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Bridgehead nitrogen heterocycles which contain the quinazoline moiety – synthesis and cycloaddition of 1,2-dihydroquinazoline 3-oxides

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A novel synthesis of 1,2-disubstituted 1,2-dihydroquinazoline 3-oxides **8** and the first ever examples of 1,3-dipolar trapping of these nitrones to homonuclear dipolarophiles is described. The new dipoles **8** reacted with *N*-methyl maleimide, generating diastereomeric adducts **14**–**16**. In the reaction between **8** and dimethyl acetylenedicarboxylate, primary cycloadducts **17** and/or stable rearrangement products, azomethine ylides **18**, are formed depending on the substitution pattern of the dipole. The structure of **18c** is unambiguously assigned by X-ray crystallographic analysis. An X-ray crystal structure determination is also presented for the cyclopropylisoxazoloquinazoline **22** formed by a [3 + 2] addition of **8a** to **21**, the dimethyl acetylenedicarboxylate tetramer.

Introduction

In connection with our studies on the formation of nitrones from oximes,[1–3] we now report the preparation of 1,2-disubstituted 1,2-dihydroquinazoline 3-oxides from *o*-aminoarylaldoximes.

Prior to the current work there have been no reported examples of the formation of aldonitrones of the 1,2-dihydroquinazoline skeleton; however, several examples of related ketonitrones and aminonitrones are known. Cyclocondensations between 2-aminobenzo(aceto)phenone oximes and dichloroethyl ethers,[4] chloroethylacetoacetate,[5] ketones[6] or aldehydes[7,8] have furnished variously substituted 1,2-dihydroquinazoline ketonitrones. The 1,2,5,6-tetrahydropyrimidine 3-oxides **1**, monocyclic analogues of quinazoline 3-oxides, have been prepared by cyclocondensation of β-benzylaminoketoximes with aldehydes.[9]

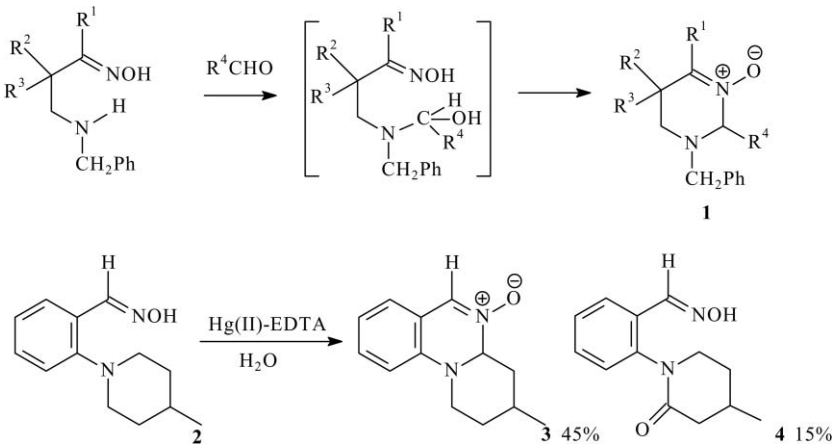
Corresponding aminonitrones have been formed from *o*-aminobenzamidoximes by cyclocondensation either to imines formed *in situ* upon reaction with an aldehyde[10] or to transient iminium ions generated by dehydrogenation [Hg(II), EDTA] of a tertiary amine.[11,12] The same laboratory have also reported formation of the tricyclic *N*-oxides **3** with a perhydro-pyrido or -pyrrolo ring fused to the 1,2-*a* edge of the quinazoline nucleus. The cyclic nitrones were generated, in the presence of Hg(II)-EDTA complex, from appropriately substituted benzaldoximes in a type of intramolecular Mannich reaction,[13–15] for some substrates, *e.g.* **2**, lactams **4** accompany the cyclic nitrones **3** as minor reaction products.

Results and discussion

Substrate preparation

The targeted *o*-aminobenzaldehydes **6a**, **b** and **c** were prepared by a nickel catalysed addition of the appropriate organozinc reagent to 2,1-benzisoxazole **5** as described in the literature.[16] The *p*-CNC_6H_4 analogue **6d** was prepared in 77% yield in a parallel manner. During the synthesis of **6c** and **6d**, by-products isolated in 12 and 6% yield respectively are identified as the 4,4′-disubstituted biphenyl derivatives **9a** and **9b**.[17]

Reaction between the *o*-aminobenzaldehydes **6** and $NH_2OH{\cdot}HCl$ (C_5H_5N, EtOH, 80 °C, 12 h) proceeded smoothly to afford the oximes **7** as single geometrical isomers in solution in $CDCl_3$. Oximes **7a**, **b** and **d** were isolated in good yields as crystalline solids. The yield of **7c** was somewhat lower with the desired oxime (60%) being accompanied by 2-methoxyacridine (11%). The formation of both 2- and 4-methoxyacridine following TFA treatment of 2-methoxydiphenylamine 2-carboxaldehyde **6c** has previously



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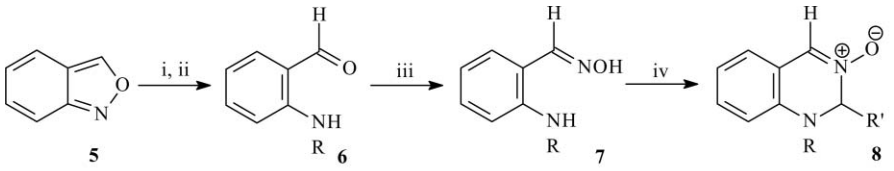
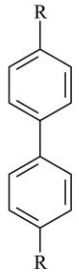


a. R = Me
b. R = Ph
c. R = p-$MeOC_6H_4$
d. R = p-CNC_6H_4

a. R = Me	R' = Ph
b. R = Ph	"
c. R = p-$MeOC_6H_4$	"
d. R = p-CNC_6H_4	"
e. R = p-$MeOC_6H_4$	R' = p-$NO_2C_6H_4$
f. .R = p-$MeOC_6H_4$	R' = p-$MeOC_6H_4$

i., RLi, $ZnCl_2$, THF, -78 °C to rt; ii., cat $Ni(acac)_2$,
iii., $NH_2OH.HCl$, C_5H_5N, EtOH, 80 °C, 12 h; iv., R'CHO



9a. R = OMe
9b. R = CN

been reported.[16] It is likely that the pyridinium hydrochloride generated during the oximation of **6c** is responsible for inducing cyclisation of unreacted aldehyde, so leading to the acridine by-product.

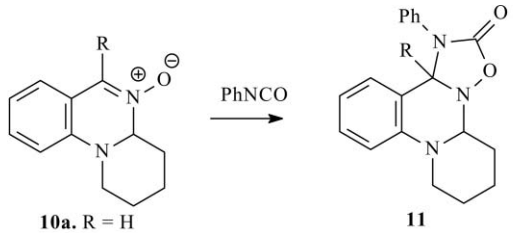
Cyclocondensation of the *o*-aminobenzaldoximes **7a** and **b** with benzaldehyde was initially attempted under conditions previously found to be successful for analogous amino oximes, *viz.* fridge temperature in solution in $Et_2O/EtOH$.[10] However, no reaction occurred between **7a** and **b** and benzaldehyde at 4 °C. Upon heating the reactants in boiling EtOH, evidence for the formation of **8a** and **b** could be seen in the ^1H NMR spectrum of the crude reaction mixture; however, the desired reaction was overshadowed by the formation of a number of ethoxy addition products. Successful generation of the quinazoline 3-oxides **8a**–**d** resulted when the components were heated at 80 °C using benzaldehyde (5 equiv.) as reactant and solvent. Reaction duration and product yield varied with the nature of the amino substituent. The *N*-methyl- and *N*-(*p*-methoxyphenyl)-substituted substrates **7a** and **7c** reacted fastest reaching completion after 16 h; the *N*-phenyl substrate **7b** required 72 h for full reaction whilst the *p*-cyanophenyl group on **7d** significantly retarded progress and reaction had only reached 77% oxime conversion after 72 h. The quinazoline 3-oxides **8** were isolated by flash column chromatography.

In an effort to probe the probe the sensitivity of the reaction to the nature of the aldehyde component, condensation between 2-(4-methoxyanilino)benzaldehyde oxime **7c** and either *p*-nitrobenzaldehyde or *p*-methoxybenzaldehyde was investigated. Both nitrobenzaldehyde and the oxime remained solids at 80 °C and ^1H NMR spectral analysis confirmed that no reaction occurred between the components at this temperature. At 120 °C the reactants formed a molten solid, and following 4 h of heating complete conversion to **8e** was observed. The same oxime **7c** reacts with *p*-methoxybenzaldehyde rather sluggishly at 80 °C and after 236 h **8f** isolated in 49% yield, starting oxime was recovered in 32% yield. Reaction progressed faster at 120 °C having reached the same level of oxime conversion after 84 h, when ^1H NMR spectral data indicated a 1 : 2 mixture of oxime : nitrone **7c** : **8f**.

In order to permit direct comparison between the nature of the *o*-amino substituent on the oxime substrate **7** and the condensing aldehyde, the reaction of **7c** with benzaldehyde was repeated at 120 °C. After 6.5 h of heating almost quantative conversion to **8c** was found. Thus, as expected, the more electron-rich the *o*-amino oxime substituent and the more electron-poor the condensing aldehyde the faster the cyclocondensation reactions leading to **8**.

