2-Vinyl Quinazoline 3-oxides; Preparation from Acid Induced Cyclocondensation of 2-Acylaminoaryloximes

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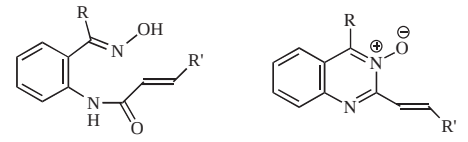
Received May 5, 2006



1 **2**

a. R = Me, R' = Ph; **b**. R = R' = Me; **c**. R = h, R' = Ph

2-Vinyl quinazoline 3-oxides **6a, 6b** and **15a** are useful modular building blocks for the construction of a range of heterocycles with potential biological activity, from *o*-[amidoalkenyl]aryloximes **5a**, **5b** and **14a**, respectively, by cyclocondensation. Conjugate addition of EtOH or MeOH to the vinyl moiety of **6b** is demonstrated.

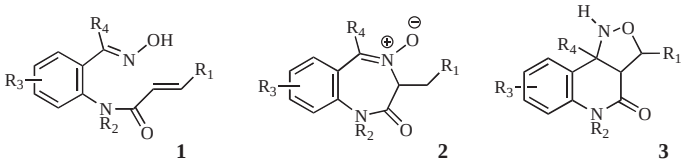
J. Heterocyclic Chem., **44**, 569 (2007).

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 *o*-[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 cyclo-addition), or (iii) no reaction [2]. In particular the aldoxime **1a** (R^1=Ph, R^4=H) was immune to thermal activation whilst the analogous ketoxime **1b** (R^1=R^4=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^4) 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**.

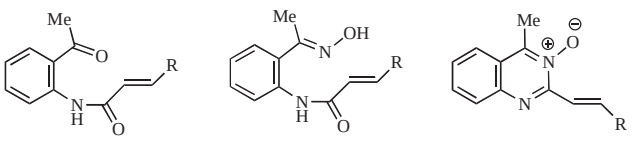
RESULTS AND DISCUSSION

Condensation between *trans*-cinnamoyl chloride and *o*-aminoacetophenone ($NaHCO_3$, CH_2Cl_2) afforded the amido derivative **4a** in 67% yield. Treatment of **4a** with $NH_2OH.HCl$ in boiling EtOH (24 h) in the presence of C_5H_5N (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 quantative yield. Since no reaction occurred on heating isolated oxime **5a** alone in boiling EtOH (24 h), it is speculated that pyridinium



1 **2** **3**

a. R_1=Ph, R_2=R_3=R_4=H
b. R_1=R_4=Ph, R_2= R_3 =H

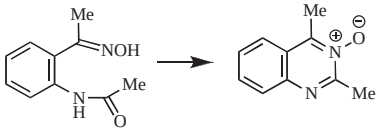


4 **5** **6**

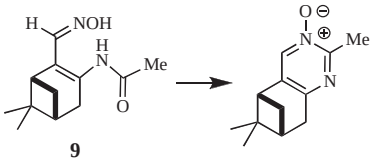
a. R = Ph; **b**. R = Me

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 nitrones 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 $NH_2OH.HCl$, 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 **9** (MeOH, 16 h) [4].

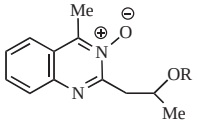


7 **8**



9

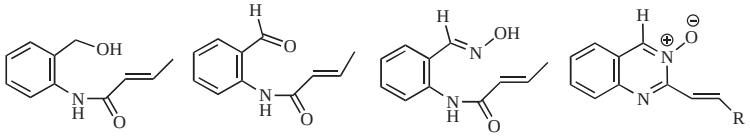
Quinazoline 3-oxides, like **6a**, which contain a formal nitrone structural moiety, could be useful modular building blocks for the synthesis of complex heterocycles, accordingly, it was important to attempt preparation of analogous compounds. Reaction between **4b**, with a methyl substituted alkene, and $NH_2OH.HCl$ proceeded after 8 h to give the oxime **5b** in 50% yield (C_5H_5N, 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 R_f 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-aminoacetophenone (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.



