAHB (resonance-assisted hydrogen bond)[11] owing to the synergistic coupling between the increased π-resonance and the strengthening hydrogen bond.

In conclusion, the low cost and availability of the reagent, easy and clean workup, and high yields make this an attractive method for organic synthesis. This simple procedure is highly selective and contamination by other products is avoided. We believed that the present methodology is an important addition to existing methodologies.

Table 1 Summary for transformations of (**1a–g**) into (**2a–g**) upon treatment with IAN/DMF at room temperature

Compound	R	Reaction time/h	M.p./°C	Yield[a]/%
2a	Ph	4.5	212–214	88
2b	*p*-Me-C_6H_4	6	200–201	85
2c	*p*-F-C_6H_4	5	231–233	90
2d	*p*-Cl-C_6H_4	5	220–222	85
2e	*p*-Me_2N-C_6H_4	7	234–235	80
2f	*p*-MeO-C_6H_4	7.5	229–230	74
2g	CH_2-Ph	4	192–194	90

[a]Isolated yield



Scheme 1

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Experimental

Melting points were determined using a Mettler FP5 apparatus and are uncorrected. IR spectra were determined using KBr pellets on a Shimadzu recording spectrophotometer, Model 435. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker 500 spectrometer in DMSO-d_6 with tetramethylsilane as internal standard. Mass spectra were taken by a Platlform II from Micromass and elemental analyses were performed using a Carlo Erba EA 1108 instrument.

6-Acylmethylphenanthridines (**1a-g**) were prepared by Goldberg and Levine method.[12]

General procedure for preparation of α-oximino-6-acylmethyl-phenanthridines (**2a–g)B**

A solution of the appropriate 6-acylmethylphenanthridine **1a-g** (1 mmol) and isoamyl nitrite (1.2 mmol) in DMF (10 ml) was stirred at room temperature. The progress of the reaction was followed by TLC. Reactions went to completion after 4–7.5 hours (Table 1). After the reaction was complete easy workup was possible by simple addition of water (10 ml) to the reaction medium, followed by vacuum filtration, washing and vacuum drying, which directly afforded the desired nitroso derivatives **(2a–g)B** with the required grade of purity and in good yields (Table 1). The physical and spectroscopic data of the compounds **2a–g** are as follows.

1-Phenanthridin-6-yl-2-phenylethane-1,2-dione 1-oxime (**2a**): M.p. 212–214°C. IR (cm^{-1}): 1650 (CO), 1595, 1364, 980. *m/z (%)* = 221 (6) [M$^+$- C_6H_5CO], 204 (100) [M$^+$- (C_6H_5CO, OH)], 177 (29) [M$^+$-C_6H_5COCH=NOH], 150 (25) [C_6H_5COCH=NOH]. ^{1}H NMR δ: 7.69–8.94 (13 H, m, $C_{19}H_{13}N$), 12.94 (1 H, s, O-H...N). ^{13}C NMR δ: 122.7, 122.9, 123.3, 123.7, 123.9, 127.1, 128.0, 128.3, 129.2, 129.6, 131.3, 131.6, 131.9, 142.1, 143.0, 149.6, 153.8, 154.0, (aryl-C), 190.1 (*C*=O). Anal. Calcd. for $C_{21}H_{14}N_2O_2$: C, 77.3; H, 4.3; N, 8.6. Found: C, 77.5; H, 4.3; N, 8.6%.

1-Phenanthridin-6-yl-2-p-tolylethane-1,2-dione 1-oxime (**2b**): M.p. 200–201°C. IR (cm^{-1}): 1645 (CO), 1600, 1365, 980. *m/z* (%) = 221 (53) [M$^+$- *p*-MeC_6H_4CO], 204 (100) [M$^+$- (*p*-MeC_6H_4CO, OH)], 177 (60) [M$^+$-*p*-MeC_6H_4COCH=NOH], 119 (70) [*p*-$MeC_6H_4CO^+$], 91 (85) [*p*-$MeC_6H_4^+$]. ^{1}H NMR δ: 2.40 (3 H, s, CH_3), 7.38–8.91 (12 H, m, $C_{19}H_{12}N$), 12.79 (1 H, s, O-H...N). ^{13}C NMR δ: 39.90 (CH_3), 122.7, 122.9, 123.7, 124.1, 127.3, 127.9, 128.2, 129.0, 129.1, 129.6, 130.4, 131.6, 131.8, 133.9, 143.0, 143.8, 153.8, 154.9, (aryl-C), 190.3 (*C*=O). Anal. Calcd. for $C_{22}H_{16}N_2O_2$: C, 77.6; H, 4.7; N, 8.2. Found: C, 77.5; H, 4.7; N, 8.3%.

1-(4-Fluorophenyl)-2-phenanthridin-6-yl-ethane-1,2-dione 2-oxime (**2c**): M.p. 231–233°C. IR (cm^{-1}): 1655 (CO), 1598, 1365, 982. *m/z* (%) = 344 (82) [M$^+$], 204 (100) [M$^+$- (*p*-FC_6H_4CO, OH)], 177 (85) [M$^+$-*p*-FC_6H_4COCH=NOH], 123 (93) [*p*-$FC_6H_4CO^+$], 95 (95) [*p*-$FC_6H_4^+$]. ^{1}H NMR δ: 7.43–8.92 (12 H, m, $C_{19}H_{12}N$), 12.99 (1 H, s, O-H...N). ^{13}C NMR δ: 115.4, 115.6, 122.7, 122.9, 123.7, 124.1, 127.2, 127.9, 128.2, 129.1, 129.6, 131.5. 131.9, 133.2, 133.3, 143.0, 153.8, 154.6, (aryl-C), 189.3 (*C*=O). Anal. Calcd. for $C_{21}H_{13}FN_2O_2$: C, 73.25; H, 3.8; N, 8.1. Found: C, 73.0; H, 3.8; N, 8.2%.

