New efficient synthesis of imidazo[2,1-b]quinazoline-2,5(1H,3H)-diones by a consecutive aza-Wittig/heterocumulene-mediated annulation

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Abstract
The carbodiimide 2, obtained from aza-Wittig reaction of iminophosphorane 1 with aromatic isocyanate, reacted with α-amino ester in the presence of triethylamine to give imidazo[2,1-b]quinazoline-2,5(1H,3H)-diones 5 (when R² is H) or quinazolinones 6 (when R² is not H). Imidazo[2,1-b]quinazoline-2,5(1H,3H)-diones 5 were prepared more generally by another route, using a consecutive aza-Wittig / heterocumulene-mediated annulation of iminophosphoranes 9 with isocyanates and catalytic sodium ethoxide.

Keywords: Imidazo[2,1-b]quinazoline-2,5(1H,3H)-dione, quinazolinone, iminophosphorane, carbodiimide, aza-Wittig reaction

Introduction
Due to the broad spectrum of biological properties of derivatives of quinazolinone their synthesis has been a focus of significant interest for many years. Some of these activities include antimicrobial, antiinflammatory, antifungal, anticancer, and AMPA receptor antagonist properties. The range of chemical structures and their biological activities have made synthetic studies of quinazolinones very attractive. Similarly, heterocycles containing the imidazolone nuclei also exhibit various biological activities, with several exhibiting antibacterial, antifungal activities, leukotriene B₄ receptor antagonist properties, and potassium channel openers. Others in the same class appear in a variety of biologically active molecules, particularly in some alkaloids in which a common structural unit is a derivatized 2-amino-4H-imidazol-4-one moiety. Thus is likely that the introduction of an imidazolone ring into the quinazolinone system would influence the biological activities significantly. In fact, some imidazo[2,1-b]quinazoline-2,5(1H,3H)-diones have been used as gastric secretion inhibitors. However, there are only few reports on the synthesis of imidazo[2,1-b]quinazoline-2,5(1H,3H)-diones.
The previously reported methods for the preparation of some representative derivatives of this ring system involve either reaction of anthranilic acid with 2-methylthioimidazolones or cyclization of 2-methylthioquinazolin-4(3H)-ones with amine. However, these methods often require multistep reaction processes or heating at high temperature. Until now, no general and simple approach to the imidazo[2,1-b]quinazoline-2,5(1H,3H)-diones has been reported.

The aza-Wittig reactions of iminophosphoranes have received increased attention in view of their utility in the synthesis of nitrogen heterocyclic compounds. Recently we have been interested in the synthesis of quinazolinones, thienopyrimidinones and imidazolones via aza-Wittig reaction, with the aim of evaluating their fungicidal activities. Here we report a new approach to the synthesis of imidazo[2,1-b]quinazoline-2,5(1H,3H)-diones via a consecutive aza-Wittig / heterocumulene-mediated annulation.

Results and Discussion

Iminophosphorane reacted with aromatic isocyanates to give carbodiimides, which were then reacted with an α-amino ester at room temperature in the presence of triethylamine. Imidazo[2,1-b]quinazoline-2,5(1H,3H)-diones were obtained exclusively where the R group is H, but only quinazolinones were produced where R group was not H (Scheme 1).

The literature suggests that the reaction of carbodiimides with an α-amino ester is likely to afford primarily guanidine intermediates of type. From, the formation of three cyclized products imidazolone (via path b), quinazolinone (via path a), and quinazolinone (via path c) could in principle take place. The formation of (R = H) is expected to come about as a result of a cascade cyclization of to an imidazolone intermediate, and further base catalytic cyclization between the imidazolone ring’s NH and ethoxylate. The result also illustrated that the imidazolone is more easily produced from intermediate than quinazolinone when the R group is H, but the quinazolinone is preferentially formed when R group is not H. The reaction selectivity is probably due to the steric hindrance of the R group which retards the cyclization of to (via path b) in the cases where the R group is not H.
Scheme 1