10 R = Et
11 R = Me

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 nitrones. However, one recent paper speculates that biosynthesis of the indole alkaloid stephacidin B may involve an acid promoted attack of an amidic 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 facilitation of 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 tolerence 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 $NH_2OH.HCl$ (EtOH, C_5H_5N, room temperature).



12 **13** **14** **15**

a. R = Ph
b. R = Me

Attempted 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 ^{1}H 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. ^{1}H and ^{13}C NMR spectra were recorded using a Bruker NMR spectrometer operating at 300 MHz for ^{1}H and 75 MHz for ^{13}C nuclei. Data were recorded at probe temperatures with, unless otherwise stated, tetramethylsilane as internal reference and deuteriochloroform as solvent, *J* values are given in Hertz. Flash column chromatography was carried out on silica gel 60 (0.040-0.063 nm) purchased from Merck**,** analytical TLC plates were purchased from Merck, aluminum backed and coated with silica gel 60 F_{254} indicator. Samples were located by *UV* 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.

[2*E*]-*N*-[2-Acetylphenyl]-3-phenylacrylamide, (4a). *trans*-Cinnamoyl chloride 3.04 g (0.02 mol) was added to a cooled suspension of 2-aminoacetophenone 2.70 g (0.02 mol) and $NaHCO_3$ 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 $MgSO_4$. The solvent was removed under reduced pressure and the crude product crystallised from DCM:hexane (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}; ^{1}H nmr: δ 2.67 (s, 3H, CH_3), 6.61 (d, 1H, *H*C=HCPh, *J* = 15.6 Hz), 7.12 (dd, 1H, ArH, *J* = 7.5, 7.5 Hz), 7.38 (m, 3H, ArH), 7.58 (m, 3H, ArH), 7.74 (d, 1H, HC=C*H*Ph, *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); ^{13}C nmr: δ 29.0 (CH_3), 121.3 (ArCH), 122.1 (C2^1), 122.5 (H*C*=HCPh), 122.8 (ArCH), 128.5 (2 x ArCH), 129.3 (2 x ArCH), 130.4 (ArCH), 132.1 (ArCH), 135.1 (ArC), 135.6 (ArCH), 141.7 (C1^1), 142.6 (HC=H*C*Ph), 165.3 (C1), 203.4 (C=O). *Anal*. Calcd. for $C_{17}H_{14}NO_2$: C, 76.96; H, 5.70; N, 5.28. Found: C, 76.78; H, 5.72; N, 5.07 %

[2*E*]-*N*-{2-[[1*E*]-*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 $MgSO_4$ 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/NOH 3549, CO 1672 cm^{-1}; ^{1}H nmr: δ 2.36 (s, 3H, CH_3), 6.50 (d, 1H, C*H*=CHPh, *J* = 15.6 Hz), 7.18 (m, 1H, ArH), 7.30 (m, 4H, ArH), 7.50 (m, 3H, ArH), 7.69 (d, 1H, CH=C*H*Ph, *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); ^{13}C nmr: δ 13.6 (CH_3), 121.9 (ArCH), 122.6 (*C*H=CHPh), 123.6 (ArCH), 123.8 (C2^1), 128.3 (ArCH), 128.9 (2 x ArCH), 129.1 (2 x ArCH), 130.2 (ArCH), 130.2 (ArCH), 135.1 (ArC), 137.3 (C1^1), 142.2 (CH=*C*HPh), 158.7 (*C*=NOH), 165.0 (C=O). *Anal*. Calcd. for $C_{17}H_{17}N_2O_2 \bullet H_2O$: 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** 1.00 g (3.77 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 $MgSO_4$ and the DCM removed under reduced pressure. The crude product was purified by flash column

chromatography (SiO_2, 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}; ^1H nmr: δ 2.90 (s, 3H, CH_3), 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=C*H*Ph, *J* = 16.0 Hz), 8.26 (d, 1H, C*H*=CHPh, *J* = 16.0 Hz); ^{13}C nmr: δ 13.2 (CH_3), 117.4 (*C*H=CHPh), 123.2 (C4a), 123.3 (ArCH), 128.2 (2 x ArCH), 128.5 (ArCH), 128.9 (2 x ArCH), 129.7 (ArCH), 131.1 (ArCH), 135.9 (ArC), 140.3 (C8a), 141.1 (CH=*C*HPh), 151.2 (C4), 153.9 (C2). *Anal*. Calcd. for $C_{17}H_{14}N_2O$: C, 77.80; H, 5.38; N, 10.68. Found: C, 77.60; H, 5.42; N, 10.59 %.

