INTRODUCTION

The application of nitrone cycloaddition chemistry to the synthesis of natural products and biologically important synthetic compounds is well known with annulation to cyclic nitrones a particularly useful synthetic tool [1]. As part of our ongoing research into the synthesis of novel heterocyclic nitrones we have previously observed a delicate balance between chemoreactivity and the substitution pattern of \(\alpha\)-[amidoalkenyl]aryloximes, of general structure 1. These oximes respond in one of three ways to thermal activation; (i) formation the 6,7-bicyclic benzodiazepinone \(N\)-oxide framework 2, (ii) formation of the 5,6,6-tricyclic isoxazoloquinolinone skeleton 3 by an IOOC reaction (intramolecular oxime olefin cycloaddition), or (iii) no reaction [2]. In particular the aldoxime 1a (\(R^1=\text{Ph}, R^4=\text{H}\)) was immune to thermal activation whilst the analogous ketoxime 1b (\(R^1=R^4=\text{Ph}\)), furnished the tricycle 3b under the same conditions of heating in boiling xylene [2]. On the basis that electronic and/or steric differences between the proton and the phenyl group \((R^3)\) on 1a/1b are responsible for the disparate reactivity we were anxious to investigate the influence of a methyl group at this position and the current work reports on the reactivity of 5a/b, C-methyl analogues of 1.

RESULTS AND DISCUSSION

Condensation between trans-cinnamoyl chloride and \(\alpha\)-aminoacetophenone (NaHCO\(_3\), CH\(_2\)Cl\(_2\)) afforded the amido derivative 4a in 67% yield. Treatment of 4a with NH\(_2\)OH.HCl in boiling EtOH (24 h) in the presence of C\(_5\)H\(_5\)N (1:1:1:1.1), furnished the oxime 5a in 56% isolated yield. However, upon extending the reaction duration the quinazoline 3-oxide 6a accompanied the oxime, and after 72 h reaction 6a was isolated in quantitative yield. Since no reaction occurred on heating isolated oxime 5a alone in boiling EtOH (24 h), it is speculated that pyridinium
hydrochloride, liberated in the generation of the free hydroxylamine, is central to the formation of the N-oxide and thus that the quinazoline skeleton of 6a arises from 5a by way of an acid promoted intramolecular cyclocondensation between the oxime and the amide functionalities.

Whilst we have not previously observed amide functionalities as electrophilic partners in generation of nitrone from oximes, a number of isolated examples of acid induced oxime-amide cyclisations are known [3,4,5]. In particular, the formation of 6a from 5a has previously been reported following treatment of the parent oxime with 16% HCl in EtOH at room temperature [3], reaction conditions much more harsh than those reported in the current paper. Significantly, however, the same paper notes that the oxime 7 reacts with excess NH₂OH.HCl in the presence of pyridine to afford the quinazoline 3-oxide 8 in 89% yield after 3 h (EtOH, 80 °C) [4]. Preformed pyridinium hydrochloride has also been used to effect oxime-amide cyclisation of the pinane derived aldoxime 5b (MeOH, 16 h) [4].

Quinazoline 3-oxides, like 6a, which contain a formal nitrone structural moiety, could be useful modular building blocks for the synthesis of complex heterocycles, accordingly, it was important to attempt preparation of analogous compounds. Reaction between 4b, with a methyl substituted alkene, and NH₂OH.HCl proceeded after 8 h to give the oxime 5b in 50% yield (C₅H₅N, EtOH, 80 °C). After 40 h reaction time the quinazoline 3-oxides 6b (8%) and 10 (14%) were present together with oxime 5b (11%). The reaction mixture was separable only in so far as the oxime could be separated from the N-oxides, which had very similar Rf values. On the hypothesis that the ethoxy derivative 10 originated from a conjugate addition of ethanol to the parent N-oxide 6b the reaction solvent was changed to t-BuOH. After 138 h a complex reaction mixture comprising unreacted ketone 4b (15%), oxime 5b (10%), 2-aminacetophenone (2%) and nitrone 6b (32%) was found. No alkoxy addition products were obtained. To optimise the yield of 6b, acid promoted cyclisation of the isolated oxime 5b was investigated and following heating 5b in boiling t-BuOH in the presence of either preformed py.HCl (16 h) or 2 M HCl (9 h) 6b resulted in 88 and 100% yield respectively.