The exclusive formation of 6 (where R² group is not H) can be rationalized in terms of a base catalytic cyclization of the guanidine intermediate 3 to give 6 across the arylamino group (R¹ = Ar) (path a) rather than the alkylamino one (path c). This is likely to be due to the preferential cyclization of more acidic –NHR¹ in the basic conditions. The same selectivity is observed in similar cases. The structure of 6 is deduced from ¹H NMR data. For example, the ¹H NMR spectrum of 6d (R² = i-Pr) shows the signals of NH at 4.53 ppm as a doublet and NCH at 4.72 ppm as two doublets, which strongly suggest the existence of a NHCH(i-Pr)COOEt group in 6d. The structure of 6 was confirmed by X-ray crystallographic analysis. A single crystal of 6b was obtained by slow evaporation from a dichloromethane-petroleum solution. X-ray structure analysis verified again the proposed structure, and showed that the quinazolinone system is approximately planar. The double bond length of C(14)=N(2) is 1.299(16) Å longer than the typical C=N(1.28 Å), while the single bond lengths of C(1)-N(2), C(14)-N(1), C(14)-N(3) and C(7)-N(1) are 1.384(18) Å, 1.385(14) Å, 1.355(2) Å and 1.410(19) Å respectively, are shorter than the typical C-N(1.47 Å), showing a degree of delocalization (Figure 1).
Table 1. Preparation of compounds 5a-5c and 6 from iminophosphorane 1

<table>
<thead>
<tr>
<th>Compound</th>
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<th>R²</th>
<th>Yield (%)&lt;sup&gt;a&lt;/sup&gt;</th>
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<td>Ph</td>
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<tr>
<td>5b</td>
<td>4-Cl-C₆H₄-</td>
<td>H</td>
<td>82</td>
</tr>
<tr>
<td>5c</td>
<td>3-CH₃-C₆H₄-</td>
<td>H</td>
<td>84</td>
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<tr>
<td>6a</td>
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<td>i-Bu</td>
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<td>6b</td>
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<td>6c</td>
<td>Ph</td>
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<tr>
<td>6d</td>
<td>Ph</td>
<td>i-Pr</td>
<td>80</td>
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<tr>
<td>6e</td>
<td>4-Cl-C₆H₄-</td>
<td>i-Pr</td>
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</tr>
<tr>
<td>6f</td>
<td>4-F-C₆H₄-</td>
<td>i-Pr</td>
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<sup>a</sup> Isolated yields based on iminophosphorane 1.

Figure 1. ORTEP diagram of the crystal structure of compound 6b (50% thermal ellipsoids).

The imidazo[2,1-b]quinazoline-2,5(1H,3H)-diones 5 were prepared more generally by another synthetic route. The iminophosphoranes 9, which were obtained from Staudinger reaction of azides 8 and triphenyl phosphine<sup>14</sup> reacted with aromatic isocyanate at room temperature and were then treated with sodium ethoxide to give imidazo[2,1-b]quinazoline-2,5(1H,3H)-diones 5 in good overall yields (65-90%, Table 2, Scheme 2). It is conceivable that the conversion of 9 into 5 involves consecutive processes where an initial aza-Wittig reaction between the iminophosphorane 9 and the isocyanate gives carbodiimide 10 as a highly reactive intermediate, which easily undergoes ring closure across the acylamino group to give the
quinazolinone 11. Further cyclization of 11 in the presence of a catalytic amount of sodium ethoxide produces imidazo[2,1-b]quinazoline-2,5(1H,3H)-dione, 5. It is noteworthy that the reaction can be carried out easily at room temperature. Unfortunately, racemization of the product 5 took place under the reaction conditions where chiral starting material 9 was used. This is probably due to the easy racemization of C-3 of the imidazo[2,1-b]quinazoline-2,5(1H,3H)-dione ring under the basic condition.

Scheme 2

The structure of imidazo[2,1-b]quinazoline-2,5(1H,3H)-diones, 5, was confirmed by their spectroscopic data. For example, the $^1$H NMR spectrum of 5d shows two signals at 4.93 ppm as quartets, and 1.91 ppm as a doublet, due to the CH and CH$_3$, respectively. The signals attributable to the 6-H and other Ar-Hs are found at 8.25 and 7.71-7.38 ppm as a doublet and multiplet, respectively. The IR spectra of 5d had two C=O absorption bands at 1756 and 1698 cm$^{-1}$, due respectively to the imidazolone and quinazolinone carbonyl group. The mass spectrum of 5d shows a strong molecular ion peak at m/z 291 with 100% abundance. Furthermore, a single crystal of 5o was obtained from its dichloromethane solution. X-ray structure analysis verified again the proposed structure, and showed that all ring atoms in the tricyclic moiety are essentially planar, with the maximum deviations -0.041(2) and 0.045(2) Å for C(10) and N(2) respectively from the heterocyclic plane (Figure 2). The imidazolone- (A), the pyrimidinone- (B) and the C(1)-C(6) benzene- (C) rings are almost planar, and the dihedral angles between them are A/B = 5.15(10)$^\circ$, B/C = 2.35(9)$^\circ$. The substituent C(15)-C(16)-C(17) and attached hydrogen atoms are disordered over two sites, with refined occupancies of 0.588(13) and 0.412(13).
Table 2. Preparation of compounds 5 from iminophosphorane 9

<table>
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<th>Compd</th>
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<th>Yield (%)&lt;sup&gt;a&lt;/sup&gt;</th>
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<sup>a</sup> Isolated yields based on iminophosphorane 9.