[2*E*]-*N*-[2-Acetylphenyl]but-2-enamide, (4b). *trans*-Crotonyl chloride 4.18 g (0.04 mol) was added to a cooled suspension of 2-aminoacetophenone 5.40 g (0.04 mol) and $NaHCO_3$ 3.80 g (0.04 mol) in anhydrous DCM (35 ml). The solution was stirred for 50 min at room temperature after which it was washed with water (3 x 30 ml) and the organic layer dried over $MgSO_4$. The solvent was removed under reduced pressure and the crude product crystallised from DCM:hexane (1:4). The pure product was isolated as a white solid 6.70 g (83%), mp 67-69 °C (DCM:hexane) ; ir: NH 3210, CO 1686, NHCO 1607 cm^{-1}; ^1H nmr: δ 1.93 (dd, 3H, HC=CHC*H*$_3$, *J* = 6.9, 1.6 Hz), 2.67 (s, 3H, C*H*$_3$C=O), 6.03 (dq, 1H, C*H*=CHCH$_3$, *J* = 15.2, 1.6 Hz), 6.99 (dq, 1H, CH=C*H*CH$_3$, *J* = 15.2, 6.9 Hz), 7.12 (m, 1H, ArH), 7.56 (m, 1H, ArH), 7.90 (dd, 1H, ArH6^1, *J* = 8.0, 1.5 Hz), 8.84 (dd, 1H, ArH3^1, *J* = 8.5, 1.0 Hz), 11.84 (br s, 1H, NH); ^{13}C nmr: δ 18.3 (HC=CH*C*H$_3$), 28.9 (*C*H$_3$C=O), 121.3 (ArC3'), 122.1 (C2^1), 122.6 (ArCH), 127.2 (*C*H=CHCH$_3$), 132.1 (ArC6'), 135.6 (ArCH), 141.6 (CH=*C*HCH$_3$), 141.8 (C1^1), 165.3 (C1), 203.3 (C=O). *Anal*. Calcd. for $C_{12}H_{13}NO_2$: C, 70.91; H, 6.45; N, 6.89. Found: C, 70.95; H, 6.47; N, 6.98 %.

***E*-*N*-[2-[Hydroxyethanimodyl]phenyl]-2-butenamide, (5b).** A solution of [2*E*]-*N*-[2-acetylphenyl]but-2-enamide **4b** 1.22 g (0.01 mol), hydroxylamine hydrochloride 0.49 g (0.01 mol) and pyridine 0.64 g (0.01 mol) in EtOH (70 ml) was heated at reflux for 8 h. The EtOH was removed under reduced pressure and the resulting residue dissolved in DCM (70 ml) and washed with water (3 x 50 ml). The organic layer was dried over $MgSO_4$ and the DCM was removed under reduced pressure. The crude oxime was purified by crystallisation from hexane:DCM (1:1) to afford the product as a white solid 0.65 g (50%), mp 112-115 °C (hexane: DCM) ; ir: NOH/NH 3202, CO 1677 cm^{-1}; ^1H nmr: δ_H 1.83 (dd, 3H, CH=CHC*H*$_3$, *J* = 6.9, 1.6 Hz), 2.35 (s, 3H, CH$_3$), 5.90 (dq, 1H, C*H*=CHCH$_3$, *J* = 15.2, 1.6 Hz), 6.90 (dq, 1H, CH=C*H*CH$_3$, *J* = 15.2, 6.9 Hz), 7.12 (m, 1H, ArH), 7.34 (m, 1H, ArH), 7.47 (dd, 1 H, ArH, *J* = 8.0, 1.5 Hz), 8.39 (s, 1H, OH/NH), 8.62 (d, 1H, ArH, *J* = 8.3 Hz), 10.94 (br s, 1H, OH/NH); ^{13}C nmr: δ 13.6 (*C*H$_3$), 18.2 (CH=CH*C*H$_3$), 121.8 (ArC3'), 123.6 (ArCH), 123.7 (C2^1), 127.1 (H*C*=CHCH$_3$), 128.8 (ArC6'), 130.1 (ArCH), 137.3 (C1^1), 141.3 (HC=*C*HCH$_3$), 158.5 (*C*=NOH), 165.1 (C=O). *Anal*. Calcd. for $C_{12}H_{14}N_2O$: C, 66.03; H, 6.47; N, 12.84. Found: C, 65.95; H, 6.50; N, 12.86 %.

