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AMINE-INDUCED REARRANGEMENT OF 4-IMINO-4*H*-3,1-BENZ-OXAZINES TO 4-QUINAZOLINONES *VIA* AMIDINE CARBOXAMIDES

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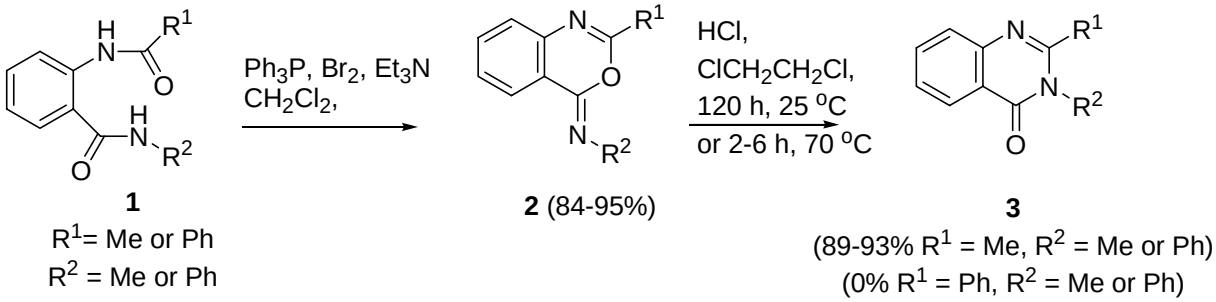
Abstract-Iminobenzoxazines (**2**) react with pyrrolidine in EtOAc at reflux to give amidine carboxamides (**11**), which cyclize to quinazolinones (**3**) on heating in 99:1 MeCN/HOAc. However, both amidines (**11d**) and (**13d**) are formed if R^1 = Ar and R^2 = Me. Hindered amidine (**11f**), R^1 = Ph, R^2 = *i*-Pr, does not cyclize to give quinazolinone (**3f**).

INTRODUCTION

Mazurkiewicz reported in 1989 that treatment of anthranilic diamide (**1**), R^1, R^2 = Me or Ph, with Ph_3P, Br_2, and Et_3N in CH_2Cl_2 for 0.2-1 h at reflux provided 84-95% of the corresponding iminobenzoxazine (**2**) (see Scheme 1).[1] Mazurkiewicz also reported that iminobenzoxazine (**2**), R^1 = Me, R^2 = Me or Ph, isomerized to quinazolinone (**3**) on treatment with excess HCl in $ClCH_2CH_2Cl$ for 120 h at 25 °C or 2-6 h at 70 °C. However, iminobenzoxazine (**2**), R^1 = Ph, R^2 = Me or Ph did not rearrange to quinazolinone (**3**) under these conditions.



1
R^1= Me or Ph
R^2 = Me or Ph

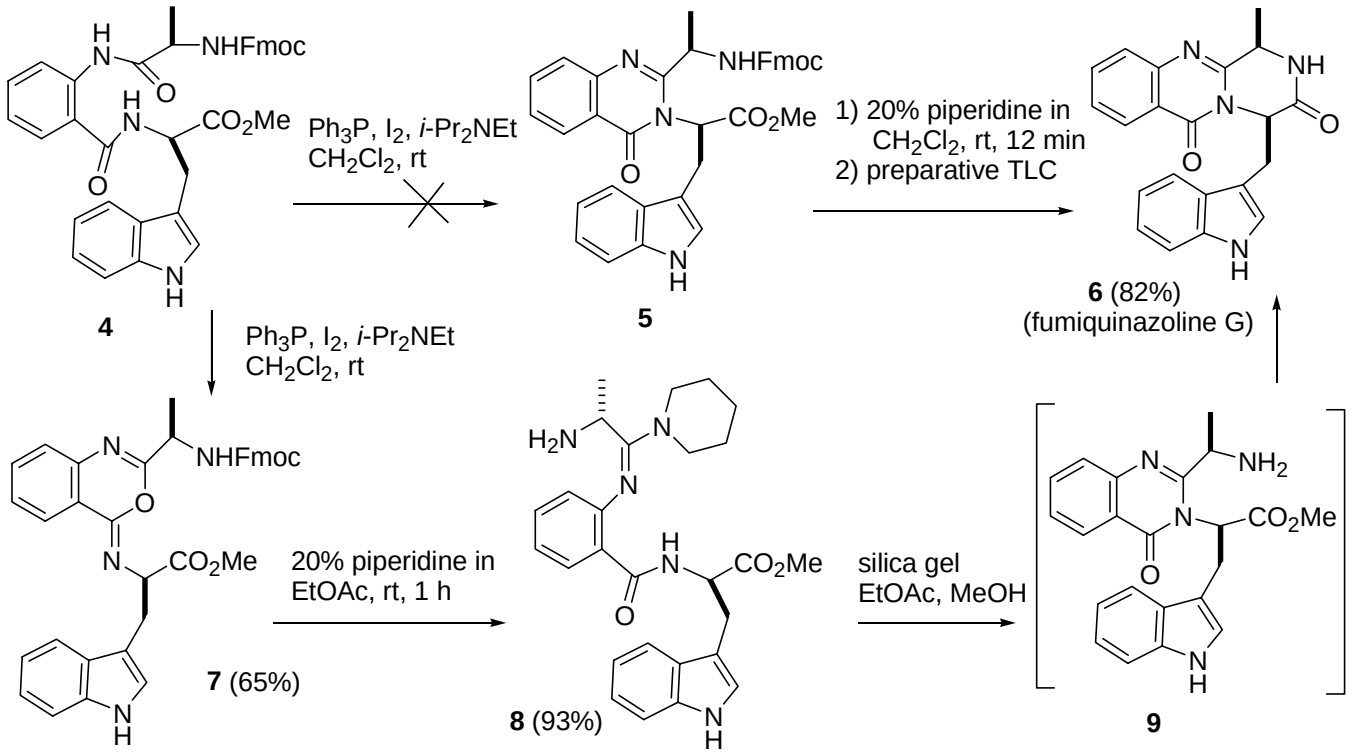
2 (84-95%)