Figure 2. ORTEP diagram of the crystal structure of tricyclic compound 5o (drawn at the 50% thermal ellipsoids). Only the major conformer is shown, and the disordered atoms have been omitted for clarity.
In conclusion, we have developed an efficient synthesis of imidazo[2,1-b]quinazoline-2,5(1H,3H)-diones via a consecutive aza-Wittig/heterocumulene-mediated annulation. This method utilizes easily accessible starting material and allows mild reaction conditions, straightforward product isolation and good yields.

Experimental Section

General Procedures. Melting points were determined using a X-4 model apparatus (Beijing Taike Company). IR spectra were recorded on a Perkin Elmer PE-983 infrared spectrometer, as KBr pellets with absorption in cm⁻¹. MS were measured on a Finnigan Trace MS spectrometer, at 70eV. NMR spectra were recorded in CDCl₃ on a Varian Mercury 400 or 600 spectrometer and resonances are given in ppm (δ) relative to TMS. Elementary analyses were taken on a Vario EL III elementary analysis instrument in the Center of Analysis and Testing, College of Chemistry, Central China Normal University.

General procedure for the preparation of imidazo[2,1-b]quinazoline-2,5(1H,3H)-diones 5a-5c and 4(3H)-quinazolinones 6a-6f from iminophosphorane 1

To a solution of iminophosphorane 1₁₅ (1.27 g, 3 mmol) in dry dichloromethane (15 mL) was added aromatic isocyanate (3 mmol) under nitrogen at room temperature. After the reaction mixture stood for 6-12 hours at 0-5 °C, the solvent was removed off under reduced pressure and ether/petroleum ether (1:2, 20 mL) was added to precipitate triphenylphosphine oxide. Filtered, the solvent was removed to give carbodiimide 2, which was directly used without further purification. A mixture of α-amino acid ester hydrochloride (3 mmol) and triethylamine (0.61 g, 6 mmol) in acetonitrile (10 mL) was stirred for 10 min and filtered. Then the filtrate was added at room temperature to the solution of carbodiimide 2 as prepared above. After stirring for 1-6 hours, the reaction mixture was condensed and the residue was recrystallized from dichloromethane / petroleum or purified on a short silica gel column to give imidazo[2,1-b]quinazoline-2,5(1H,3H)-diones 5a-5c or 4(3H)-quinazolinones 6a-6f.

1-Phenylimidazo[2,1-b]quinazoline-2,5(1H,3H)-dione (5a). White solid, m.p. 283-285 °C. IR (KBr): 1764, 1694, 1638, 1467, 1321 cm⁻¹. ¹H NMR (CDCl₃, 400 MHz): δ 8.27 (d, J = 8.0 Hz, 1H, Ar-H), 7.72-7.39 (m, 8H, Ar-H), 4.73 (s, 2H, CH₂). MS (m/z, %): 277 (M⁺, 100), 248 (44), 220 (13), 110 (25), 89 (43). Anal. Calc. for C₁₆H₁₁N₃O₂: C, 69.31; H, 4.00; N, 15.15. Found C, 69.10; H, 4.20; N, 15.50.

1-(4-Chlorophenyl)imidazo[2,1-b]quinazoline-2,5(1H,3H)-dione (5b). Colorless crystals, m.p. 264-266 °C. IR (KBr): 1763, 1693, 1638, 1468, 1319 cm⁻¹. ¹H NMR (CDCl₃, 400 MHz): δ 8.27 (d, J = 8.0 Hz, 1H, Ar-H), 7.72-7.43 (m, 7H, Ar-H), 4.73 (s, 2H, CH₂). MS (m/z, %): 311 (M⁺, 100), 282 (12), 248 (44), 220 (13), 110 (25), 89 (43). Anal. Calc. for C₁₆H₁₀ClN₃O₂: C, 61.65; H, 3.23; N, 13.48. Found C, 61.78; H, 3.53; N, 13.70.
1-(3-Methylphenyl)imidazo[2,1-b]quinazoline-2,5(1H,3H)-dione (5c). White solid, m.p. 225-227 °C. IR (KBr): 1763, 1691, 1638, 1470, 1323 cm\(^{-1}\). \(^1\)H NMR (CDCl\(_3\), 400 MHz): \(\delta\) 8.26 (d, J = 8.0 Hz, 1H, Ar-H), 7.70-7.30 (m, 7H, Ar-H), 4.71 (s, 2H, CH\(_2\)), 2.45 (s, 3H, CH\(_3\)). MS (m/z, %): 291 (M\(^+\), 100), 262 (32), 248 (77), 234 (40), 101 (9), 90 (43). Anal. Calc. for C\(_{17}\)H\(_{13}\)N\(_3\)O\(_2\): C, 70.09; H, 4.50; N, 14.42. Found C, 69.95; H, 4.70; N, 14.62.