4-Methyl-2-[[1*E*]-prop-l-enyl]quinazoline-3-oxide, (6b).

***Method A*: From [2*E*]-*N*-[2-*A*cetylphenyl]but-2-enamide, (4b).** A solution of **4b** 0.60 g (2.95 mmol), pyridine 0.30 g (3.25 mmol) and hydroxylamine hydrochloride 0.23 g (3.25 mmol) was heated at reflux for 138 h in ^{t}BuOH (70 ml). The solvent was removed under reduced pressure and the residue dissolved in DCM (70 ml). It was washed with water (3 x 50 ml) and the organic layer dried over $MgSO_4$. The DCM was removed under reduced pressure and the resulting crude mixture purified by flash column chromatography (SiO_2, ether). A single product was isolated as a yellow solid 0.15 g (32%). mp 147-150 °C (ether); ir: CH=CH 2926, C=C 1646, C=N 1558 cm^{-1}; ^1H nmr (benzene-d_6): δ 1.68 (dd, 3H, CH=CHC*H*$_3$, *J* = 7.0, 1.6 Hz), 2.40 (s, 3H, C*H*$_3$), 6.90 (m, 2H, 2 x ArH), 7.10 (m, 1H, ArH), 7.50 (dq, 1H, CH=C*H*CH$_3$, *J* = 15.5, 7.0 Hz), 7.81 (d, 1H, ArH, *J* = 8.3 Hz), 8.00 (dq, 1H, C*H*=CHCH$_3$, *J* = 15.5, 1.6 Hz); ^{13}C nmr (benzene-d_6): δ 12.7 (CH=CH*C*H$_3$), 18.8 (*C*H$_3$), 122.3 (*C*H=CHCH$_3$), 122.8 (ArCH), 123.7 (C4a), 127.6 (ArCH), 128.7 (ArCH), 129.5 (ArCH), 139.6 (C8a), 140.1 (CH=*C*HCH$_3$), 149.6 (C4), 154.2 (C2). *Anal*. Calcd. for $C_{12}H_{12}N_2O$: C, 71.98; H, 6.04; N, 13.99. Found: C, 71.85; H, 5.87; N, 13.51 %.

***Method B*: From *E*-*N*-[2-[hydroxyethanimodyl]phenyl]-2-butenamide, (5b).** A solution of **5b** 0.20 g (0.92 mmol) was allowed to heat at reflux in dry ^{t}BuOH (50 ml) for 9 h in the presence of 2M HCl (1.84 ml). The ^{t}BuOH was removed under reduced pressure and the residue dissolved in DCM (50 ml). It was washed with water (3 x 30 ml) and the organic layer dried over $MgSO_4$. The DCM was removed under reduced pressure and the resulting crude product purified by flash column chromatography (SiO_2, ether). The title nitrone **6b** was isolated as a yellow solid 0.18 g (100%).