3
(89-93% R^1 = Me, R^2 = Me or Ph)
(0% R^1 = Ph, R^2 = Me or Ph)

Scheme 1. Cyclization of diamides (**1**) to iminobenzoxazines (**2**)

In 1998, Wang and Ganesan reported a short synthesis of fumiquinazoline G (**6**) (see Scheme 2).[2a] The key step was the dehydrative cyclization of *N*-acylanthranilamide (**4**) with Ph_3P, I_2, and *i*-Pr_2NEt in CH_2Cl_2 at

25 ºC to give a cyclization product that they reported to be quinazolinone (**5**) in 65% yield. Deprotection of the Fmoc group with 20% piperidine in CH_2Cl_2 followed by preparative TLC of the crude product gave 75% of fumiquinazoline G (**6**) from the cyclization product. In 1999, we reported that the dehydrative cyclization product of **4** with Ph_3P, I_2, and *i*-Pr_2NEt is not quinazolinone (**5**), but the hydrolytically unstable 4-imino-4*H*-3,1-benzoxazine (**7**) expected from Mazurkiewicz's earlier report.[3] Treating **7** with piperidine not only deprotected the Fmoc group of **7**, but also opened the iminobenzoxazine ring to form amidine (**8**). Stirring **8** with silica gel in EtOAc and MeOH induced cyclization to give quinazolinone (**9**), which spontaneously cyclized with loss of MeOH to afford fumiquinazoline G (**6**).[3] These conditions for the rearrangement were not optimized, but were chosen to mimic the preparative TLC that was claimed to be needed for the conversion of **5** to **6**. We have used this rearrangement in the syntheses of the more complex fumiquinazolines A, B, C, E, H, and I.[4] Hart showed that iminobenzoxazines can be rearranged to the quinazolinones with excess $LiAlMe_3SPh$ at low temperature and used this in the synthesis of *ent*-alantyrpinone.[5]



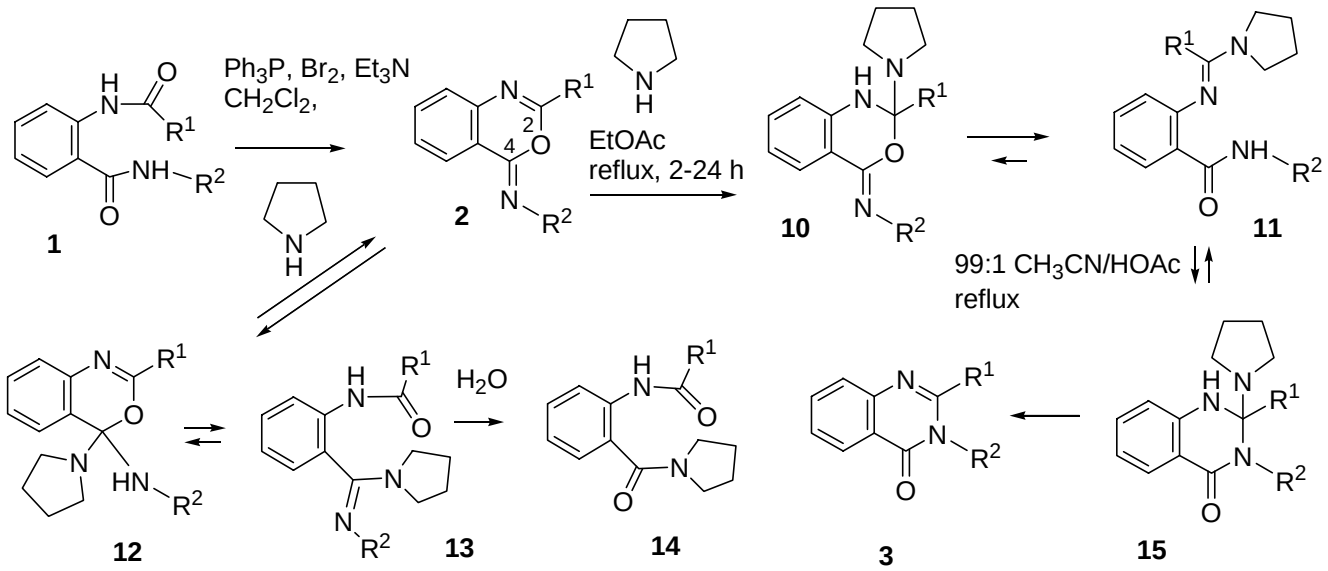
Scheme 2. Synthesis of fumiquinazaoline G (**6**) via iminobenzoxazine (**7**)