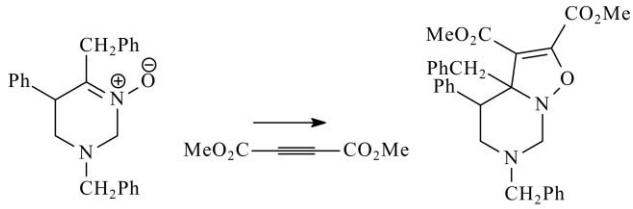
Cycloaddition to quinazoline 3-oxides

The reactivity of 1,2-dihydroquinazoline 3-oxides has not been extensively investigated. Aromatisation,[18,19] ring expansion[5,20] and hydrolysis[6] of ketonitrones has been demonstrated, whilst Dimroth rearrangements to isomeric 1,2-dihydro-4-quinaxolone oximes are facile with aminonitrones.[10] The trapping of **10a** with phenyl isocyanate represents the only reported example of 1,3-dipolar cycloaddition to 1,2-dihydroquinazoline-3-oxides.[13] The same heterodipolarophile trapped the amidonitrone **10b**[11] furnishing **11b**. Aside from these two reactions there has been no exemplification of the 1,3-dipolar character of the 1,2-dihydroquinazoline 3-oxide skeleton. However, a related reaction is the trapping of the tetrahydropyrimidine *N*-oxide **12** with dimethyl acetylenecarboxylate (4 h, $CHCl_3$), furnishing **13** (75%) as a single diastereomeric cycloadduct.[9]

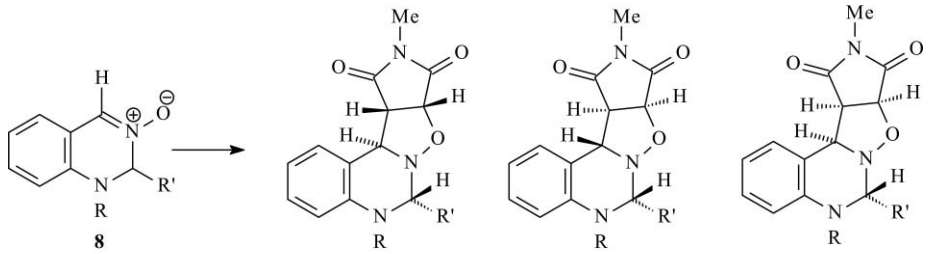


10a. R = H
10b. R = NMe_2

11



12 **13**



a. R = Me, R' = Ph; b. R = Ph, R' = Ph; c. R = p-$MeOC_6H_4$, R' = Ph;
d. R = p-CNC_6H_4, R' = Ph; e. R = p-$MeOC_6H_4$, R' = p-$NO_2C_6H_4$

Reaction between the quinazoline 3-oxides **8** and *N*-methyl maleimide proceeded under mild conditions (CH_2Cl_2, rt, 18 h) to afford, with varying selectivity, diastereomeric cycloadducts **14**–**16**. The relative stereochemistry of the adducts arising from reaction of **8b** was established by nuclear Overhauser effect difference spectra (nOeds) studies and that of the others by analogy.

The major diastereomer **14b** (55%) displays a 3.6% enhancement on the signal for H-11b following irradiation of H-11a, no cross-ring enhancements between H-6 and any of H-8a, H-11a or H-11b are found. The intermediate isomer **15b** (35%) displays a 2.8% enhancement on the signal representing H-11b following irradiation of H-11a, and mutual cross-ring enhancements are observed between H-6 and H-11b. The minor isomer **16b** (10%) shows no cross-ring enhancements between H-6 and any of H-8a, H-11a or H-11b; however, there is an 8.5% enhancement on the signal for H-11a following irradiation of H-11b. These observations imply that the major product **14b** is the product of an *exo*-addition of the dipolarophile to the top face of the dipole.† The intermediate adduct **15b** arises from an *exo*-addition of the dipolarophile to the lower face of the dipole. The minor adduct **16b** is a product of an *endo*-addition to the top face of the dipole.

Within each family of diastereomeric cycloadducts **14**–**16a**–**e** a distinct pattern can be identified in the ^{1}H NMR resonance positions for the non-aromatic protons *viz.* H-6, H-8a, H-11a and H-11b. Thus, for all the major adducts **14**, H-11a resonates between 3.77 and 3.84 ppm; H-11b resonates between 4.47 and 4.58 ppm; and H-8a resonates between 4.77 and 4.87 ppm. For the adducts **15** the H-11b signal experiences a downfield shift of *ca.* 0.7 ppm with respect to the corresponding signal in the diastereomers **14**. The proton with the most significant difference in resonance position between adducts **14** and **16** is H-11a which appears *ca.* 0.4 ppm downfield in the adducts **16** with respect to **14**.

The similarity between the ^{1}H NMR spectral data of the adducts **14a**,**c**–**e**, **15a**,**c**–**e** and **16a**,**c**–**e** with **14b**, **15b** and **16b** suggests that each diastereomer has a favoured conformation in solution and permits extrapolation of the nOeds data acquired for the latter to complete the assignment of the relative stereochemistry of the former.

Reaction between the dipoles **8** and dimethyl acetylenedicarboxylate also proceeded to completion upon stirring an equimolar ratio of the reactants in CH_2Cl_2 at rt for 18 h. The reaction products varied with the nature of the *N*-1 substituent on the dipole. All the *N*-1 aryl substrates **8b**–**e** reacted to afford primary cycloaddition products **17b**–**e**, accompanied, in the cases of **8b** and **8c**, by secondary products **18b**,**c**. The *N*-1 methyl derivative **8a** reacted rather differently.

† The 3-Si,4-Re face of the quinazoline 3-oxides is designated as the top face.

Analysis of the ^{1}H NMR spectral data of the crude mixture following reaction between **8c** and dimethyl acetylenedicarboxylate indicated the presence of two new reaction products. Purification by flash column chromatography afforded pure samples of each. The major product (32%), a red powder, was characterised as the primary cycloaddition product **17c**. No enhancements were observed on either H-5 or H-10b upon irradiation of the other, thus it is tentatively proposed that the relative stereochemistry of **17c** is as shown in the diagram.

The minor product (24%), a red crystalline solid, was unambiguously identified by single crystal X-ray analysis as the stable bicyclic azomethine ylide **18c** (Fig. 1). There is

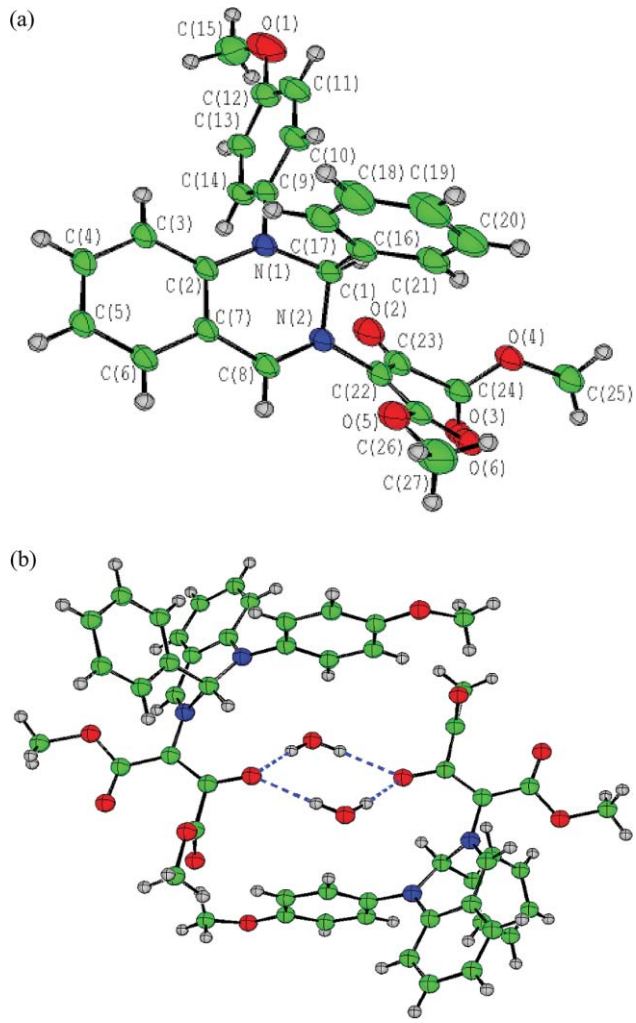


Fig. 1 X-Ray crystallographic presentation of **18c**: (a) showing monomer unit, and (b) showing water of crystallization and H-bonded dimers.

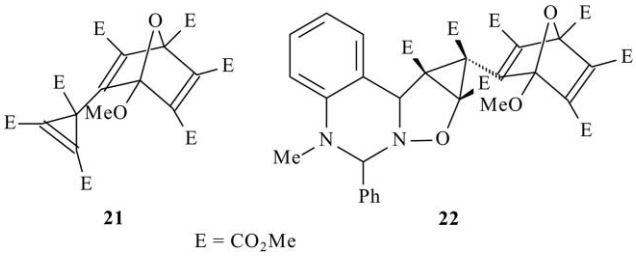
water of crystallization in the ylide structure. The crystal structure contains H-bonded dimers with the water molecules H-bonded to the keto-carbonyl oxygen atom O(2) [Fig. 1(b)]. The determination of the structure of **18c** is significant since, in as far as we can gather to-date, only a handful of azomethine ylides have been characterised in this way.[21–27] The C–N bonds of the dipolar system differ significantly in length with the N(2)–C(22) bond [1.443(2) Å] being close to a typical $^{sp^3}$N–C$^{sp^3}$ bond (1.48Å) whilst the N(2)–C(8) bond [1.298(3) Å] is slightly shorter than a typical C=N double bond. These measurements suggest strong bond localisation, a feature characteristic of those isolable azomethine ylides for which X-ray structural analysis has been performed.[21–27] A twist angle of 64.5° between the planes defined by C(8)–N(2)–C(1) and C(22)–C(23)–C(26) further testifies to the low degree of conjugative interaction between the iminium and the anionic functionalities of the dipolar system. The lack of π-conjugation coupled with the non-planarity of the dipole unit suggest a role for steric features and/or electronic interactions at the ionic centres as the driving force(s) for stabilisation of **18c**. These structural parameters also call into question the classification of **18c** as a 1,3-dipole and experiments are currently on-going to probe this hypothesis.

Azomethine ylides are widely recognised as key intermediates in a variety of thermal rearrangements of 4-isoxazolines;[28] however, aside from when the C=N bond is part of an aromatic system, the ylides have seldom been observed to be isolable. Exceptions include an example where the C=N moiety is part of a 3,4-dihydroisoquinoline structure[29] or where the C atom of the C=N unit bears a phenyl or styryl group.[30,31] Eberbach and co-workers have recently reported the first examples of isoxazolines which transform to stable, isolable, azomethine ylides having stabilising groups only at one end of the dipole.[21,32] To the best of our knowledge, compounds **18** represent a new type of stable azomethine ylide where the C=N moiety is part of a dihydroquinazoline ring system.

The *N*-1 phenyl dipole **8b** reacted in a parallel fashion to that observed for **8c** and the primary cycloaddition product **17b** was isolated with the stable dipole **18b** in 63 and 14% yield respectively. It was subsequently found that smooth conversion between **17b**,**c** and **18b**,**c** could be achieved upon stirring the primary adducts in solution in MeOH.

Reaction between dipoles **8d** and **8e** and dimethyl acetylenedicarboxylate furnished only the primary cycloaddition products **17d** (quantative yield) and **17e** (79%). The *N*-1 methyl derivative **8a** reacted rather differently from its aryl counterparts with dimethyl acetylenedicarboxylate. No primary cycloaddition products were found in the reaction mixture. ^{1}H NMR spectral analysis indicated the presence of one main product together with a number of minor products. Purification by flash column chromatography gave a pure sample of the main product, a red crystalline solid, characterised as the stable azomethine ylide **18a** (60%). A number of minor products with varying stability were also isolated but we are not in a position to confirm their structure.