2-[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 Py.HCl 0.16 g (0.99 mmol). The solution was cooled and neutralised by the addition of $NaHCO_3$ 0.20 g (2.00 mmol). The solvent was removed under reduced pressure. The residual oil was dissolved in DCM (50 ml) and washed with water (3 x 40 ml). The organic layer was dried over $MgSO_4$. The DCM was removed under reduced pressure to give the crude product as an oil which was purified by flash column chromatography (SiO_2, ether). The pure product was isolated as a brown oil 0.13 g (51%); ir: ArCH 2929, C=C 1613, C=N 1562 cm^{-1}; ^1H nmr: δ 1.13 (t, 3H, OCH$_2$C*H*$_3$, *J* = 7.0 Hz), 1.33 (d, 3H, CH$_3$, *J* = 6.2 Hz), 2.88 (s, 3H, C*H*$_3$), 3.25 (dd, 1H, 1 x H CH$_2$, *J* = 14.8, 6.2 Hz), 3.60 (m, 3H, OC*H*$_2$CH$_3$ and 1 x H CH$_2$), 4.30 (m, 1H, CH), 7.65 (m, 1H, ArH), 7.75 (m, 1H, ArH), 7.90 (m, 1H, ArH), 7.98 (m, 1H, ArH); ^{13}C nmr: δ 11.9 (CH$_3$), 14.5 (OCH$_2$*C*H$_3$), 19.5 (C3^1), 39.2 (CH$_2$), 63.0 (O*C*H$_2$CH$_3$), 70.8 (C2^1), 122.1 (ArCH), 122.3 (C4a), 127.6 (ArCH), 127.8 (ArCH), 129.7 (ArCH), 138.7 (C8a), 149.6 (C4), 156.2 (C2). *Anal*. Calcd. for $C_{14}H_{18}N_2O_2$: C, 68.27; H, 7.37; N, 11.38. Found C, 68.77; H, 7.40; N, 11.41 %.

2-[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 $NaHCO_3$ 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 $MgSO_4$. The DCM was removed under reduced pressure to give the crude product as an oil which was purified by flash column chromatography (SiO_2, ether). The isolated product was a cream solid 0.14 g (62%), mp 73-74 °C (ether); ir: ArCH 2975, C=C 1611, C=N 1562 cm^{-1}; ^1H nmr: δ 1.33 (d, 3H, 3^1-CH$_3$, *J* = 6.2 Hz), 2.88 (s, 3H, CH$_3$), 3.33 (dd, 1H, 1H from CH$_2$, *J* = 14.8, 5.9 Hz), 3.38 (s, 3H, OCH$_3$), 3.60 (dd, 1H, 1H from CH$_2$, *J* = 14.8, 6.8 Hz), 4.24 (m, 1 H, 2^1-CH), 7.62 (m, 1H, ArH), 7.71 (m, 1H, ArH), 7.88 (d, 1H, ArH, *J* = 8.2 Hz), 7.97 (m, 1H, ArH); ^{13}C nmr: δ 12.9 (CH$_3$), 19.7 (C3^1), 40.1 (CH$_2$),

56.3 (OCH_3), 73.6 (C2[1]), 123.1 (ArCH), 123.4 (C4a), 128.7 (ArCH), 128.9 (ArCH), 130.7 (ArCH), 139.8 (C8a), 150.7 (C4), 157.2 (C2). *Anal.* Calcd. for $C_{13}H_{16}N_2O_2$: C, 67.22; H, 6.94; N, 12.06. Found: C, 67.06; H, 7.06; N, 11.90 %).

2-[[*E*]-2-Phenylvinyl]quinazoline 3-oxide, (15a). A solution of [2*E*]-*N*-{[[*E*]-[hydroxyimino]methyl]phenyl}-3-phenylacrylamide **1a** [2] 0.20 g (0.75 mol) in EtOH (20 ml) was allowed to heat to reflux for 1 h in the presence of HCl (26 ml, 18%). The solvent was removed under reduced pressure and the residue dissolved in DCM (50 ml) and washed with 2 *M* solution of $NaHCO_3$. The DCM extract was dried over $MgSO_4$ and the solvent removed under reduced pressure. The crude oil was purified by flash column chromatography (SiO_2, hexane:ether 6:4) to afford a yellow solid 0.58 g (93%), mp 182-185 °C (hexane:ether); ir: CH=CH 3057, C=C 1626, C=N 1574 cm^{-1}; ^1H nmr (benzene-d_6): δ 6.62 (d, 1H, ArH, *J* = 8.2 Hz), 6.83 (m, 1H, ArH), 6.96 (m, 4H, ArH), 7.43 (m, 2H, ArH), 7.77 (d, 1H, ArH, *J* = 8.4 Hz), 8.19 (s, 1H, CH=N), 8.37 (d, 1H, CH=C*H*-Ph, *J* = 16.2 Hz), 8.63 (d, 1H, C*H*=CH-Ph, *J* =16.2 Hz); ^{13}C nmr (benzene-d_6): δ 117.7 (*C*H=CH-Ph), 124.2 (ArCH), 124.5 (C4a), 128.6 (ArCH), 128.8 (ArCH), 128.9 (2 x ArCH), 129.5 (2 x ArCH), 130.1 (ArCH), 130.7 (ArCH), 136.8 (ArC), 139.7 CH aldehyde, 140.8 (C8a), 141.6 (CH=*C*H-Ph), 155.9 (C2). *Anal.* Calcd. for $C_{16}H_{12}N_2O$: C, 77.39; H, 4.87; N, 11.28. Found: C, 77.55; H, 4.87; N, 11.03 %.