RESULTS AND DISCUSSION

We report here a study of the scope of this two-step rearrangement of iminobenzoxazines (**2**) to quinazolinones (**3**) with respect to the substituents R^1 and R^2 on the iminobenzoxazine. We have previously described the structural evidence for **2a**, **11a**, and **3a**;[3] the structures of **2b-h**¸**11b-h**, and **3b-h** were assigned analogously. Cyclization of **1** using the original Mazurkiewicz conditions with Ph_3P, Br_2 and Et_3N was complete in 1-2 h and gave high yields of iminobenzoxazines (**2**) as shown in Table 1. Much

longer reaction times were required with Ph_3P, I_2 and *i*-$PrNEt_2$ and the yields were lower. Both procedures are suitable with the more highly functionalized fumiquinazoline precursors such as **4**, which cyclize much more rapidly than **1**.[2-4]

Formation of amidine (**11**) was carried out by heating **2** with 2 equiv. of pyrrolidine in EtOAc at reflux for 2-24 h as indicated in the Experimental (see Scheme 3). Excess pyrrolidine can be removed more easily by concentration and it is slightly more reactive than piperidine so that a smaller excess of amine can be used. These conditions were chosen to minimize the excess pyrrolidine required. Amidine (**11**) can be formed at lower temperatures and more rapidly if a larger excess of pyrrolidine or piperidine is used. Iminobenzoxazine (**2**) formed amidine (**11**) more slowly than the highly functionalized fumiquinazoline precursors such as **7** formed amidines such as **8**.[2-4]



Scheme 3. Isomerization of benzoxazines (**2**) to quinazolinones (**3**).

Table 1. Conversion of Bisamides (**1**) to Quinazolinones (**3**)

Entry	R^1	R^2	% **2**	% **11**[a]	% **3**[b]	% **14**[c]
a	Me	Me	92%[d]	82%[e]	100%[e]	0%
b	Ph	Ph	88%	54-97%	92%[f]	0%
c	*i*-Pr	Ph	78%	99%	91%	0%
d	Ph	Me	78%	[g]	50%[h]	48%[h]
e	*p*-$PhNO_2$	Me	78%	[g]	79%[h]	8%[h]
f	Ph	*i*-Pr	81%	100%	0%	0%
g	*p*-$PhNO_2$	*i*-Pr	52%	100%	64%[i]	0%
h	*i*-Pr	*i*-Pr	81%	99%	92%	0%

[a] yield from **2**. [b] yield from **11**. [c] yield from **2**. [d] See reference 1. [e] See reference 3. [f] Overall yield from **2**, not **11**. [g] **11** and **13** react further to give **3** and **14**, respectively. [h] Overall yield from **2**, not **11**. [i] 18% of **11g** was recovered.

Iminobenzoxazine (**2**) has two imino esters and, in principle, attack of the secondary amine can occur at either carbon-2 to give **10**, which will open to amidine (**11**), or at carbon-4 to give **12**, which will open to amidine (**13**). The aromatic ring makes carbon-4 inherently less reactive than carbon-2 when R^1 is an alkyl group (Entries a, c and h). Even when R^1 is a phenyl group, attack still occurred only at carbon-2 if R^2 is a phenyl group (Entry b) or a sterically bulky isopropyl group (Entries f and g).

However, if R^1 is Ph and R^2 is a small methyl group, ring opening occurred to give a 1:1 mixture of amidines (**11d**) and (**13d**) (Entry d). Changing R^1 from a phenyl group to an electron withdrawing *p*-nitrophenyl group favored attack at C-2, giving a 10:1 mixture of amidines (**11e**) and (**13e**) (Entry e). Amidines (**11d**) and (**11e**) cannot be isolated, but cyclize during the reaction of **2d** and **2e** with pyrrolidine to give quinazolines (**3d**) (50% overall from **1d**) and (**3e**) (79% overall from **1e**), while amidines (**13d**) and (**13e**) are hydrolyzed by adventitious water or on workup to give diamides (**14d**) (48% from **1d**) and (**14e**) (8% from **1e**).