Ethyl N-(4-oxo-3-phenyl-3,4-dihydro-2-quinazolinyl)leucinate (6a). Light yellow oil. IR (KBr): 3438, 1738, 1688, 1586, 1315, 1259, 1098 cm\(^{-1}\). \(^1\)H NMR (CDCl\(_3\), 400 MHz): \(\delta\) 8.13 (d, J = 8.0 Hz, 1H, Ar-H), 7.65-7.18 (m, 8H, Ar-H), 4.82-4.78 (m, 1H, CH), 4.43 (d, J = 8.0 Hz, 1H, NH), 4.21-4.15 (m, 2H, OCH\(_2\)), 1.64-1.57 (m, 2H, CH\(_2\)), 1.47-1.44 (m, 1H, CH), 1.31-1.26 (m, 3H, CH\(_3\)). MS (m/z, %): 379 (M\(^+\), 7), 322 (62), 262 (42), 247 (100), 235 (98), 143 (44), 102 (50), 90 (98). Anal. Calc. for C\(_{22}\)H\(_{22}\)N\(_3\)O\(_3\): C, 69.64; H, 6.64; N, 11.07. Found C, 70.61; H, 6.76; N, 11.42.

Ethyl N-(4-oxo-3-phenyl-3,4-dihydro-2-quinazolinyl)alaninate (6b). White solid, m.p. 122-124 °C. IR (KBr): 3439, 1737, 1688, 1586, 1316, 1259, 1098 cm\(^{-1}\). \(^1\)H NMR (CDCl\(_3\), 400 MHz): \(\delta\) 8.14 (d, J = 8.0 Hz, 1H, Ar-H), 7.63-7.18 (m, 8H, Ar-H), 4.83-4.77 (m, 1H, CH), 4.68 (br, 1H, NH), 4.19-4.14 (m, 2H, OCH\(_2\)), 1.41 (d, J = 7.2 Hz, 3H, CH\(_3\)), 1.26 (t, J = 7.2 Hz, 3H, CH\(_3\)). \(^13\)C NMR (CDCl\(_3\), 150 MHz): \(\delta\) 173.1, 162.2, 148.9, 148.3, 134.3, 130.3, 130.2, 129.7, 128.7, 128.4, 126.9, 124.8, 122.6, 117.6, 61.2, 50.0, 18.0, 13.9. MS (m/z, %): 337 (M\(^+\), 50), 291 (79), 264 (76), 248 (39), 221 (95), 186 (100), 146 (38), 86 (31). Anal. Calc. for C\(_{19}\)H\(_{19}\)N\(_3\)O\(_3\): C, 67.64; H, 5.68; N, 12.46. Found C, 67.73; H, 5.69; N, 12.23.

Ethyl N-(4-oxo-3-phenyl-3,4-dihydro-2-quinazolinyl)phenylalaninate (6c). White solid, m.p. 127-129 °C. IR (KBr): 3411, 1744, 1684, 1586, 1310, 1270, 1097 cm\(^{-1}\). \(^1\)H NMR (CDCl\(_3\), 400 MHz): \(\delta\) 8.13 (d, J = 8.0 Hz, 1H, Ar-H), 7.63-6.88 (m, 13H, Ar-H), 5.00-4.95 (m, 1H, CH), 4.48 (d, J = 6.8 Hz, 1H, NH), 4.18-4.12 (m, 2H, OCH\(_2\)), 3.22-3.03 (m, 2H, CH\(_2\)), 1.23 (t, J = 7.2 Hz, 3H, CH\(_3\)). MS (m/z, %): 413 (M\(^+\), 8), 278 (43), 262 (59), 236 (100), 221 (22), 119 (11). Anal. Calc. for C\(_{25}\)H\(_{23}\)N\(_3\)O\(_3\): C, 72.62; H, 5.61; N, 10.16. Found C, 72.40; H, 5.69; N, 10.13.