[2*E*]-*N*-[2-[Hydroxymethyl]phenyl]but-2-enamide, (12). A cooled suspension of [2-aminophenyl]methanol 5.49 g (0.05 mol) and sodium hydrogen carbonate 4.07 g (0.05 mol) in anhydrous DCM (50 ml) was treated with *trans*-crotonyl chloride 4.68 g (0.05 mol). The resulting mixture was left to stir for 1 h at room temperature. The organic layer was washed with water (3 x 50 ml) dried over $MgSO_4$ and the solvent removed under reduced pressure. The crude product was purified by flash column chromatography (SiO_2, DCM:ether 9:1) to yield the title product as a white solid 1.79 g (47%), mp 105-108 °C (DCM:ether); ir: OH/NH 3255, NHCO 1668 cm^{-1}; ^1H nmr: δ 1.87 (dd, 3H, CH_3, *J* = 6.9, 1.6 Hz), 3.24 (br s, 1H, OH/NH), 4.64 (2 s, H, CH_2), 5.62 (dq, 1H, C*H*=CHCH$_3$, *J* = 15.2, 1.6 Hz), 6.89 (dq, 1H, CH=C*H*CH$_3$, *J* = 15.2, 6.9 Hz), 7.05 (m, 1H, ArH), 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); ^{13}C nmr: δ 17.9 (CH_3) 64.3 (CH_2), 122.5 (ArCH), 124.3 (ArCH), 125.8 (*C*H=CH-CH$_3$), 128.8 (ArCH), 128.9 (ArCH), 129.9 (ArC), 137.5 (ArC-N), 141.2 (CH=*C*H-CH$_3$), 164.6 (C=O). *Anal.* Calcd. for $C_{11}H_{13}NO_2$: C, 69.00; H, 6.85; N, 7.33. Found: C, 68.56; H, 6.76; N, 7.17%.

[2*E*]-*N*-[2-Formylphenyl]but-enamide, (13). A solution of **12** 3.60 g (0.02 mol) in anhydrous DCM (40 ml) was added to a suspension of pyridinum 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 (4 x 100 ml) and the washings passed through celite. The solvent was removed under reduced pressure and the solid purified by flash column chromatography (SiO_2, DCM:ether 9:1) to yield a brown oil (100%); ir: NH 3265, CHO 1687, NHCO 1610 cm^{-1}; ^1H nmr: δ 1.95 (d, 3H, CH_3, *J* = 6.4 Hz), 6.05 (d, 1H, C*H*=CHCH$_3$, *J* = 15.1 Hz), 7.02 (m, 1H, CH=C*H*CH$_3$), 7.23 (m, 1H, ArH), 7.63 (m, 2H, ArH), 8.82 (d, 1H, ArH, *J* = 8.3 Hz), 9.93 (s, 1H, CH), 11.22 (br s, 1H, NH); ^{13}C nmr: δ 18.4 (CH_3); 120.4 (ArCH); 122.1 (ArC); 123.2 (ArCH); 126.7 (*C*H=CHCH$_3$); 136.5 (ArCH); 136.6 (ArCH); 141.7 (ArC-N); 142.4 (CH=*C*HCH$_3$); 165.4 (C(O)N); 196.0 (CHO). *Anal.* Calcd. for $C_{11}H_{11}NO_2$: C, 69.83; H, 5.36; N, 7.40. Found: C, 69.43; H, 5.61; N, 7.47 %.