Significantly, during the isolation of **18a** a colourless crystalline solid fell from the early column fractions following standing at rt, and this material was subsequently found by X-ray crystal structure analysis to be the cyclopropaisoxazoloquinazoline **22** (5%) shown in Fig. 2. Dimethyl acetylenedicarboxylate is known to undergo spontaneous tetramerisation[33] and it may be the case that a small amount of the tetramer was indeed present in the starting ester – a situation previously alluded to in the literature.[34] Whilst [4 + 2]-cycloaddition of cyclopentadienes to the dimethyl acetylenedicarboxylate tetramer have previously been noted[35] to the best of our knowledge the formation of **22** represents the first example of a [3 + 2]-cycloaddition to the DMAD tetramer **21**. Indeed, the formation of **22** represents only the second publication of a cycloaddition reaction between a nitrone and a cyclopropene moiety[36] and only the third report on the formation of cyclopropyl fused isoxazolidines.[37]



Rearrangement of 4-isoxazolines to azomethine ylides is well known and it is accepted that mechanistically the transformation proceeds in a concerted fashion by way of an acyl aziridine intermediate. If **17** rearranges to **18** directly by way of the aziridine **19** (Fig. 3, Path A) it is difficult to explain the relative stability of the *N*-6 aryl derivatives **17b**–**e** with respect to the *N*-6

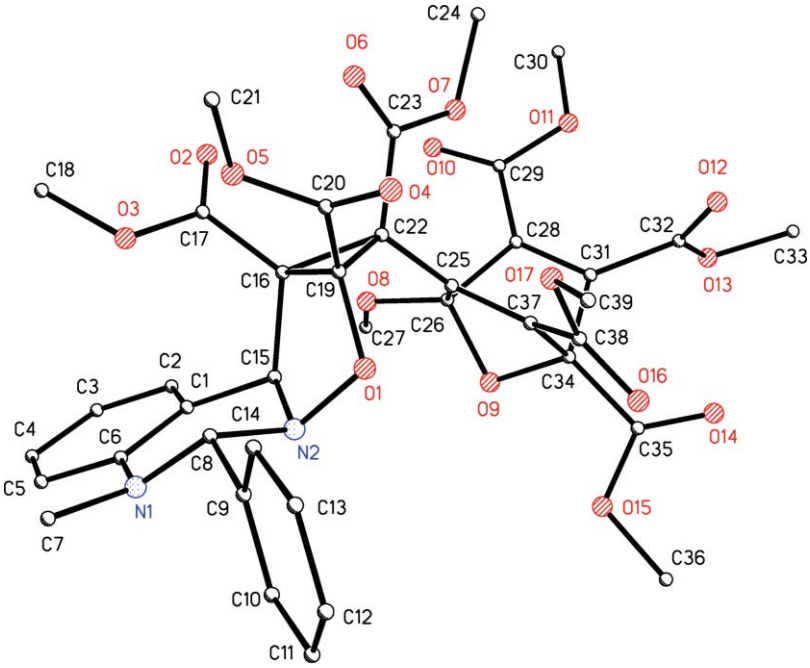


Fig. 2 X-Ray crystallographic presentation of **22**.

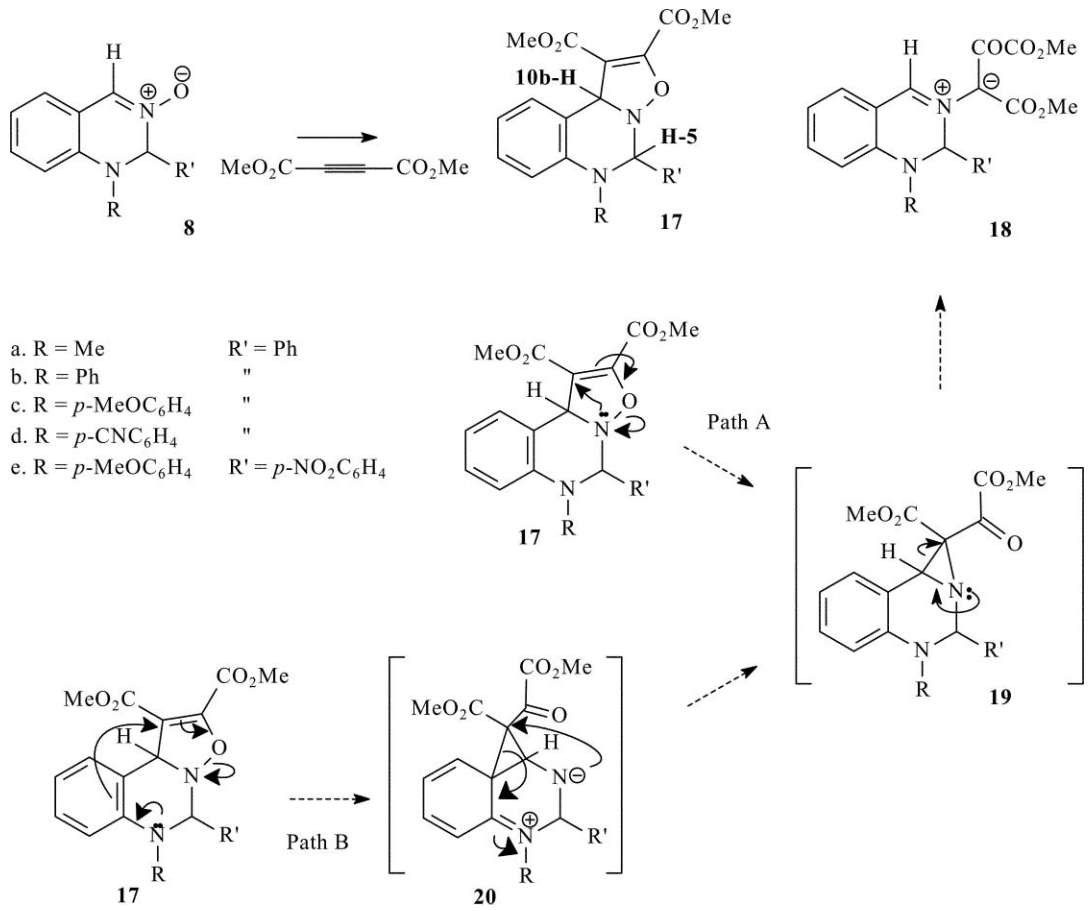


Fig. 3 Proposed mechanistic origin of ylides **18** from the cycloadducts **17**.

methyl analogue **17a**. We suggest that an alternative rearrangement pathway may also operate. A two-step process, shown in Fig. 3 (Path B), invoking **20** as a precursor to the aziridine **19** accounts for the increase in lability of the isoxazoline ring with increasing electron releasing power on the *N*-6 substituent. The proposal of the intermediary cyclopropyl fused ring skeleton **20** is in parallel with Freeman's ring contraction mechanism for isoxazolobenzodiazepines[38]

Conclusions

It has been shown that 1,2-dihydroquinazoline 3-oxides **8** are readily prepared from *o*-aminoarylaldoximes and aryl aldehydes in a cyclocondensation reaction. For the first time this family of heterocyclic *N*-oxides have been demonstrated to have 1,3-dipolar character being trapped, under mild reaction conditions, by *N*-methyl maleimide affording the diastereomeric primary cycloaddition products **14**–**16**. In reaction with dimethyl acetylenedicarboxylate the products comprise primary **17** and or secondary **18** products of cycloaddition depending on the nature of the *N*-1 substituent. The dipole **8a** has also been trapped by the cyclopropene moiety of the dimethyl acetylenedicarboxylate tetramer **21**.

Experimental

Melting points were determined on a Stuart 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, aluminium-backed and coated with silica gel 60 F_{254} indicator. Samples were located by UV illumination using a portable UVtec lamp ($\lambda = 254$ 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, and samples were prepared as KBr discs.

Preparation of the 2-aminobenzaldehydes 6

The substrates **6a** (1.30 g, 90%), **6b** (1.70 g, 86%) and **6c** (1.40 g, 65%) were prepared by addition of the appropriate organozinc reagent to 2,1-benzisoxazole by the method of Baum *et al*. In each case the ^{1}H NMR spectral data agree with those published.[16] 4′-Methoxy-[1,1′-biphenyl]-4-yl methyl ether **9a** (0.26 g, 12%) was formed as by-product during the preparation of **6c**; the ^{1}H NMR spectral data of isolated **9a** agree with the literature.[17]

4-(2-Formylanilino)benzonitrile 6d

To a solution of 4-bromobenzonitrile (3.66 g, 20 mmol) in anhydrous THF (25 cm^3) under nitrogen at −78 °C was added dropwise a solution of 1.6 M *n*-butyllithium in hexane (12.5 cm^3, 20 mmol). The resulting suspension was added rapidly, *via* a cannula (18 gauge double tipped needle), to a stirred slurry of anhydrous $ZnCl_2$ (3.41 g, 25 mmol) in THF (75 cm^3) under nitrogen at 0 °C. When the solution had warmed to rt, 2,1-benzisoxazole (10 mmol) in THF (10 cm^3) was added followed by anhydrous $Ni(acac)_2$ (1.00 g, 4 mmol) in THF (20 cm^3). Reaction progress was monitored by periodically working up 1 cm^3 aliquots and observing the loss of the starting 2,1-benzisoxazole by TLC analysis. Upon completion the reaction was quenched with 6 M HCl (5 cm^3). The reaction mixture was

poured into water (100 cm^3) and extracted with diethyl ether (2 × 100 cm^3). The ether extracts were combined, washed with water (50 cm^3) and concentrated under reduced pressure to give the crude product. Purification by flash column chromatography (hexane–diethyl ether; 9 : 1) afforded the pure aldehyde as a yellow crystalline solid (1.70 g, 77%) along with [1,1′-biphenyl]-4,4′-dicarbonitrile **9b** (0.10 g, 6%). The ^{1}H NMR spectral data of the biphenyl agree with those reported.[17]

6d. Mp 102–104 °C (from EtOH). (Found: C, 75.13; H, 4.45; N, 12.46. $C_{14}H_{10}N_2O$ requires: C, 75.68; H, 4.50; N, 12.60%). δ_H: 10.21 (s, 1H, NH), 9.93 (s, 1H, HC=O), 7.63 (m, 3H, Ar-H, including 7.62, d, 2H, *J* 8.8, H-2′ and H-6′), 7.47 (m, 2H, Ar-H), 7.34 (d, 2H, *J* 8.8, H-3′ and H-5′), 7.02 (m, 1H, Ar-H). δ_C: 195.0 (C=O), 145.2, 144.9 (ArC–N), 137.2, 136.0, 134.0 121.3, 120.6 (Ar–CH), 120.0 (C≡N), (Ar–CH), 119.4 (Ar*C*-CHO), 114.5 (Ar–CH), 105.9 (Ar*C*–C≡N). IR/cm^{-1}: ν = 3424, 3108, 2844, 2764, 2219, 1659, 1595, 1529.