Ethyl N-(4-oxo-3-phenyl-3,4-dihydro-2-quinazolinyl)valinate (6d). White solid, m.p. 68-70 °C. IR (KBr): 3411, 1747, 1689, 1583, 1309, 1268, 1118 cm\(^{-1}\). \(^1\)H NMR (CDCl\(_3\), 400 MHz): \(\delta\) 8.14 (d, J = 8.0 Hz, 1H, Ar-H), 7.67-7.17 (m, 8H, Ar-H), 4.72 (dd, J\(_1\) = 8.0 Hz, J\(_2\) = 4.4 Hz, 1H, CH), 4.53 (d, J = 8.0 Hz, 1H, NH), 4.17 (q, J = 7.2 Hz, 2H, OCH\(_2\)), 2.18-2.13 (m, 1H, CH), 1.25 (t, J = 7.2 Hz, 3H, CH\(_3\)), 0.89 (d, J = 6.8 Hz, 3H, CH\(_3\)), 0.76 (d, J = 7.2 Hz, 3H, CH\(_3\)). MS (m/z, %): 365 (M\(^+\), 24), 291 (99), 248 (100), 234 (99), 219 (95), 205 (44), 191 (58), 143 (63), 100 (65), 88 (98), 75 (99). Anal. Calc. for C\(_{21}\)H\(_{21}\)N\(_3\)O\(_3\): C, 69.02; H, 6.34; N, 11.50. Found C, 69.34; H, 6.47; N, 11.40.

Ethyl N-[3-(4-chlorophenyl)-4-oxo-3,4-dihydro-2-quinazolinyl]valinate (6e). Colorless oil. IR (KBr): 3413, 1738, 1688, 1585, 1313, 1264, 1084 cm\(^{-1}\). \(^1\)H NMR (CDCl\(_3\), 400 MHz): \(\delta\) 8.12 (d, J = 8.0 Hz, 1H, Ar-H), 7.64-7.18 (m, 7H, Ar-H), 4.74 (dd, J\(_1\) = 8.4 Hz, J\(_2\) = 4.8 Hz, 1H, CH), 4.50 (d, J = 8.0 Hz, 1H, NH), 4.19 (q, J = 7.2 Hz, 2H, OCH\(_2\)), 2.20-2.16 (m, 1H, CH), 1.28 (t, J = 7.2 Hz, 3H, CH\(_3\)), 0.91 (d, J = 6.4 Hz, 3H, CH\(_3\)), 0.79 (d, J = 6.8 Hz, 3H, CH\(_3\)). MS (m/z, %): 399
(M+, 8), 344 (22), 271 (90), 217 (78), 198 (55), 175 (49), 161 (100), 144 (99). Anal. Calc. for C21H22ClN3O3: C, 63.08; H, 5.55; N, 10.51. Found C, 63.20; H, 5.71; N, 10.43.

Ethyl N-[3-(4-fluorophenyl)-4-oxo-3,4-dihydro-2-quinazolinyl]valinate (6f). White solid, m.p. 72-74 °C. IR (KBr): 3412, 1731, 1691, 1588, 1313, 1264, 1084 cm⁻¹. ¹H NMR (CDCl₃, 400 MHz): δ 8.13 (d, J = 8.0 Hz, 1H, Ar-H), 7.64-7.18 (m, 7H, Ar-H), 4.74 (dd, J₁ = 8.4 Hz, J₂ = 4.4 Hz, 1H, CH), 4.51 (d, J = 8.4 Hz, 1H, NH), 4.18 (q, J = 7.2 Hz, 2H, OCH₂), 2.20-2.16 (m, 1H, CH), 1.28 (t, J = 7.2 Hz, 3H, CH₃), 0.91 (d, J = 6.8 Hz, 3H, CH₃), 0.78 (d, J = 6.8 Hz, 3H, CH₃). MS (m/z, %): 383 (M⁺, 16), 310 (35), 255 (100), 216 (14), 199 (17), 90 (25). Anal. Calc. for C21H22FN3O3: C, 65.78; H, 5.78; N, 10.96. Found C, 65.93; H, 5.70; N, 10.91.

X-Ray crystal structure analysis for compound 6b. The crystal is of monoclinic, space group P2(1)/c with a = 9.5141(10) Å, b = 19.973(2) Å, c = 9.2022(10) Å, β = 106.225(2)°, V = 1679.0(3) Å³, Z = 4, Dc = 1.335 g/cm³, F(000) = 712, μ = 0.092 mm⁻¹, R = 0.0562 and wR = 0.1494 for 3876 observed reflections with I > 2σ(I). Crystallographic data (excluding structure factors) for the structure of 6b reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-711287. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax.: (internat.) + 44 1223/336-033; e-mail: deposit@ccdc.cam.ac.uk].