[2*E*]–*N*-{2-[[*E*]-[Hydroxyimino]methyl]phenyl}but-2-enamide, (14). A solution of **13** 3.70 g (0.02 mol), hydroxylamine hydrochloride 1.60 g (0.02 mol), and pyridine 2.07 g (0.02 mol) in EtOH (50 ml) was heated at reflux for 8 h. The EtOH was removed under reduced pressure and the resulting residue dissolved in DCM (50 ml) and washed with water (3 x 40 ml). The organic layer was dried over $MgSO_4$ and the DCM was removed under reduced pressure. The crude oxime was purified by flash column chromatography (SiO_2, hexane:ether 7:3) to afford a white solid 1.62 g (40%), mp 123-126 °C (hexane:ether); ir: NH/OH 3205, CH=CH 2976, NHCO 1677 cm^{-1}; ^1H nmr: δ 1.82 (s, 3H, CH_3), 5.94 (m, 1H, C*H*=CHCH$_3$), 6.97 (m, 1H, CH=C*H*CH$_3$), 7.11 (m, 1H, ArH), 7.23 (m, 1H, ArH), 7.36 (m, 1H, ArH), 8.26 (s, 1H, CH=N), 8.75 (d, 1H, ArH, *J* = 7.4 Hz), 8.90 (s, 1 H, OH/NH), 10.78 (br s, 1H, OH/NH); ^{13}C nmr: δ 18.0 (CH_3), 118.7 (ArC), 120.3 (ArCH), 123.2 (ArCH), 126.5 (*C*H=CHCH$_3$), 130.7 (ArCH), 132.0 (ArCH), 138.0 (ArC-N), 141.4 (CH=*C*HCH$_3$), 153.1 (C=N), 165.1 (C=O). *Anal.* Calcd. for $C_{11}H_{12}N_2O_2$: C, 64.69; H, 5.90; N, 13.70. Found: C, 64.36; H, 6.04; N, 13.52 %.

2-[[1*E*]-Prop-1-enyl]quinazoline 3-oxide, (15b). A solution of oxime **14** 0.10 g (0.49 mmol) and 18% HCl (4.4 ml) in THF (13 ml) was allowed to stir in an ice-bath for 30 min. prior to removal of the solvent under reduced pressure. The residue was dissolved in DCM followed by washing with a 2 *M* solution of $NaHCO_3$. The organic layer was dried over $MgSO_4$ and the DCM was removed under reduced pressure. Analysis of the crude reaction mixture by ^1H NMR spectroscopy showed evidence for the presence of aldehyde, oxime and the nitrone in a 0.2:1:4.2 ratio. Efforts to purify the mixture by flash column chromatography using various mobile phases failed to afford **15b** in a synthetically useful yield. A small quantity was obtained which was used for characterisation. **15b**, a yellow solid, mp 148-150 °C; ir: CH=CH 2966, C=C 1618, C=N 1576 cm^{-1}; ^1H nmr (DMSO-d_6): δ 2.06 (d, 3H, CH_3, *J* = 5.4 Hz), 7.38 (m, 2H, CH=CH-CH$_3$), 7.60 (m, 1H, ArH), 7.77 (m, 1H, ArH), 7.88 (m, 2H, ArH); ^{13}C nmr (DMSO-d_6): δ 19.1 (CH_3), 120.6 (*C*H=CH-CH$_3$); 123.9 (C4a); 125.2 (ArCH); 127.6 (ArCH): 129.2 (ArCH); 131.9 (ArCH); 140.2 (C8a); 140.7 (CH=*C*H-CH$_3$); 140.9 (CH); 153.9 (C2). *Anal.* Calcd. for $C_{11}H_{10}N_2O$: C, 70.95; H, 5.42; N, 15.04. Found C, 70.07; H, 5.45; N, 14.92 %.

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