In order to probe further the mechanistic origin of 10 an attempt was made to react the N-oxide 6b by heating alone in boiling EtOH (18 h), it was subsequently discovered that the addition of EtOH to 6b requires acid catalysis – and in the presence of an equimolar amount of pyridinium hydrochloride 10 resulted in 51% yield after 72 h. The corresponding methoxy derivative 11 was obtained in 62% yield following analogous reaction in boiling MeOH for 7 d. Whilst direct addition of nucleophiles to nitrone functionalities is well established there is scant literature precedent for conjugate addition to vinyl nitrone. However, one recent paper speculates that biosynthesis of the indole alkaloid stephacidin B may involve an acid promoted attack of an amido nitrogen on a nitrone Michael acceptor [6]. There has also been a report on the redirection of nucleophilic thiol addition [base promoted] from the more usual β- to the α-position in ethyl 3-[1-oxidopyrimidin-2-yl]propenoate with respect to the deoxy-parent, suggesting the utility of a pyrimidine N-oxide moiety as a Michael type acceptor [7]. The acid induced addition of alcohols to 6b may represent the first example of a quinazoline N-oxide as a π-deficient moiety in facilitating conjugate addition, however, the possibility that the acceptor character of 6b is, at least partly, conferred by the quinazoline N-1 can not be ruled out since it is known that vinyl substituted purines [8] and pyrimidines [9] readily participate as Michael acceptors in nucleophilic additions. The styryl substituted quinazoline 3-oxide 6a failed to react with ethanol, even under the influence of pyridinium hydrochloride, this is likely attributable to the electronic and/or steric properties of the phenyl group.

The tolerance of the acid catalysed oxime-amide cyclisation to an aldoxime functionality was next investigated. Accordingly the aldoximes 1a and 14 bearing phenyl and methyl substituted alkene moieties respectively were targeted. Oxime 1a was prepared as previously reported [2], a parallel series of reactions lead to 14. The amidoalcohol 12, obtained following coupling between 2-aminobenzylalcohol and trans-cinnamyl chloride gave upon PCC oxidation the aldehyde 13 from which the desired oxime 14 was obtained on treatment with NH₂OH.HCl (EtOH, C₅H₅N, room temperature).
Attempting cyclisation of 1a in t-BuOH under the influence of pyridinium hydrochloride lead to inconsistent and irreproducible results whilst the oxime 14, proposed precursor to the quinazoline 3-oxide 15b, failed to yield any N-oxide under the influence of py.HCl. However, following heating for 1 h in refluxing EtOH, in the presence of HCl [18%], cyclisation of 1a was facile and 15a was isolated in 93% yield. On the other hand whilst 1H nmr spectral analysis of the crude products resulting from HCl promoted reaction of 14 (9-18% HCl) did provide evidence for the formation of 15b isolation of the propenyl variant proved very difficult and it was possible only to obtain sufficient sample for characterisation by spectral methods.

CONCLUSION

o-[Amidoalkenyl]aryloximes 5a,b, 1a and 14 are found to be useful precursors to 2-vinylquinazoline-3-oxides 6 and 15 undergoing a cyclocondensation reaction under acidic conditions in preference to cyclisation to benzodiazepines or IOOC reaction leading respectively, to products of general structure 2 or 3. The reaction is not trivial and the optimal conditions vary with individual substrates, however, the new heteroaromatic N-oxides 6 and 15 are likely to be important substrates for the construction of a variety of new ring systems. Preliminary investigations into the cycloaddition behaviour of the novel N-oxides reported in this paper has recently been described [10]. Conjugate addition of EtOH and MeOH to 2-vinylquinazoline-3-oxide, 6b a reaction also requiring acidic conditions represents the first example of conjugate addition to vinyl substituted quinazoline N-oxides.

EXPERIMENTAL

Mps. were determined on a Stuaroom temperature Scientific (Bibby) melting point apparatus and are uncorrected. Elemental analyses were performed on a CE-440 analytical instrument. Infrared spectra were recorded on a Perkin Elmer 2000 FT-IR instrument, samples were prepared as KBr discs.