General procedure for the preparation of imidazo[2,1-b]quinazoline-2,5(1H,3H)−diones 5a-5p from iminophosphorane 9
To a solution of iminophosphorane 9 (2 mmol) in dry dichloromethane (15 mL) was added isocyanate (2 mmol) under nitrogen at room temperature. The reaction mixture was stirred for 24 h at room temperature and then several drops of EtONa in ethanol were added. The mixture was stirred for 1-6 h at room temperature. The solution was concentrated under reduced pressure and the residue recrystallized from EtOH or purified by a short silica gel column to give imidazo[2,1-b]quinazoline-2,5(1H,3H)−diones 5a-5p.


1-(4-Chlorophenyl)imidazo[2,1-b]quinazoline-2,5(1H,3H)−dione (5b). Colorless crystals, m.p. 265-267 °C.

1-(3-Methylphenyl)imidazo[2,1-b]quinazoline-2,5(1H,3H)−dione (5c). White solid, m.p. 227-228 °C.

1-(4-Chlorophenyl)-3-methylimidazo[2,1-b]quinazoline-2,5(1H,3H)−dione (5e). White solid, m.p. 220-221 °C. IR (KBr): 1756, 1698, 1638, 1498, 1321 cm⁻¹. ¹H NMR (CDCl₃, 400 MHz): δ 8.25 (d, J = 8.0 Hz, 1H, Ar-H), 7.72-7.41 (m, 7H, Ar-H), 4.93 (q, J = 6.8 Hz, 1H, CH), 1.90 (d, J = 3.4 Hz, 3H, CH₃). MS (m/z, %): 291 (M⁺, 100), 262 (62), 236 (14), 220 (48), 90 (16), 77 (31). Anal. Calc. for C₁₇H₁₃N₃O₂: C, 70.09; H, 4.50; N, 14.42. Found C, 69.86; H, 4.71; N, 14.74.
3-Methyl-1-(3-methylphenyl)imidazo[2,1-b]quinazoline-2,5(1H,3H)-dione (5f). White solid, m.p. 166-168 °C. IR (KBr): 1758, 1695, 1635, 1498, 1324 cm⁻¹. ¹H NMR (CDCl₃, 400 MHz): δ 8.25 (d, J = 8.0 Hz, 1H, Ar-H), 7.68-7.31 (m, 7H, Ar-H), 4.92 (q, J = 6.8 Hz, 1H, CH), 2.45 (s, 3H, CH₃), 1.90 (d, J = 7.2 Hz, 3H, CH₃). MS (m/z, %): 305 (M⁺, 100), 276 (69), 234 (39), 101 (4), 90 (31). Anal. Calc. for C₁₅H₁₇N₃O₂: C, 70.81; H, 4.95; N, 13.76. Found C, 70.74; H, 4.70; N, 13.88.

1-Butyl-3-methylimidazo[2,1-b]quinazoline-2,5(1H,3H)-dione (5g). White solid, m.p. 98-100 °C. IR (KBr): 1750, 1690, 1638, 1467, 1319 cm⁻¹. ¹H NMR (CDCl₃, 400 MHz): δ 8.23 (d, J = 8.0 Hz, 1H, Ar-H), 7.73-7.36 (m, 3H, Ar-H), 4.74 (q, J = 6.8 Hz, 1H, CH), 3.85-3.81 (m, 2H, NCH₂), 1.79-1.37 (m, 7H, CH₂CH₂ and CH₃), 0.99 (t, J = 7.2 Hz, 3H, CH₃). MS (m/z, %): 271 (M⁺, 87), 256 (29), 229 (100), 215 (64), 200 (94), 186 (99), 145 (33), 90 (31). Anal. Calc. for C₁₅H₁₇N₃O₂: C, 76.40; H, 6.32; N, 15.49. Found C, 76.74; H, 6.15; N, 15.77.

1-Isopropyl-3-methylimidazo[2,1-b]quinazoline-2,5(1H,3H)-dione (5h). White solid, m.p. 141-142 °C. IR (KBr): 1748, 1688, 1638, 1467, 1316 cm⁻¹. ¹H NMR (CDCl₃, 400 MHz): δ 8.22 (d, J = 8.0 Hz, 1H, Ar-H), 7.71-7.35 (m, 3H, Ar-H), 4.75-4.67 (m, 2H, CH₂), 1.76 (d, J = 7.2 Hz, 3H, CH₃), 1.58 (d, J = 6.8 Hz, 3H, CH₃), 1.57 (d, J = 6.8 Hz, 3H, CH₃). MS (m/z, %): 257 (M⁺, 55), 214 (63), 186 (100), 172 (15), 145 (38), 89 (36). Anal. Calc. for C₁₄H₁₅N₃O₂: C, 65.35; H, 5.88; N, 16.33. Found C, 65.21; H, 5.93; N, 16.70.