General procedure for the formation of 2-aminobenzaldoximes 7

A solution of the aldehyde (8 mmol), pyridine (8.1 mmol) and $NH_2OH{\cdot}HCl$ (8.1 mmol) were heated in boiling EtOH (50 cm^3) for 18 h. Following evaporation of the solvent the residue was taken up in chloroform (50 cm^3) and extracted with water (3 × 40 cm^3). The combined organic extracts were dried over $MgSO_4$ and concentrated to yield the crude product which was purified by flash column chromatography or crystallization. 2-Methoxyacridine was isolated (11%) during preparation of **7c**.

2-Methylaminobenzaldehyde oxime **7a**[40] and 2-anilinobenzaldehyde oxime **7b**[41] are known compounds; ^{1}H NMR spectral data of the prepared samples agree with published data.

2-(4-Methoxyanilono)benzaldehyde oxime 7c. White crystalline solid (1.62 g, 60%), mp 90–92 °C (from diethyl ether and hexane). (Found: C, 68.90; H, 5.83; N, 11.35. $C_{14}H_{14}N_2O_2$ requires: C, 69.42; H, 5.42; N, 11.62%). δ_H: 8.63 (br, s, 1H, NH/OH), 8.29 (s, 1H, HC=N), 7.16 (m, 4H, Ar-H including d at 7.16, 2H, *J* 8.8, H-3′ and H-5′), 7.00 (m, 1H, Ar–H), 6.90 (d, 2H, *J* 8.8, H-2′ and H-6′), 6.73 (m, 1H, Ar–H), 3.82 (s, 3H, OCH_3). δ_C: 156.8 (ArC–O), 154.1 (HC=N), 145.9, 134.2 (ArC–N) 133.2, 130.9, 125.9 (Ar–CH), 117.3 (ArC-2′ and 6′) 115.1 (Ar*C*–C=NOH), 115.0, 112.9 (Ar–CH), 56.0 (OCH_3).

[42,43]

2-Methoxyacridine. Colourless crystalline solid (0.13 g, 11%) mp 89–91 °C (from diethyl ether and hexane). δ_H: 8.56 (s, 1H, C=CH), 8.19 (d, 1H, *J* 8.6, Ar–H), 8.12 (d, 1H, *J* 8.6, Ar–H), 7.92 (d, 1H, *J* 8.4, Ar–H), 7.70 (m, 1H, Ar–H), 7.48 (m, 2H, Ar–H), 7.11 (d, 1H, *J* 2.6, Ar–H), 3.95 (s, 3H, OMe).

4-{2-[(Hydroxyimino)methyl]anilino}benzonitrile 7d. Yellow crystalline solid (1.00 g, 72%), mp 166–170 °C (from toluene). (Found: C, 71.08; H, 4.74; N, 17.18. $C_{14}H_{11}N_3O$ requires: C, 70.88; H, 4.64; N, 17.72%). δ_H: 9.06 (br, s, 1H, NH/OH), 8.26 (s, 1H, HC=N), 7.53 (m, 2H, Ar–H), 7.44 (m, 2H, Ar–H), 7.30 (m, 2H, Ar–H), 7.21 (m, 2H, Ar–H), 6.98 (m, 1H, Ar–H). δ_C: 153.5 (CH=N), 146.5, 141.1 (ArC–N), 134.1, 133.3, 130.7, 121.2 (Ar–CH), 119.9, 118.9 (C≡N and Ar*C*–C=N), 118.2, 116.6 (Ar–CH), 103.9 (Ar*C*–C≡N). IR/cm^{-1}: ν = 3335, 2222, 1625, 1610, 1591, 1528.

1-Methyl-2-phenyl-1,2-dihydroquinazolin-3-ium-3-olate 8a

2-Methylaminobenzaldehyde oxime **7a** (6.8 mmol, 1.00 g) was stirred with benzaldehyde (34 mmol, 3.60 g) at 80 °C for 16 h. Purification by flash column chromatography (diethyl ether) afforded **8a** as a green solid (1.30 g, 80%), mp 132–136 °C (from diethyl ether and hexane). (Found: C, 75.61; H, 5.83; N, 11.90. $C_{15}H_{14}N_2O$ requires: C, 75.63; H, 5.88; N, 11.76%). δ_H: 7.68 (s, 1H, HC=N), 7.35 (m, 6H, Ar–H), 7.04 (dd, 1H, *J* 7.6 and 1.5, Ar–H), 6.81 (ddd, 1H, *J* 8.5, 8.5 and 0.9, Ar–H), 6.68 (d, 1H, *J* 8.2, Ar–H), 5.95 (s, 1H, H–2), 2.93 (s, 3H, Me). δ_C: 141.0 (C-8a), 135.5 (C-1′), 132.0 (CH=N), 131.8, 130.1, 129.2, 129.0, 128.8, 127.0, 126.4, 119.6 (Ar–CH), 116.6 (C-4a), 111.7 (Ar–CH), 86.9 (C-2), 36.1 (NMe).

1,2-Diphenyl-1,2-dihydroquinazolin-3-ium-3-olate 8b

2-Phenylaminobenzaldehyde oxime **7b** (1.90 g, 9 mmol) was stirred with benzaldehyde (4.80 g, 45 mmol) at 80 °C for 72 h. Purification by flash column chromatography (diethyl ether) afforded **8b** as a yellow solid (2.10 g, 76%), mp 68–70 °C (from diethyl ether and hexane). (Found: C, 75.25; H, 5.43; N, 8.44. $C_{20}H_{16}N_2O[H_2O]$ requires: C, 75.47; H, 5.66; N, 8.81%). δ_H: 7.73 (s, 1H, CH=N), 7.68 (m, 2H, Ar–H), 7.32 (m, 5H, Ar–H), 7.23 (m, 2H, Ar–H), 7.14 (m, 4H, Ar–H), 6.98 (m, 1H, Ar–H), 6.51 (s, 1H, H-2). δ_C: 145.1 (C-8a), 137.5 (C-1′), 135.7 (C-7′), 132.5 (CH=N), 132.5, 130.3, 130.1, 129.9, 129.6, 129.3, 128.7, 128.2, 126.6, 126.0, 124.8, 122.4, 121.9 (Ar–CH), 119.9 (C-4a), 118.8 (Ar–CH), 86.2 (C-2). IR/cm^{-1}: ν = 3436 3034, 2833, 1605, 1596, 1560, 1523, 1509, 1488, 1461.

1-(4-Methoxyphenyl)-2-phenyl-1,2-dihydroquinazolin-3-ium-3-olate 8c

The oxime **7c** (408 mg, 1.7 mmol) was stirred with benzaldehyde (8.4 mmol, 893 mg) for 16 h at 80 °C. Purification by flash column chromatography (diethyl ether) gave **8c** as a yellow solid (526 mg, 94%), mp 40 °C (from diethyl ether). (Found: C, 74.16; H, 5.42; N, 7.80. $C_{21}H_{18}N_2O_2[0.5H_2O]$ requires: C, 74.33; H, 5.60; N, 8.26%). δ_H: 7.71 (s, 1H, HC=N), 7.61 (m, 2H, Ar–H), 7.32 (m, 3H, Ar–H), 7.21 (m, 1H, Ar–H), 7.05 (m, 4H, Ar–H), 6.87 (m, 3H, Ar–H), 6.37 (s, 1H, CH), 3.79 (s, 3H, OCH_3). δ_C: 157.3 (ArC–O), 138.6, 137.9, 136.3 (Ar–C), 130.4 (Ar–CH), 130.1 (CH=N), 129.3, 128.7, 126.7, 125.9, 124.9, 121.4 (Ar–CH), 118.9 (C-4a), 117.5, 114.9 (Ar–CH), 86.6 (C-2), 55.5 (OCH_3). IR/cm^{-1}: ν = 3409, 3059, 2834, 1584, 1557, 1509, 1487, 1459.

1-(4-Cyanophenyl)-2-phenyl-1,2-dihydroquinazolin-3-ium-3-olate 8d

The oxime **7d** (152 mg, 0.64 mmol) was stirred with benzaldehyde (340 mg, 3.2 mmol) at 80 °C for 72 h. Purification by flash column chromatography afforded **8d** as a white solid (93.6 mg, 45%), mp 220–225 °C (from diethyl ether). (Found: C, 77.09; H, 4.62; N, 12.48. $C_{21}H_{17}N_3O$ requires: C, 77.54; H, 4.62; N, 12.92%). δ_H: 7.74 (s, 1H, CH=N), 7.60 (m, 4H, Ar–H), 7.32 (m, 4H, Ar–H), 7.18 (m, 5H, Ar–H), 6.51 (s, 1H, H-2). δ_C: 149.3 (C-8a), 135.6 (C-1′), 134.6 (C-7′), 134.2, 130.6 (Ar–CH), 130.0 (CH=N), 129.4, 126.8, 126.6, 124.7, 121.7, 120.8, 120.4 (Ar–CH), 119.0 (C-4a and C≡N), 107.3 (C-4′), 86.1 (C-2). IR/cm^{-1}: ν = 3396, 3057, 2216, 1598, 1586, 1556, 1506, 1486.