[2E]-N-[2-(Acetylphenyl)-3-phenylacrylamide, (4a). trans-Cinnamyl chloride 3.04 g (0.02 mol) was added to a cooled suspension of 2-aminoacetophenone 2.70 g (0.02 mol) and NaHCO3, 1.90 g (0.02 mol) in anhydrous DCm (17 ml). The solution was stirred for 50 min at room temperature after which it was washed with water (2 x 20 ml) and the organic layer dried over MgSO4. The solvent was removed under reduced pressure and the crude product crystallised from DCM:hexene (1:3) to yield the product as a white solid 3.56 g (67%), mp 75-79 °C (DCM:hexane); ir: NH 3205, CO 1681, NHCO 1651 cm⁻¹; 1H nmr: δ 2.67 (s, 3H, CH3), 6.61 (d, 1H, H-C=CHPh, J = 8.5 Hz), 7.12 (d, 1H, ArH, J = 7.5, 7.5 Hz), 7.38 (m, 3H, ArH), 7.58 (m, 3H, ArH), 7.74 (d, 1H, 1H, H-C=CHPh, J = 15.6 Hz), 7.90 (d, 1H, ArH, J = 7.9 Hz), 8.90 (d, 1H, ArH, J = 8.5 Hz), 12.03 (br s, 1H, NH); 13C nmr: δ 29.0 (CH3), 121.3 (ArCH), 122.1 (C2), 122.5 (H-C=CHPh), 128.2 (ArCH), 128.5 (2 x ArCH), 129.3 (2 x ArCH), 130.4 (ArCH), 132.1 (ArC), 135.6 (ArCH), 141.7 (C1), 142.6 (H-C=CHPh), 165.3 (C1), 203.4 (C=O). Anal. Calcd. for C17H14NO2: C, 76.96; H, 5.70; N, 5.28. Found: C, 76.78; H, 5.72; N, 5.07 %.

[2E]-N-[2-[[1E]-N-Hydroxyethanimidoyl]phenyl]-3-phenylacrylamide, (5a). A solution of 4a 0.30 g (1.13 mmol), hydroxylamine hydrochloride 0.09 g (1.24 mmol), and pyridine 0.11 g (1.24 mmol) in EtOH (30 ml) was heated at reflux for 24 h. The EtOH was removed under reduced pressure and the resulting residue dissolved in DCM (50 ml) and washed with water (3 x 50 ml). The organic layer was dried over MgSO4 and the DCM was removed under reduced pressure. The crude oxime was crystallised from hexane:DCM (1:1) to yield the pure product as a white solid 0.18 g (56%), mp 108 – 111 °C (hexane:DCM); ir: NH 3205, CO 1681, NHCO 1651 cm⁻¹; 1H nmr: δ 2.67 (s, 3H, CH3), 6.50 (d, 1H, CH=CHPh, J = 15.6 Hz), 7.18 (m, 1H, ArH), 7.30 (m, 3H, ArH), 7.50 (m, 3H, ArH), 7.60 (d, 1H, CH=CHPh, J = 15.6 Hz), 8.31 (s, 1H, OH/NH), 8.69 (d, 1H, ArH, J = 8.2 Hz), 11.14 (s, 1H, OH/NH); 13C nmr δ 13.6 (CH3), 121.9 (ArCH), 122.6 (CH=CHPh), 123.6 (ArCH), 123.8 (C2), 128.3 (ArCH), 128.9 (2 x ArCH), 129.1 (2 x ArCH), 130.2 (ArCH), 130.2 (ArC), 135.1 (ArCH), 137.3 (C1), 142.2 (CH=CHPh), 158.7 (C=NOH), 165.0 (C=O). Anal. Calcd. for C15H14NO3: C, 68.44; H, 6.08; N, 9.38. Found: C, 68.22; H, 6.14; N, 9.56 %.

4-Methyl-2-[[E]-2-phenylvinyl]quinazoline-3-oxide, (6a). A solution of 5a 1.60 g (5.77 mmol), pyridine 0.38 g (4.15 mmol) and hydroxylamine hydrochloride 0.29 g (4.15 mmol) was heated at reflux in EtOH (80 ml) for 3 d. The EtOH was removed under reduced pressure and the residue dissolved in DCM (80 ml) and washed with water (3 x 50 ml). The organic layer was dried over MgSO4 and the DCM removed under reduced pressure. The crude product was purified by flash column illumination using a portable UVtec lamp (λ, 254 nm) or by the use of iodine staining. Mass spectra were recorded on a Profile Kratos Analytical instrument. Infrared spectra were recorded on a Perkin Elmer 2000 FT-IR instrument, samples were prepared as KBr discs.
chromatography (SiO₂, ether) to afford the title product as a yellow solid 0.99 g (100%), mp 170-174 °C (ether); in all other presentations of IR data the fg is recorded first (without parenthesis), followed by the absorption ir: 3022 (C=C); 1627 (C=N); 1571 cm⁻¹; H nmr: δ 2.90 (s, 3H, CH₃), 7.41 (m, 3H, ArH), 7.58 (m, 1H, ArH), 7.72 (m, 3H, ArH); 7.84 (m, 1H, ArH), 7.97 (d, 1H, ArH, J = 8.4 Hz), 8.18 (d, 1H, CH=CH₂, J = 16.0 Hz), 8.26 (d, 1H, CH=CH₂, J = 16.0 Hz); ¹³C nmr: δ 13.2 (CH₃), 117.4 (CH=CH₂), 123.2 (C₆H₅), 123.3 (ArCH), 128.2 (2 x ArCH), 128.5 (ArCH), 129.7 (ArCH), 131.1 (ArCH), 135.9 (ArCH), 140.2 (C₆H₅), 151.2 (C₆H₅), 153.9 (C₆H₅). Anal. Calcld. for C₅₁H₄₄N₂O₄: C, 77.60; H, 5.42; N, 10.59 %.