3-Benzyl-1-phenylimidazo[2,1-b]quinazoline-2,5(1H,3H)-dione (5i). White solid, m.p. 225-227 °C. IR (KBr): 1758, 1694, 1636, 1469, 1322 cm⁻¹. ¹H NMR (CDCl₃, 400 MHz): δ 8.32 (d, J = 8.4 Hz, 1H, Ar-H), 7.66-7.04 (m, 13H, Ar-H), 5.21 (dd, J₁ = 5.2 Hz, J₂ = 2.8 Hz, 1H, CH), 4.08-3.48 (m, 2H, CH₂). MS (m/z, %): 367 (M⁺, 100), 338 (9), 262 (15), 236 (54), 220 (31), 131 (37), 90 (56). Anal. Calc. for C₂₃H₁₇N₃O₂: C, 75.19; H, 4.66; N, 11.44. Found C, 75.43; H, 4.70; N, 11.27.

3-Benzyl-1-(4-chlorophenyl)imidazo[2,1-b]quinazoline-2,5(1H,3H)-dione (5j). White solid, m.p. 152-154 °C. IR (KBr): 1763, 1691, 1637, 1468, 1323 cm⁻¹. ¹H NMR (CDCl₃, 400 MHz): δ 8.33 (d, J = 6.8 Hz, 1H, Ar-H), 7.68-6.99 (m, 12H, Ar-H), 5.21 (dd, J₁ = 4.4 Hz, J₂ = 2.8 Hz, 1H, CH), 4.06-3.46 (m, 2H, CH₂). ¹³C NMR (CDCl₃, 150 MHz): δ 169.1, 159.2, 148.3, 147.6, 134.7, 132.8, 129.3, 129.2, 128.9, 128.5, 127.9, 127.6, 126.6, 125.5, 119.6, 59.4, 33.5. MS (m/z, %): 401 (M⁺, 63), 372 (4), 296 (9), 270 (44), 255 (17), 131 (59), 90 (100). Anal. Calc. for C₂₃H₁₆ClN₃O₂: C, 68.74; H, 4.01; N, 10.46. Found C, 68.96; H, 4.24; N, 10.36.

3-Benzyl-1-butylimidazo[2,1-b]quinazoline-2,5(1H,3H)-dione (5k). White solid, m.p. 133-135 °C. IR (KBr): 1756, 1692, 1636, 1467, 1321 cm⁻¹. ¹H NMR (CDCl₃, 400 MHz): δ 8.29 (d, J = 8.0 Hz, 1H, Ar-H), 7.71-6.99 (m, 8H, Ar-H), 4.99 (dd, J₁ = 4.8 Hz, J₂ = 2.8 Hz, 1H, CH), 3.99-3.39 (m, 4H, CH₂ and NCH₂), 1.39-1.01 (m, 4H, CH₂CH₂), 0.84 (t, J = 7.2 Hz, 3H, CH₃). MS (m/z, %): 347 (M⁺, 37), 305 (81), 290 (32), 214 (100), 185 (73) 144 (76), 90 (46). Anal. Calc. for C₂₁H₂₁N₃O₂: C, 72.60; H, 6.09; N, 12.10. Found C, 72.84; H, 5.92; N, 12.04.
3-Isobutyl-1-phenylimidazo[2,1-b]quinazoline-2,5(1H,3H)-dione (5l). White solid, m.p. 206-208 °C. IR (KBr): 1762, 1695, 1634, 1470, 1326 cm⁻¹. ¹H NMR (CDCl₃, 400 MHz): δ 8.24 (d, J = 8.0 Hz, 1H, Ar-H), 7.70-7.37 (m, 8H, Ar-H), 4.95 (dd, J₁ = 7.2 Hz, J₂ = 3.6 Hz, 1H, CH), 2.34-2.24 (m, 2H, CH₂), 2.01-1.96 (m, 1H, CH), 1.02 (d, J = 6.4 Hz, 3H, CH₃), 0.95 (d, J = 6.8 Hz, 3H, CH₃). MS (m/z, %): 333 (M⁺, 4), 277 (100), 248 (46), 236 (21), 220 (52), 192 (6), 90 (11). Anal. Calc. for C₂₀H₁₉N₃O₂: C, 72.05; H, 5.74; N, 12.60. Found C, 72.18; H, 5.71; N, 12.63.