1-(4-Methoxyphenyl)-2-(4-nitrophenyl)-1,2-dihydroquinazolin-3-ium-3-olate 8e

The oxime **7c** (1.3 mmol, 315 mg) was stirred in with 4-nitrobenzaldehyde (980 mg, 6.6 mmol) at 120 °C for 4 h. Purification by flash column chromatography (diethyl ether–MeOH; 9.5 : 0.5) afforded **8e** as a yellow solid (0.50 g, 100%), mp 143–145 °C (diethyl ether and hexane). (Found: C, 66.83; H, 4.67; N, 11.08. $C_{21}H_{17}N_3O_4$ requires: C, 67.20; H, 4.40; N, 11.08%). δ_H: 8.17 (d, 2H, *J* 8.7, H-9′ and H-11′), 7.86 (d, 2H, *J* 8.7, H-8′ and H-11′), 7.76 (s, 1H, CH=N), 7.24 (m, 1H, Ar–H), 7.05 (d, 2H, *J* 8.0, H-2′ and H-6′) 6.99 (m, 3H, Ar–H), 6.88 (d, 2H, *J* 8.0, H-3′ and H-5′) 6.45 (s, 1H, 2-H), 3.81 (s, 1H, OCH_3). δ_C: 158.0 (ArC–O), 148.9 (ArC–NO_2), 143.4 (C-8a), 138.3, 138.2 (Ar–C), 131.2 (Ar–CH), 130.8 (CH=N), 128.3, 126.5, 125.1, 124.3, 122.7 (Ar–CH), 119.4 (C-4a), 118.7, 115.5 (Ar–CH), 86.4 (C-2), 56.0 (OCH_3). IR/cm^{-1}: ν = 3413, 3059, 2835, 1585, 1557, 1510, 1488, 1459.

1,2-Bis-(4-methoxyphenyl)-1,2-dihydroquinazolin-3-ium-3-olate 8f

The oxime **7c** (266 mg, 1.1 mmol) and *p*-methoxybenzaldehyde (750 mg, 5.5 mmol) were heated at 80 °C. Reaction progress reached its limit after 236 h (68% oxime consumption). Purification by flash column chromatography (diethyl ether–MeOH; 9.5 : 0.5) gave **8f** (192 mg, 49%) as a clear green oil. δ_H: 7.68 (s, 1H, CH=N), 7.52 (d, 1H, *J* 8.6, Ar–H), 7.18 (m, 1H, Ar–H), 7.06 (d, 2H, *J* 8.6, Ar–H), 7.00 (d, 1H, *J* 8.3, Ar–H), 6.91 (d, 1H, *J* 7.4, Ar–H), 6.88 (m, 4H, Ar–H), 6.30 (s, 1H, H-2), 3.80, 3.76 (2 × OCH_3).

5,10-Dimethyl-6-phenyl-5,8a,11a,11b-tetrahydropyrrolo[3′,4′:4,5]isoxazolo[2,3-*c*]quinazoline-9,11(6*H*,10*H*)-diones 14a, 15a and 16a

A solution of the nitrone **8a** (0.5 g, 2.1 mmol) and *N*-methyl maleimide (0.24 g, 2.1 mmol) in DCM (20 cm^3) was stirred at rt for 18 h. The solvent was removed under reduced pressure to give the crude reaction products, the ^{1}H NMR spectral analysis of which indicated the presence of three diastereomeric cycloadducts **14a**, **15a** and **16a** in a 5 : 6 : 1 ratio. Purification by flash column chromatography (DCM) followed by crystallisation (diethyl ether and hexane) afforded pure samples of **14a** (0.257 g, 37%) and **15a** (220 mg, 32%), and only a trace amount of the minor isomer **16a** was isolated.

Microanalytical data were obtained on a mixed sample of **14a** and **15a**. (Found: C, 67.55; H, 5.42; N, 11.65. $C_{20}H_{19}O_3N_3[0.5H_2O]$ requires: C, 67.03; H, 5.59; N, 11.73%).

14a. White powder, mp 220–223 °C (diethyl ether and hexane). δ_H: 7.25 (m, 4H, Ar–H), 7.11 (m, 3H, Ar–H), 6.76 (m, 2H, Ar–H), 5.57 (s, 1H, H-6), 4.77 (d, 1H, *J* 7.3, H-8a), 4.50 (s, 1H, H-11b), 3.77 (d, 1H, *J* 7.3, H-11a), 3.07 (s, 3H, NCH_3), 3.06 (s, 3H, NCH_3). δ_C: 175.7 (C=O), 175.6 (C=O), 143.1 (C-4a), 137.4 (C-1′), 129.3, 129.2, 128.9, 127.4, 127.3 (Ar–CH), 118.2 (C-11c), 117.4, 111.2 (Ar–CH), 77.4 (C-6), 75.6 (C-8a), 59.5 (C-11b), 56.5 (C-11a), 37.7 (NCH_3), 25.5 [C(O)NCH_3]. IR/cm^{-1}: ν = 3460, 2919, 2839, 1786, 1698, 1603, 1577, 1508, 1448.

*nOeds results for **14a**.* Irradiation of H-8a caused a 5.4% enhancement on the signal representing H-11a; irradiation of H-11a caused enhancements on H-8a (7.1%) and on H-11b (3.2%); irradiation of H-11b caused a 2.3% enhancement on H-11a.

15a. White powder, mp 220–225 °C (from diethyl ether and hexane). δ_H: 7.53 (m, 2H, Ar–H), 7.38 (m, 3H, Ar–H), 7.24 (m, 2H, Ar–H), 6.90 (m, 2H, Ar–H), 5.22 (s, 1H, H-6), 5.12 (s, 1H, H-11b), 4.77 (d, 1H, *J* 7.3, H-8a), 3.73 (d, 1H, *J* 7.3, H-11a), 3.02 [s, 3H, C(O)NCH_3], 2.70 (s, 3H, NCH_3). δ_C: 175.3 (C=O), 174.6 (C=O), 146.5 (C-4a), 137.0 (C-1′), 129.0 (Ar–CH), 128.6 (C-11c), 128.5, 127.3, 120.7, 119.3, 115.3 (Ar–CH), 77.9 (C-6), 75.5 (C-8a), 65.3 (C-11b), 55.7 (C-11a), 36.9 (NCH_3), 25.2 [C(O)NCH_3].

*nOeds results for **15a**.* Irradiation of H-8a caused a 7.1% enhancement on the signal representing H-11a; irradiation of H-11a caused enhancements on H-8a (7.3%) and on H-11b (2.1%); irradiation of H-11b caused a 2.5% enhancement on H-11a.

10-Methyl-5,6-diphenyl-5,8a,11a,11b-tetrahydropyrrolo[3′,4′:4,5]isoxazolo[2,3-*c*]quinazoline-9,11(6*H*,10*H*)-diones 14b, 15b and 16b

A solution of the nitrone **8b** (153 mg, 0.51 mmol) and *N*-methyl maleimide (57 mg, 0.51 mmol) was stirred in DCM (20 cm^3) at rt for 18 h. The solvent was removed under reduced pressure to give the crude reaction products, the ^{1}H NMR spectral analysis of which indicated a mixture of three isomeric cycloadducts **14b**, **15b** and **16b** in 2.5 : 2 : 1 ratio. Purification by flash column chromatography (DCM) followed by crystallization (diethyl ether and hexane) afforded **14b** (119 mg, 55%), **15b** (75 mg, 35%) and **16b** (24 mg, 10%).

Microanalytical and mp data were obtained on a sample of mixed diastereomers; white powder, mp 250–252 °C (from diethyl ether and hexane). (Found: C, 72.38; H, 5.08; N, 10.07. $C_{25}H_{21}N_3O_3$ requires: C, 72.99; H, 5.25; N, 10.50%).

14b. δ_H: 7.39 (m, 2H, Ar–H), 7.28 (m, 5H, Ar–H), 7.18 (m, 2H, Ar–H), 7.1 (m, 4H, Ar–H), 6.87 (m, 1H, Ar–H), 5.99 (s, 1H, H-6), 4.85 (d, 1H, *J* 7.2, H-9a), 4.55 (s, 1H, H-11b), 3.82 (d, 1H, *J* 7.2, H-11a), 3.11 (s, 3H, NCH_3). δ_C: 175.7 (C=O), 175.6 (C=O), 148.0 (C-4a), 140.9 (C-1′), 137.9 (C-7′), 129.8, 129.2, 128.9, 128.5, 127.8, 127.6, 124.5, 123.9 (Ar–CH), 121.1 (C-11c), 120.5, 118.1 (Ar–CH), 77.9 (C-6), 75.7 (C-8a), 60.00 (C-11b), 56.4 (C-11a), 25.6 (NCH_3). IR/cm^{-1}: ν = 3473, 2951, 2834, 1788, 1699, 1595, 1578, 1496.

*nOeds results for **14b**.* Irradiation of H-8a caused a 6.1% enhancement on the signal representing H-11a; irradiation of H-11a caused enhancements on H-8a (8.3%) and on H-11b (3.6%); irradiation of H-11b caused a 3.0% enhancement on H-11a.

15b. δ_H: 7.35 (m, 3H, Ar–H), 7.13 (m, 5H, Ar–H), 7.00 (m, 4H, Ar–H), 6.88 (t, 1H, *J* 7.3, Ar–H), 6.66 (d, 1H, *J* 8.2, Ar–H), 5.68 (s, 1H, H-6), 5.23 (1H, s, H-11b), 4.84 (1H, d, *J* 7.4, H-8a), 3.74 (1H, d, *J* 7.4, H-11a), 3.01 (3H, s, NCH_3). δ_C: 175.7 (C=O), 174.8 (C=O), 145.6, 144.4 (C-1′ and C-4a), 136.8 (C-7′), 130.7, 130.4, 129.4, 128.6, 128.5, 128.2, 127.8, 126.5 (Ar–CH), 120.2 (C-11c), 120.0, 117.2 (Ar–CH), 78.9 (C-6), 76.2 (C-8a), 65.8 (C-11b), 56.2 (C-11a), 25.6 (NCH_3). IR/cm^{-1}: ν = 3471, 3035, 2922, 1783, 1709, 1603, 1593, 1576, 1491.

*nOeds results for **15b**.* Irradiation of H-6 caused a 5.7% enhancement on the signal representing H-11b; irradiation of H-8a caused a 6.3% enhancement on the signal representing H-11a; irradiation of H-11a caused enhancements on H-8a (7.0%) and on H-11b (2.8%); irradiation of H-11b caused a 3.9% enhancement on H-6.

16b. δ_H: 7.40 (m, 2H, Ar–H), 7.29 (m, 5H, Ar–H), 7.08 (m, 6H, Ar–H), 6.75 (t, 1H, *J* 6.3, Ar–H), 5.95 (s, 1H, H-6), 4.97 (d, 1H, *J* 8.0, H-8a), 4.70 (d, 1H, *J* 8.0, H-11b), 4.24 (dd, 1H, *J* 8.0 and 8.0, H-11a), 2.63 (s, 3H, NCH_3).

*nOeds results for **16b**.* Irradiation of H-6 caused a 4.1% enhancement on the signal representing H-11a; irradiation of H-8a caused a 9.5% enhancement on the signal representing H-11a; irradiation of H-11a caused enhancements on H-8a (6.6%) and on H-11b (6.2%); irradiation of H-11b caused a 8.5% enhancement on H-11a.