Method B: From E-N-[2-(Hydroxyethyl)phenyl]-2-butenamide, (5b). A solution of 6b 0.20 g (0.92 mmol) was allowed to heat at reflux in dry BuOH (50 ml) for 9 h in the presence of 2M HCl (1.84 ml). The BuOH was removed under reduced pressure and the residue dissolved in DCM (50 ml). It was washed with water (3 x 50 ml) and the organic layer dried over MgSO₄. The DCM was removed under reduced pressure and the resulting crude mixture purified by flash column chromatography (SiO₂, ether). The mixture nitro 6b was isolated as a yellow solid 0.18 g (100%).

2-[Ethoxypropyl]-4-methylquinazoline-3-oxide, (10). A solution of 6b 0.20 g (0.99 mmol) was heated at reflux for 72 h in dry EtOH (50 ml) in the presence of 2M HCl (1.60 g 0.99 mmol). The solution was cooled and neutralized by the addition of NaHCO₃, 0.20 g (2.00 mmol). The solvent was removed under reduced pressure. The residue was dissolved in DCM (50 ml) and washed with water (3 x 40 ml). The organic layer was dried over MgSO₄. The DCM was removed under reduced pressure to give the crude product as an oil which was purified by flash column chromatography (SiO₂, ether). The pure product was isolated as a brown oil 0.13 g (51%); ir: Ar=CH₂ 2929, C=O 1613, C=N 1576 cm⁻¹; H nmr: δ 1.13 (t, 3H, OCH₂CH₃), 3.68 (m, 3H, OCH₂CH₃), 4.58 (m, 2H, CH₂), 7.81 (d, 1H, ArH, J = 14.8 Hz), 7.99 (m, 1H, ArH), 8.01 (m, 1H, ArH). Anal. Calcld. for C₁₄H₁₂N₂O₂: C, 70.01; H, 6.45; N, 11.38. Found: C, 70.85; H, 6.47; N, 11.31 %.

2-[Methoxypropyl]-4-methylquinazoline-3-oxide, (11). A solution of 6b 0.20 g (0.99 mmol) was heated at reflux for 7 d in dry MeOH (50 ml) in the presence of Py.HCl 0.16 g (0.99 mmol). The solution was cooled and neutralized by the addition of NaHCO₃, 0.20 g (2.00 mmol). The MeOH was removed under reduced pressure. The residue was dissolved in DCM (50 ml) and washed with water (3 x 50 ml). The organic layer was dried over MgSO₄. The DCM was removed under reduced pressure to give the crude product as an oil which was purified by flash column chromatography (SiO₂, ether). The isolated product was a cream solid 0.14 g (62%); ir: Ar=CH=CH₂ 2929, C=O 1613, C=N 1576 cm⁻¹; H nmr: δ 1.13 (t, 3H, OCH₂CH₃), 3.68 (m, 3H, OCH₂CH₃), 4.58 (m, 2H, CH₂), 7.81 (d, 1H, ArH, J = 14.8 Hz), 7.99 (m, 1H, ArH). Anal. Calcld. for C₁₄H₁₂N₂O₂: C, 70.01; H, 6.45; N, 11.38. Found: C, 68.78; H, 7.40; N, 11.41 %.
solid purified by flash column chromatography (SiO\textsubscript{2}, celite. The solvent was removed under reduced pressure and the anhydrous ether (4 x 100 ml) and the washings passed through celite. The insoluble residue was washed further with anhydrous DCM (40 ml). The resulting mixture was left stirring for 1 h at room temperature for 1.5 h. Anhydrous ether (100 ml) was added to the reaction mixture and the resulting mixture filtered at room temperature for 1.5 h. Anhydrous ether (100 ml) was added to a reaction mixture and the resulting mixture filtered at room temperature for 1.5 h. Anhydrous DCM (40 ml). The resulting mixture was left stirring for 1 h at room temperature. The organic layer was washed with water (x 30 ml) dried over MgSO\textsubscript{4} and the solvent removed under reduced pressure. The crude product was purified by flash column chromatography (SiO\textsubscript{2}, DCM:ether 9:1) to yield the title compound. 1H nmr: 6.89 (dq, 1H, CH=CH=CH\textsubscript{2}), 7.19 (m, 1H, ArH), 7.28 (m, 1H, ArH), 8.03 (d, 1H, ArH, J = 7.6 Hz), 8.73 (br s, 1H, OH/NH; 13C nmr: δ 17.9 (CH\textsubscript{3}), 64.3 (CH\textsubscript{3}), 122.5 (ArCH), 124.3 (ArCH), 125.8 (CH=CH-CH=CH), 128.8 (ArCH), 128.9 (ArCH), 129.9 (ArC), 137.5 (ArC), 141.2 (CH=CH=CH\textsubscript{2}), 164.6 (CO) Anal. Calcd for C\textsubscript{11}H\textsubscript{10}N\textsubscript{2}O: C, 69.00; H, 6.85; N, 7.33. Found: C, 68.56; H, 6.76; N, 7.17%.