1-(4-Chlorophenyl)-3-isobutylimidazo[2,1-b]quinazoline-2,5(1H,3H)-dione (5m). White solid, m.p. 198-200 °C. IR (KBr): 1754, 1692, 1637, 1470, 1310 cm⁻¹. ¹H NMR (CDCl₃, 400 MHz): δ 8.25 (d, J = 8.0 Hz, 1H, Ar-H), 7.72-7.39 (m, 7H, Ar-H), 4.95 (dd, J₁ = 7.2 Hz, J₂ = 3.6 Hz, 1H, CH), 2.32-2.24 (m, 2H, CH₂), 2.01-1.96 (m, 1H, CH), 1.02 (d, J = 6.8 Hz, 3H, CH₃). ¹³C NMR (CDCl₃, 150 MHz): δ 170.5, 159.4, 148.8, 148.0, 134.7, 130.9, 129.3, 128.9, 126.7, 125.4, 120.0, 57.6, 37.4, 24.2, 23.2, 22.2. MS (m/z, %): 367 (M⁺, 92), 324 (26), 311 (100), 296 (47), 282 (89), 254 (74), 248 (99), 220 (36), 192 (30), 110 (30), 90 (65). Anal. Calc. for C₂₀H₁₈ClN₃O₂: C, 65.31; H, 4.93; N, 11.42. Found C, 65.14; H, 4.77; N, 11.48.

3-Isobutyl-1-(3-methylphenyl)imidazo[2,1-b]quinazoline-2,5(1H,3H)-dione (5n). White solid, m.p. 146-148 °C. IR (KBr): 1758, 1692, 1634, 1471, 1311 cm⁻¹. ¹H NMR (CDCl₃, 400 MHz): δ 8.24 (d, J = 8.0 Hz, 1H, Ar-H), 7.70-7.30 (m, 7H, Ar-H), 4.94 (dd, J₁ = 7.2 Hz, J₂ = 3.6 Hz, 1H, CH), 2.45 (s, 3H, CH₃), 2.32-2.24 (m, 2H, CH₂), 2.01-1.96 (m, 1H, CH), 1.02 (d, J = 6.8 Hz, 3H, CH₃). MS (m/z, %): 347 (M⁺, 88), 332 (16), 303 (20), 290 (100), 276 (27), 262 (84), 248 (99), 234 (94), 220 (13), 192 (20), 90 (43). Anal. Calc. for C₂₁H₂₁N₃O₂: C, 72.60; H, 6.09; N, 12.10. Found C, 72.87; H, 6.21; N, 12.04.

3-Isobutyl-1-isopropylimidazo[2,1-b]quinazoline-2,5(1H,3H)-dione (5o). White solid, m.p. 95-97 °C. IR (KBr): 1758, 1694, 1636, 1467, 1322 cm⁻¹. ¹H NMR (CDCl₃, 400 MHz): δ 8.22 (d, J = 8.0 Hz, 1H, Ar-H), 7.73-7.36 (m, 3H, Ar-H), 4.76-4.69 (m, 2H, 2CH), 2.23-2.08 (m, 2H, CH₂), 1.90-1.85 (m, 1H, CH), 1.59-1.56 (m, 6H, 2xCH₃), 0.95 (d, J = 6.8 Hz, 3H, CH₃), 0.95 (d, J = 6.8 Hz, 3H, CH₃). MS (m/z, %): 299 (M⁺, 43), 243 (99), 234 (67), 213 (100), 145 (99), 90 (37). Anal. Calc. for C₁₇H₂₁N₃O₂: C, 68.20; H, 7.07; N, 14.04. Found C, 66.44; H, 7.25; N, 13.86.

X-Ray crystal structure analysis for compound 5o. Formula C₁₇H₂₁N₃O₂, colorless crystal. The crystal is of monoclinic, space group P2(1)/c with a = 8.9420(6) Å, b = 18.1103(12) Å, c = 10.365(7) Å, β = 102.067(1)°, V = 1641.4(11) Å³, Z = 4, Dc = 1.211 g/cm³, F(000) = 640, μ = 0.081 mm⁻¹, R = 0.0614 and wR = 0.1681 for 3206 observed reflections with I > 2σ(I). Crystallographic data (excluding structure factors) for the structure of 5o reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-711288. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax.: (internat.) + 44 1223/336-033; e-mail: deposit@ccdc.cam.ac.uk].
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References