5-(4-Methoxyphenyl)-10-methyl-6-phenyl-5,8a,11a,11b-tetrahydropyrrolo[3′,4′:4,5]isoxazolo[2,3-*c*]quinazoline-9,11(6*H*,10*H*)-diones 14c, 15c and 16c

A solution of the nitrone **8c** (0.30 g, 0.91 mmol) and *N*-methyl maleimide (101 mg, 0.91 mmol) in DCM (20 cm^3) was stirred at rt for 18 h. The solvent was removed under reduced pressure to give the crude reaction products, the ^{1}H NMR spectral analysis of which indicated the presence of a mixture of three isomeric cycloadducts **14c**, **15c** and **16c** in a ratio of 4.5 : 2.5 : 1. Purification by flash column chromatography (DCM) followed by crystallisation (diethyl ether and hexane) afforded **14c** (0.175 g, 46%), **15c** (0.102 g, 27%) and **16c** (10 mg, 3%).

Microanalytical data were obtained on a mixed sample of **14c** and **15c**. (Found: C, 69.60; H, 5.38; N, 9.23. $C_{26}H_{23}N_3O_4[0.5H_2O]$ requires: C, 69.33; H, 5.33, N, 9.33%).

14c. White powder, 190–192 °C (from diethyl ether). δ_H: 7.37 (m, 2H, Ar–H), 7.27 (m, 3H, Ar–H), 7.13 (m, 4H, Ar–H), 6.84 (m, 4H, Ar–H), 5.84 (s, 1H, H-6), 4.84 (d, 1H, *J* 7.5, H-8a), 4.53 (s, 1H, H-11b), 3.80 (d, 1H, *J* 7.5, H-11a), 3.79 (s, 3H, OCH_3), 3.09 (s, 3H, NCH_3). δ_C: 175.4 (C=O), 175.2 (C=O), 157.1 (C-4′), 141.7 (C-1′), 140.1, 137.9 (Ar–C), 128.8, 128.4, 128.2, 127.2, 126.8 (Ar–CH), 119.4 (C-11c), 119.0, 116.3, 114.8 (Ar–CH), 77.7 (C-6), 75.4 (C-8a), 59.5 (C-11b), 56.1 (C-11a), 55.5

(OCH_3), 25.2 (NCH_3). IR/cm^{-1}: ν = 3473, 2951, 2834, 1788, 1701, 1597, 1576, 1508, 1493.

*nOeds results for **14c**.* Irradiation of H-8a caused a 6.4% enhancement on the signal representing H-11a; irradiation of H-11b caused a 2.9% enhancement on H-11a.

15c. White powder, 190–195 °C (from diethyl ether). δ_H: 7.38 (m, 2H, Ar–H), 7.27 (m, 1H, Ar–H), 7.14 (m, 3H, Ar–H), 7.01 (m, 1H, Ar–H), 6.93 (d, 2H, *J* 8.8, H-3′ and H-5′), 6.92 (m, 1H, Ar–H), 6.66 (d, 2H, *J* 8.8, H-2′ and H-6′), 6.35 (d, 1H, *J* 8.3, Ar–H), 5.62 (s, 1H, H-6), 5.26 (s, 1H, H-11b) 4.88 (d, 1H, *J* 7.2, H-8a), 3.78 (d, 1H, *J* 7.2, H-11a), 3.70 (s, 3H, OCH_3), 3.02 (s, 3H, NCH_3).

*nOeds results for **15c**.* Irradiation of H-6 caused a 5.6% enhancement on the signal representing H-11b; irradiation of H-8a caused enhancements on H-6 (2.3%) and on H-11a (6.5%); irradiation of H-11b caused a 6.7% enhancement on H-6 and a 2.5% enhancement on H-11a.

16c. Isolated as a white powder, 190–192 °C (from diethyl ether). δ_H: 7.39 (m, 2H, Ar–H), 7.28 (m, 3H, Ar–H), 7.12 (d, 2H, *J* 9.0, H-3′ and H-5′), 7.05 (m, 2H, Ar–H), 6.93 (m, 1H, Ar–H), 6.86 (d, 2H, *J* 9.0, H-2′ and H-6′) 6.70 (m, 1H, Ar–H), 5.81 (s, 1H, H-6), 4.97 (d, 1H, *J* 8.0, H-8a), 4.67 (br, d, 1H, *J* 6.2, H-11b), 4.25 (br, dd, 1H, *J* 8.0 and 8.0, H-11a), 3.79 (s, 3H, OCH_3), 2.70 (s, 3H, NCH_3).

*nOeds results for **16c**.* Irradiation of H-8a caused a 5.6% enhancement on the signal representing H-11a; irradiation of H-11a caused enhancements on H-8a (7.8%) and on H-11b (1.2%); irradiation of H-11b caused a 4.3% enhancement on H-11a.

4-[10-Methyl-9,11-dioxo-6-phenyl-8a,9,10,11,11a,11b-hexahydropyrrolo[3′,4′:4,5]isoxazolo[2,3-*c*]quinazolin-5(6*H*)-yl]benzonitriles 14d, 15d and 16d

A solution of the nitrone **8d** (111 mg, 0.5 mmol) and *N*-methyl maleimide (55 mg, 0.5 mmol) in DCM (10 cm^3) was stirred at rt for 18 h. The solvent was removed under reduced pressure. ^{1}H NMR spectral analysis of the crude product indicated the presence of three isomeric cycloadducts **14d**, **15d** and **16d** in a 1 : 0.2 : 1 ratio. Purification by flash column chromatography (DCM) followed by crystallization (diethyl ether and hexane) afforded **14d** (0.11 g, 50%), **16d** (0.067 g, 30%) and only a trace amount of **15d**.

Microanalytical and mp data were obtained on a mixed sample of **14d** and **16d**, white powder, decomposes at 270–280 °C (from diethyl ether). (Found: C, 70.73; H, 4.60; N, 12.51. $C_{26}H_{20}N_4O_3[0.5H_2O]$ requires: C, 70.11; H, 4.72; N, 12.58%).

14d. δ_H: 7.54 (d, 2H, *J* 8.3, H-3′ and H-5′), 7.26 (m, 10H, Ar–H) 7.01 (t, 1H, *J* 7.7, Ar–H), 6.10 (s, 1H, H–6), 4.83 (d, 1H, *J* 7.3, H-8a), 4.58 (s, 1H, H-11b), 3.82 (d, 1H, *J* 7.3, H-11a), 3.12 (s, 3H, N–Me). δ_C: 175.0 (C=O), 174.7 (C=O), 152.2 (C-4a), 138.2 (C-1′), 136.0 (C-7′), 133.6, 129.1, 128.9, 128.5, 127.8, 127.0 (Ar–CH), 122.9 (C-11c), 122.8, 121.3, 119.6 (Ar–CH), 119.2 (C≡N), 105.5 (C-4′), 77.6 (C-6), 75.2 (C-8a), 59.6 (C-11b), 56.0 (C-11a), 25.3 (NCH_3). IR/cm^{-1}: ν = 3473, 3042, 2947, 2231, 1789, 1701, 1608, 1600, 1585, 1509, 1493.

*nOeds results for **14d**.* Irradiation of H-8a caused a 6.8% enhancement on the signal representing H-11a; irradiation of H-11a caused enhancements on H-8a (7.9%) and on H-11b (3.1%); irradiation of H-11b caused a 2.7% enhancement on H-11a.

16d. δ_H: 7.57 (d, 2H, *J* 8.5, H-3′ and H-5′), 7.37 (m, 2H, Ar–H), 7.25 (m, 7H, Ar–H, including 7.16, d, *J* 8.5, H-2′ and H-6′), 7.05 (d, 1H, *J* 7.2, Ar–H), 6.90 (m, 1H, *J* 3.9, Ar–H), 6.08 (s, 1H, H-6), 4.96 (d, 1H, *J* 8.2, H-8a), 4.75 (d, 1H, *J* 8.2, H-11b), 4.29 (dd, 1H, *J* 8.2 and 8.2, H-11a), 2.66 (s, 3H, NCH_3). δ_C: 173.0 (C=O), 172.6 (C=O), 152.2 (C-4a) 139.4 (C-1′), 136.2 (C-7′), 134.0, 129.4, 129.2, 128.9, 127.5, 122.7, 121.3 (Ar–CH), 120.7 (C-11c), 120.4 (Ar–CH), 119.6 (C≡N), 105.8 (C-4′), 79.0 (C-6), 76.8 (C-8a), 58.4 (C-11b), 55.5 (C-11a), 24.9 (NCH_3).

Preparation of 10-methyl-6-(4-nitrophenyl)-5-(4-methoxyphenyl)-5,8a,11a,11b-tetrahydropyrrolo[3′,4′:4,5]isoxazolo[2,3-*c*]quinazoline-9,11(6*H*,10*H*)-diones 14e, 15e and 16e

A solution of the nitrone **8e** (161 mg, 0.43 mmol) and *N*-methyl maleimide (48 mg, 0.43 mmol) in DCM (10 cm^3) was stirred at rt for 18 h. The solvent was removed under reduced pressure to give a crude product, the ^{1}H NMR spectral analysis of which indicated the presence of three isomeric cycloadducts **14e**, **15e** and **16e** in a ratio of 5 : 1 : 1. Purification by flash column chromatography (DCM) followed by crystallisation (diethyl ether and hexane) afforded **14e** (0.14 g, 67%), **15e** (0.02 g, 10%) and **16e** (0.027 g, 13%).

Microanalytical data were obtained on a mixture of **14e**, **15e** and **16e**. (Found: C, 63.19; H, 4.41; N, 11.44. $C_{26}H_{22}N_4O_6[0.5H_2O]$ requires: C, 63.03; H, 4.65; N, 11.52%).

14e. Light yellow solid, decomposes at 240 °C (from diethyl ether and hexane). δ_H: 8.15 (d, 2H, *J* 8.6, H-9′ and 11′), 7.60 (d, 2H, *J* 8.6, H-8′ and H-12′), 7.12 (m, 4H, Ar–H), 6.86 (m, 4H, Ar–H), 5.91 (s, 1H, H–6), 4.87 (d, 1H, *J* 7.2, H-8a), 4.47 (s, 1H, H-11b), 3.84 (d, 1H, *J* 7.2, H-11a), 3.79 (s, 3H, OCH_3), 3.09 (s, 3H, NCH_3). δ_C: 175.4, 175.2 (C=O), 157.8 (ArC–O) 148.4, 145.3, 141.4, 140.1 (Ar–C), 128.9, 128.8, 127.7, 127.2, 124.5, 120.3 (Ar–CH), 119.7 (C-11c), 117.3, 115.3 (Ar–CH), 77.6 (C-6), 75.8 (C-8a), 59.9 (C-11b), 56.5 (C-11a), 55.9 (OCH_3).