[2E]-N-[2-Hydroxyimino][methylphenyl]but-2-enamide, (12). A cooled suspension of [2E]-[2-Hydroxyimino][methylphenyl]but-2-enamide (3.70 g, 0.02 mol) in anhydrous DCM (50 ml) was treated with trans-crotonyl chloride 4.68 (0.05 mol). The resulting mixture was left to stir for 1 h at room temperature. The organic layer was washed with water (x 30 ml) dried over MgSO\textsubscript{4} and the solvent removed under reduced pressure. The crude product was purified by flash column chromatography (SiO\textsubscript{2}, DCM:ether 9:1) to yield the title product as a white solid 1.79 g (47%), mp 105-108 °C (DCM:ether). Anal. Calcd for C\textsubscript{11}H\textsubscript{11}NO\textsubscript{2}: C, 69.83; H, 5.36; N, 7.40. Found: C, 69.43; H, 5.61; N, 7.47%.

[2E]-N-[2-Formylphenyl]but-2-enamide, (13). A solution of 12 3.60 g (0.02 mol) in anhydrous DCM (40 ml) was added to a suspension of pyridinium chlorochromate 6.05 g (0.03 mol) in anhydrous DCM (40 ml). The resulting mixture was left stirring at room temperature for 1.5 h. Anhydrous ether (100 ml) was added to the reaction mixture and the resulting mixture filtered through celite. The insoluble residue was washed further with anhydrous ether (x 4 ml) and the washings passed through celite. The solvent was removed under reduced pressure and the solid purified by flash column chromatography (SiO\textsubscript{2}, DCM:ether 9:1) to yield a brown oil (100%); ir: CH=CHO\textsubscript{1687}, NHCO\textsubscript{1610} cm\textsuperscript{-1}; 1H nmr: δ 1.95 (d, 3H, CH\textsubscript{3}, J = 6.4 Hz), 6.05 (d, 1H, CH=CHO\textsubscript{3}), J = 15.1 Hz), 7.02 (m, 1H, CH=CH=CH\textsubscript{2}), 7.23 (m, 1H, ArH), 7.63 (m, 2H, ArH), 8.82 (d, 1H, ArH, J = 8.3 Hz), 9.93 (s, 1H, CH\textsubscript{3}), 11.22 (br s, 1H, NH); 13C nmr: δ 18.4 (CH\textsubscript{3}), 120.4 (ArCH); 122.1 (ArC); 123.2 (ArCH); 126.7 (CH=CH=CH\textsubscript{2}); 136.5 (ArCH); 141.7 (ArC-N); 142.4 (CH=CHCH\textsubscript{2}); 165.4 (CO\textsubscript{2}); 196.0 (CHO). Anal. Calcd for C\textsubscript{12}H\textsubscript{12}N\textsubscript{2}O\textsubscript{2}: C, 69.83; H, 5.36; N, 7.40. Found: C, 69.43; H, 5.61; N, 7.47%.

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