1-(4-Chlorophenyl)-2-phenanthridin-6-yl-ethane-1,2-dione 2-oxime (**2d):** M.p. 220–222°C. IR (cm^{-1}): 1655 (CO), 1585, 1363, 980. *m/z* (%) = 315 (4) [M$^+$-H_2C=N-OH], 221 (11) [M$^+$-*p*-ClC_6H_4CO], 204 (100) [M$^+$- (*p*-ClC_6H_4CO, OH)], 177 (30) [M$^+$-*p*-ClC_6H_4COCH=NOH], 139 (43) [*p*-$ClC_6H_4CO^+$], 111 (60) [*p*-$ClC_6H_4^+$]. ^{1}H NMR δ: 7.65–8.90 (12 H, m, $C_{19}H_{12}N$), 13.03 (1 H, s, O-H...N). ^{13}C NMR δ: 122.7, 122.9, 123.7, 124.0, 127.2, 128.0, 128.5, 128.6, 129.1, 129.6, 131.5, 131.9, 132.1, 135.2, 138.2, 143.0, 153.8, 154.4, (aryl-C), 189.7 (*C*=O). Anal. Calcd. for $C_{21}H_{13}ClN_2O_2$: C, 69.9; H, 3.6; N, 7.8. Found: C, 70.1; H, 3.6; N, 7.8%.

1-(4-Dimethylaminophenyl)-2-phenanthridin-6-yl-ethane-1,2-dione 2-oxime (**2e**): M.p. 234–235°C. IR (cm^{-1}): 1630 (CO), 1590, 1465, 980. *m/z* (%) = 369 (77) [M$^+$], 204 (78) [M$^+$- (*p*-$Me_2NC_6H_4CO$, OH)], 148 (80) [*p*-$Me_2NC_6H_4CO^+$]. ^{1}H NMR δ: 3.10 [6 H, s, $N(CH_3)_2$], 6.70–8.70 (12 H, m, $C_{19}H_{12}N$), 12.01 (1 H, s, O-H...N). ^{13}C NMR δ: 39.90 [$N(CH_3)_2$], 110.4, 122.0, 122.2, 123.8, 123.9, 124.7, 127.4, 127.6, 127.9, 128.6, 129.2, 130.0, 131.0, 132.2, 133.1, 143.4, 153.6, 154.3, (aryl-C), 187.8 (*C*=O). Anal. Calcd. for $C_{23}H_{19}N_3O_2$: C, 74.8; H, 5.2; N, 11.4. Found: C, 74.6; H, 5.2; N, 11.4%.

1-(4-Methoxyphenyl)-2-phenanthridin-6-yl-ethane-1,2-dione 2-oxime (**2f**): M.p. 229–230°C. IR (cm^{-1}): 1640 (CO), 1600, 1362, 980. *m/z* (%) = 311 (4) [M$^+$-H_2C=N-OH], 221 (7) [M$^+$-*p*-$MeOC_6H_4CO$], 204 (100) [M$^+$-(*p*-$MeOC_6H_4CO$, OH)], 177 (18) [M$^+$- *p*-$MeOC_6H_4COCH$ =NOH], 135 (22) [*p*-$MeOC_6H_4CO^+$]. ^{1}H NMR δ: 3.82 (3 H, s, O-CH_3), 7.07–8.86 (12 H, m, $C_{19}H_{12}N$), 12.68 (1 H, s, O-H...N). ^{13}C NMR δ: 55.6 (O-CH_3), 113.9, 122.6, 122.9, 123.7, 124.1, 127.4, 127.9, 128.2, 128.9, 129.1, 129.6, 131.5, 131.9, 132.8, 143.0, 153.8, 155.1, 163.5, (aryl-C), 188.9 (*C*=O). Anal. Calcd. for $C_{22}H_{16}N_2O_3$: C, 74.2; H, 4.5; N, 7.9. Found: C, 74.3; H, 4.5; N, 7.8%.

1-Phenanthridin-6-yl-3-phenylpropane-1,2-dione 1-oxime (**2g**): M.p. 192–194°C. IR (cm^{-1}): 1690 (CO), 1610, 1363, 1005. *m/z* (%) = 221 (4) [M$^+$- $C_6H_5CH_2CO$], 204 (100) [M$^+$- ($C_6H_5CH_2CO$, OH)], 177 (19) [M$^+$-$C_6H_5CH_2COCH$=NOH], 118 (12) [$C_6H_5CH_2CO^+$], 91 (41) [$C_6H_5CH_2^+$]. ^{1}H NMR δ: 4.40 (2 H, s, CH_2), 7.20–8.82 (13 H, m, $C_{20}H_{13}N$), 12.93 (1 H, s, O-H...N). ^{13}C NMR δ: 43.91 (CH_2), 122.7, 122.9, 123.6, 123.9, 126.7, 126.7, 127.8, 128.1, 128.4, 129.1, 129.6, 129.9, 131.4, 131.8, 134.6, 143.0, 154.0, 154.1, (aryl-C), 195.8 (C=O). Anal. Calcd. for $C_{22}H_{16}N_2O_2$: C, 77.6; H, 4.7; N, 8.2. Found: C, 77.6; H, 4.8; N, 8.2%.

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