*nOeds results for **14e**.* Irradiation of H-8a caused a 6.3% enhancement on the signal representing H-11a; irradiation of H-11b caused a 3.6% enhancement on H-11a.

15e. Yellow solid, decomposes at 235 °C (from diethyl ether and hexane). δ_H: 8.01 (d, 2H, *J* 8.6, H-9′ and H-11′), 7.59 (d, 2H, *J* 8.6, H-9′ and H-12′), 7.28 (m, 1H, Ar-H), 6.96 (m, 4H, Ar-H, including d at 6.94, 2H, *J* 8.7, H-2′ and H-6′), 6.69 (d, 2H, *J* 8.7, H-3′ and 5′), 6.34 (d, 1H, *J* 8.3, Ar-H), 5.72 (s, 1H, H-6), 5.30 (s, 1H, H-11b), 4.92 (d, 1H, *J* 7.3, H-8a), 3.84 (d, 1H, *J* 7.3, H-11a), 3.70 (s, 3H, OCH_3), 3.02 (s, 3H, NCH_3). δ_C: 175.5, 174.8 (C=O), 158.5 (ArC–O), 147.9, 146.0, 143.6 (Ar–C), 136.1 (C-7′), 132.1, 131.3, 128.6, 127.6, 123.4, 120.2 (Ar–CH), 119.6 (C-11c), 116.9, 115.0 (Ar–CH), 78.0 (C-6), 75.8 (C-8a), 65.6 (C-11b), 55.9 (C-11a), 55.6 (OMe), 25.6 (NMe).

16e. Isolated as a yellow crystalline solid, decomposes at 248 °C (from diethyl ether and hexane). δ_H: 8.15 (d, 2H, *J* 8.6, H-9′ and H-11′), 7.59 (d, 2H, *J* 8.6, H-8′ and H-12′), 7.08 (m, 4H, Ar–H), 6.88 (m, 3H, Ar–H), 6.76 (m, 1H, Ar–H), 5.81 (s, 1H, H-6), 4.98 (d, 1H, *J* 8.1, H-8a), 4.66 (br, 1H, H-11b), 4.25 (dd, 1H, *J* 8.1 and 8.1, H-11a), 3.80 (s, 3H, OCH_3), 2.71 (s, 3H, NCH_3). δ_C: 172.9, 172.9 (C=O), 157.5 (ArC–O), 148.3, 142.1, 140.0 (Ar–C), 129.4, 129.3, 128.4, 126.1, 124.3, 120.2 (Ar–CH), 118.3, 117.7 (Ar–C), 115.3 (Ar–CH), 78.8 (C-6), 77.2 (C-8a), 59.2 (C-11b), 55.9 (OCH_3), 53.8 (C-11a), 25.0 (NCH_3).

*nOeds results for **16e**.* Irradiation of H-8a caused a 6.4% enhancement on the signal representing H-11a; irradiation of H-11b caused a 2.9% enhancement on H-11a.

Dimethyl 5,6-diphenyl-6,10*b*-dihydro-5*H*-isoxazolo[2,3-*c*]quinazoline-1,2-dicarboxylate 17b and (*Z*)-3-(1,2-diphenyl-1,2-dihydroquinazolin-3-ium-3-yl)-1,4-dimethoxy-1,4-dioxo-2-buten-2-olate 18b.

A solution of the nitrone **8b** (226 mg, 0.75 mmol) and DMAD (107 mg, 0.75 mmol) was stirred in DCM (10 cm^3) at rt for 18 h. The solvent was removed under reduced pressure to give a crude product. ^{1}H NMR spectral analysis indicated the formation of two new products, **17b** and **18b**, in a ratio of 4 : 1. Purification by flash column chromatography (diethyl ether–hexane; 2 : 8, followed by diethyl ether–MeOH; 99 : 1) gave pure samples of **17b** (0.21 g, 63%) and **18b** (0.046 g, 14%).

17b. Red amorphous solid, mp 134–136 °C (from methanol). (Found: C, 70.42; H, 4.99; N, 6.38. $C_{26}H_{22}N_2O_3$

requires: C, 70.58; H, 4.77; N, 6.33%). δ_H: 7.48 (m, 2H, Ar–H), 7.24 (m, 11H, Ar–H), 6.77 (m, 1H, Ar–H), 6.29 (s, 1H, H-5), 5.59 (s, 1H, H-10b), 3.80 (s, 3H, OCH_3), 3.74 (s, 3H, OCH_3). δ_C: 163.01 (C=O), 159.40 (C=O), 152.53 (C=*C*–O), 148.18, 141.15 (ArC–N), 136.95 (Ar–C), 129.79, 129.06, 128.67, 128.18, 127.22 (Ar–CH), 126.48 (C-10a), 123.39, 122.01, 121.70, 119.19 (Ar–CH), 111.63 (*C*=C–O), 78.70 (C-5), 61.80 (C-10b), 53.38 (OCH_3), 52.09 (OCH_3).

18b. Red crystalline solid, mp 128–130 °C (from diethyl ether and methanol). (Found: C, 66.85; H, 5.27; N, 6.17. $C_{26}H_{22}N_2O_5[1.5H_2O]$ requires: C, 66.52; H, 5.33; N, 6.10%). δ_H: 8.66 (s, 1H, H-4), 7.45 (m, 6H, Ar–H), 7.30 (m, 6H, Ar–H), 7.09 (s, 1H, H-2), 6.99 (m, 2H, Ar–H), 3.83 (s, 3H, OCH_3), 3.46 (OCH_3). The sample was insufficiently stable upon standing in $CDCl_3$ to acquire ^{13}C NMR spectral analysis.

(*Z*)-3-(1,2-Diphenyl-1,2-dihydroquinazolin-3-ium-3-yl)-1,4-dimethoxy-1,4-dioxo-2-buten-2-olate 18b from 17b

A solution of **17b** (0.020 g, 0.04 mmol) in MeOH (5 cm^3) was heated at reflux for 18 h. Removal of the solvent afforded the crude product which was purified by flash column chromatography (diethyl ether–MeOH; 99 : 1). The ylide **18c** was isolated as a red amorphous solid in 70% yield (0.007 g), and data agree with those reported above.

(*Z*)-1,4-Dimethoxy-3-(1-methyl-2-phenyl-1,2-dihydroquinazolin-3-ium-3-yl)-1,4-dioxo-2-buten-2-olate 18a and tetramethyl 3-[8a,9,9a-tris(methoxycarbonyl)-5-methyl-5,6,8a,9,9a,9b-hexahydrocyclopropa[4,5]isoxazolo[2,3-*c*]quinazolin-9-yl]-7-oxabicyclo[2.2.1]hepta-2,5-diene-1,2,5,6-tetracarboxylate 22

A solution of the nitrone **8a** (888 mg, 3.7 mmol) and DMAD (530 mg, 3.7 mmol) in DCM (30 cm^3) was stirred for 18 h at rt. The solvent was removed under reduced pressure. A ^1H NMR spectrum of the crude products indicated the presence of a complex mixture comprising one main product together with a number of more minor products. Purification by flash column chromatography (diethyl ether–hexane; 1 : 1, followed by diethyl ether–methanol; 9 : 1) gave a pure sample of the major product **18a** (0.75 g, 60%). The cyclopropyl-fused isoxazolidine **22** (150 mg, 5%) was isolated as colourless crystals that fell out of the first 20 column fractions.

18a. Red crystalline solid, mp 126–128 °C (from diethyl ether and methanol). (Found: C, 63.55; H, 5.53; N, 7.04. $C_{21}H_{20}N_2O_5[H_2O]$ requires: C, 63.32; H, 5.53; N, 7.04%). δ_H: 8.45 (s, 1H, H-4), 7.55 (m, 1H, Ar–H), 7.34 (m, 6H, Ar–H), 6.85 (t, 1H, *J* 7.2, Ar–H), 6.74 (s, 1H, H-2), 6.72 (d, 1H, *J* 8.7, Ar–H), 3.81 (s, 3H, OCH_3), 3.61 (s, 3H, OCH_3), 3.15 (s, 3H, NCH_3). δ_C: 172.7 [*C*(O)CO_2CH_3], 168.4 (*C*O_2CH_3), 164.7 (*C*O_2CH_3), 161.1 (C-4), 147.0 (C-8a), 140.1 (Ar–CH), 134.5 (C-1′), 133.2, 130.6, 129.2, 126.7, 119.7 (Ar–CH), 114.8 (C-4a) 113.1 (Ar–CH) 102.2 (N^+–C^-), 79.2 (C-2), 52.3 (OCH_3), 51.3 (OCH_3), 36.9 (NCH_3). IR/cm^{-1}: ν = 3496, 3428, 3064, 2944, 1735, 1660, 1627, 1593, 1554, 1522, 1494.

22. Colourless crystalline solid characterised by X-ray crystallographic analysis. (Found: C, 58.01; H, 4.94; N, 3.55. $C_{39}H_{38}N_2O_{17}$ requires: C, 58.06; H, 4.71; N, 3.47%). δ_H: 7.38 (m, 2H, Ar–H), 7.28 (m, 3H, Ar–H), 7.20 (m, 2H, Ar–H), 6.76 (m, 2H, Ar–H), 5.38 (s, 1H, H-2), 5.10 (s, 1H, H-4c), 3.93, 3.91, 3.79, 3.70, 3.67, 3.53, 3.54, 3.51 (8 × OCH_3).

X-Ray crystal structure determination of 22. Data were collected at 150(2) K on a Bruker SMART 1000 diffractometer. The structure was solved (in the centrosymmetric space group $P2_1/n$) by direct methods and refined by full-matrix least-squares on F^2 using the SHELXTL suite of programs.[39] All the non-hydrogen atoms were refined with anisotropic atomic displacement parameters, and the hydrogen atoms were inserted at calculated positions using a riding model. Details of the data collection and structure refinement are given in Table 1.

Table 1 Crystal data and structure refinement for **22**

Identification code	tomas1
Empirical formula	$C_{39}H_{38}N_2O_{17}$
Formula weight	806.71
T/K	150(2)
λ/Å	0.71073
Crystal system	Monoclinic
Space group	$P2_1/n$
a/Å	11.1011(12)
b/Å	21.952(2)
c/Å	15.9307(17)
α/°	90
β/°	103.285(2)
γ/°	90
V/Å^3	3778.2(7)
Z	4
D_c/Mg m^{-3}	1.418
μ/mm^{-1}	0.113
F(000)	1688
Crystal size/mm	0.43 × 0.22 × 0.03
Crystal description	Colourless lath
θ range for data collection/°	1.61 to 25.00
Index ranges	$-13 \leqslant h \leqslant 11$
	$-16 \leqslant k \leqslant 26$
	$-16 \leqslant l \leqslant 18$
Reflections collected	18 415
Independent reflections	6642 (R_{int} = 0.0488)
Completeness to θ = 25.00° (%)	99.8
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	1.000000 and 0.824622
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	6642/0/523
Goodness-of-fit on F^2	1.010
Final R indices [$I > 2\sigma(I)$]	R_1 = 0.0475, wR_2 = 0.1027
R indices (all data)	R_1 = 0.0958, wR_2 = 0.1226
Largest diff. peak and hole/e Å^{-3}	0.267 and −0.251

CCDC reference number 282677. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b511998g.

Dimethyl 6-(4-methoxyphenyl)-5-phenyl-6,10b-dihydro-5*H*-isoxazolo[2,3-*c*]quinazoline-1,2-dicarboxylate 17c and (*Z*)-1,4-dimethoxy-3-[1-(4-methoxyphenyl)-2-phenyl-1,2-dihydroquinazolin-3-ium-3-yl]-1,4-dioxo-2-buten-2-olate 18c

A solution of the nitrone **8c** (0.846 g, 2.6 mmol) and DMAD (0.365 g, 2.6 mmol) in DCM (20 cm^3) was stirred at rt for 18 h. The solvent was removed under reduced pressure to give the crude reaction products, the ^1H NMR spectral analysis of which indicated the formation of two new products, **17c** and **18c**, in a ratio of 4 : 1. Trace amounts of other undetermined products were also evident. Purification by flash column chromatography (diethyl ether–hexane; 1 : 1, followed by diethyl ether–MeOH; 9 : 1) gave pure samples of **17c** (449 mg, 32%) and **18c** (278 mg, 24%). The structure of the latter is confirmed by X-ray crystallographic analysis (see below).

17c. Red powder, mp 109–112 °C (from diethyl ether and hexane). (Found: C, 68.31; H, 5.15; N, 5.90. $C_{27}H_{22}N_2O_5$ requires: C, 68.64; H, 5.08; N, 5.93%). δ_H: 7.50 (m, 2H, Ar–H), 7.24 (m, 6H, Ar–H) 7.16 (d, 2H, *J* 8.9, H-2′ and H-6′), 7.04 (m, 1H, Ar–H), 6.85 (d, 2H, *J* 8.9, H-3′ and H-5′), 6.73 (m, 1H, Ar–H), 6.16 (s, 1H, H-5), 5.55 (s, 1H, H-10b), 3.84 (s, 3H, OCH_3), 3.80 (s, 3H, OCH_3), 3.75 (s, 3H, OCH_3). δ_C: 163.1 (C=O), 159.6 (C=O), 156.5 (Ar*C*–OCH_3) 152.5, 141.9, 141.2 (2 × ArC–N and C=*C*–O) 137.1 (C-7′), 129.1, 128.7, 128.3, 127.0 (Ar–CH), 125.5 (C-10a), 124.7, 120.9, 118.9, 115.1 (Ar–CH), 111.9 (*C*=C–O), 78.8 (C-5), 61.4 (C-10b), 55.9 (OCH_3), 53.6 (OCH_3), 52.3 (OCH_3).

18c. Red crystalline solid. (Found: C, 66.43; H, 5.19; N, 5.62. $C_{27}H_{22}N_2O_5[H_2O]$ requires: C, 66.12; H, 5.31; N, 5.71%). δ_H: 8.57 (s, 1H, CH=N), 7.45 (m, 4H, Ar–H), 7.25 (m, 4H, Ar–H),

6.93 (m, 4H, 3 × Ar–H, H-2), 6.81 (d, 1H, *J* 8.1, Ar–H), 3.82 (s, 3H, OCH_3), 3.81 (s, 3H, OCH_3), 3.52 (s, 3H, OCH_3). δ_C: 172.9 [*C*(O)CO_2CH_3], 168.4 (*C*O_2CH_3), 164.6 (*C*OCH_3), 159.3 (Ar*C*–OCH_3), 158.7 (C-4), 145.7 (C-8a), 138.6 (Ar–CH), 135.7, 135.6 (C-1′ and C-7′), 132.4, 130.2, 129.0, 128.2, 127.3, 121.0, 116.9 (Ar–CH), 116.6 (C-4a), 115.7 (Ar–CH), 103.3 (N^+–C^-), 80.0 (C-2), 55.6, 52.4, 51.1 (3 × OCH_3).

X-Ray crystal structure determination of 18c. Single crystals were analyzed using a Nonius Kappa CCD diffractometer. Details of the data collection, solutions, and refinements are given in Table 2. The model was solved and subsequently refined using full-matrix least-squares in SHELXL-97.[44]

CCDC reference number 282676. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b511998g.

(*Z*)-1,4-Dimethoxy-3-[1-(4-methoxyphenyl)-2-phenyl-1,2-dihydroquinazolin-3-ium-3-yl]-1,4-dioxo-2-buten-2-olate 18c from 17c

A solution of **17c** (0.020 g, 0.04 mmol) in MeOH (10 cm^3) was stirred at rt for 18 h. Removal of the solvent afforded the crude product which was purified by flash column chromatography (diethyl ether–MeOH; 99 : 1). The ylide **18c** was isolated as a red amorphous solid in 50% yield (0.010 g); data agree with those reported above.

Dimethyl 6-(4-cyanophenyl)-5-phenyl-6,10b-dihydro-5*H*-isoxazolo[2,3-*c*]quinazoline-1,2-dicarboxylate 17d

The nitrone **8d** (0.267 g, 0.82 mmol) and DMAD (117 mg, 0.82 mmol) were stirred in DCM (10 cm^3) at rt for 18 h. The solvent was removed under reduced pressure to leave a red solid, the ^{1}H NMR spectrum of which revealed the presence of a single product, **8d** which was purified by crystallization.

17d. Red amorphous solid (0.384g, 100%), mp 78–83 °C (from diethyl ether and hexane). (Found: C, 66.75; H, 4.72; N, 8.63. $C_{27}H_{21}N_3O_5[H_2O]$ requires: C, 66.80; H, 4.74; N, 8.66%).

Table 2 Crystal data and structure refinement for **18c**

Identification code	k04pma2
Empirical formula	$C_{27}H_{26}N_2O_7$
Formula weight	490.50
T/K	150(2)
λ/Å	0.71073
Crystal system	Triclinic
Space group	$P\bar{1}$
a/Å	11.2500(2)
b/Å	11.2910(2)
c/Å	11.7080(2)
α/°	76.459(1)
β/°	64.710(1)
γ/°	64.809(1)
V/Å^3	1214.28(4)
Z	2
D_c/Mg m^{-3}	1.342
μ/mm^{-1}	0.098
F(000)	516
Crystal size/mm	0.20 × 0.15 × 0.15
θ range for data collection/°	3.72 to 27.53
Index ranges	$-14 \leqslant h \leqslant 14$
	$-14 \leqslant k \leqslant 14$
	$-15 \leqslant l \leqslant 15$
Reflections collected	21 369
Independent reflections	5534 ($R_{int} = 0.0399$)
Reflections observed (>2σ)	4325
Data completeness	0.987
Absorption correction	None
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	5534/3/335
Goodness-of-fit on F^2	1.028
Final R indices [$I > 2\sigma(I)$]	$R_1 = 0.0634$, $wR_2 = 0.1751$
R indices (all data)	$R_1 = 0.0837$, $wR_2 = 0.1938$
Largest diff. peak and hole/e Å^{-3}	0.672 and −0.480

δ_H: 7.57 (d, 2H, *J* 8.7, H-9′ and H-11′), 7.45 (m, 2H, Ar–H), 7.24 (m, 8H, Ar–H), 6.90 (dd, 1H, *J* 6.5 and 6.5, H-4′), 6.43 (s, 1H, H-5), 5.67 (s, 1H, H-10b), 3.80 (s, 3H, OCH_3), 3.74 (s, 3H, OCH_3).

Preparation of dimethyl 6-(4-methoxyphenyl)-5-(4-nitrophenyl)-6,10b-dihydro-5*H*-isoxazolo[2,3-*c*]quinazoline-1,2-dicarboxylate 17e

A solution of the nitrone **8e** (107 mg, 0.29 mmol) and DMAD (41 mg, 0.29 mmol) in DCM (10 cm^3) was stirred at rt for 18 h. The solvent was removed under reduced pressure. A ^{1}H NMR spectrum of the crude product revealed the presence of only one product, the cycloadduct **17e**. Purification by flash column chromatography (diethyl ether–hexane; 1 : 1) provided a pure sample of **17e** (118 mg, 79%).

17e. Red amorphous solid, decomposes at 220 °C (from diethyl ether and hexane). (Found: C, 61.67; H, 4.47; N, 7.72. $C_{27}H_{23}N_3O_8[0.5H_2O]$ requires: C, 61.60; H, 4.56; N, 7.98%). δ_H: 8.14 (d, 2H, *J* 8.6, H-3′ and H-5′), 7.71 (d, 2H, *J* 8.6, H-2′ and H-6′), 7.23 (m, 1H, Ar–H), 7.13 (d, 2H, *J* 8.8, H-7′ and H-11′), 7.06 (m, 2H, Ar–H), 6.87 (d, 2H, *J* 8.8, H-8′ and H-10′), 6.78 (m, 1H, Ar–H), 6.19 (s, 1H, H-5), 5.55 (s, 1H, H-10b), 3.84 (s, 3H, OCH_3), 3.81 (s, 3H, OCH_3), 3.75 (s, 1H, OCH_3). δ_C: 160.1, 159.3 (*C*O_2CH_3), 156.83 (Ar*C*–OCH_3), 148.29, 144.66, 141.50, 140.90 (3 × ArC–N and C=*C*–O), 129.44, 129.16 (C-1′ and Ar–CH) 127.28 (Ar–CH), 125.51 (C-10a), 124.51, 124.30, 121.65, 119.67, 115.32, 117.71 (Ar–CH), 111.80 (*C*=C–O) 78.54 (C-5) 61.79 (C-10b), 55.94, 53.65, 52.33 (OCH_3).

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