Heating amidines (**11b**) or (**11c**) in 99:1 MeCN/HOAc at reflux for 2 h afforded quinazolinones (**3b**) (92% from **2b**) or (**3c**) (91% from **11c**). The isomerization of **11** to **3** is probably acid catalyzed since it proceeds more rapidly in 99:1 MeCN/HOAc than in pure MeCN and does not proceed in EtOAc containing pyrrolidine. A plausible mechanism involves protonation of amidine (**11**) and cyclization of the amide nitrogen to give **15**, which will lose pyrrolidine to give **3**. Cyclization could of course occur from the amide oxygen to give **10**, which could lose pyrrolidine to give iminobenzoxazine (**2**). In the presence of pyrrolidine this cyclization is probably thermodynamically controlled so that the more stable quinazolinone (**3**) is formed. In the conversion of **1** to **2** an activated intermediate is formed, which cyclizes under conditions of kinetic control to give **2**.

The substitution pattern of **11h** was closest to that of the fumiquinazolines and its rearrangement was therefore investigated in more detail. Heating **11h** in MeCN at reflux for 10 h or in 99:1 MeCN/HOAc at 45 ºC for 4 h afforded **3h** cleanly. Alternatively, heating **2h**, 2 equiv. of pyrrolidine, and 2 equiv. of HOAc in MeCN at reflux for 36 h afforded 64% of **3h**.

Finally, amidine (**11f**) did not cyclize to quinazolinone (**3f**) on heating in MeCN with or without HOAc. The isopropyl group R^2 makes the amide nitrogen more hindered. The phenyl group R^1 makes the amidine less susceptible to nucleophilic attack. Amidine (**11g**) with an electron withdrawing *p*-nitrophenyl group R^1 is more reactive and cyclized slowly on heating in 99:1 MeCN/HOAc at reflux for 50 h to give 64% of **3g** and 18% unreacted **11g**.

In conclusion, we have established the scope and limitations of the amine-catalyzed rearrangements of iminobenzoxazines (**2**) to quinazolinones (**3**). The reaction works well with R^1 = alkyl in all cases. With R^1 = Ph, ring opening occurs at both carbons-2 and -4 to give amidines (**11d**) and (**13d**) if the nitrogen substituent R^2 is small, but the resulting quinazolinone (**3d**) is formed cleanly from amidine (**11d**). With a large nitrogen substituent R^2, amidine (**11f**) is formed cleanly, but doesn't rearrange to **3f**. When R^1 is a more electron withdrawing 4-nitrophenyl group, good yields of quinazolinones (**3e**) and (**3g**) are obtained. Quinazolines (**3b**) and (**3d**) could not be prepared by isomerization of **2b** and **2d** with HCl,[1] but are easily prepared by this two-step method proceeding through amidine (**11**).

EXPERIMENTAL

General. NMR spectra were recorded in $CDCl_3$ at 400 MHz. Chemical shifts are reported in δ, coupling constants are reported in Hz, and IR spectral data are reported in cm^{-1}.

***N*-(2-Phenyl-4*H*-3,1-benzoxazin-4-ylidene)benzenamine (2b).** A solution of Br_2 (193 mg, 1.2 mmol) in CH_2Cl_2 (0.50 mL) was added dropwise to a solution of Ph_3P (315 mg, 1.2 mmol) in CH_2Cl_2 (5 mL) under N_2. The solution was stirred for 30 min, and Et_3N (0.42 mL, 3.0 mmol) and diamide (**1b**) (316 mg, 1.0 mmol) were added. The reaction mixture was refluxed for 1.5 h, and quenched with 10% aqueous $NaHCO_3$ solution. The organic phase was separated, dried (Na_2SO_4), and concentrated. The dark residue was purified by flash chromatography on silica gel (5:1 hexane/EtOAc containing 2% Et_3N) to give 263 mg (88%) of **2b** as a white solid: mp 117-118 ºC (lit.,[1] mp 118.5-119 ºC); ^{1}H NMR 8.30 (dd, 1H, *J* = 8.0, 2.0), 8.10 (ddd, 2H, *J* = 8.4, 1.6, 1.6), 7.65 (ddd, 1H, *J* = 8.0, 8.0, 1.2), 7.55 (dd, 1H, *J* = 8.0, 1.2), 7.38-7.53 (m, 6H), 7.25 (dd, 2H, *J* = 8.0, 1.2), 7.19 (dddd, 1H, *J* = 7.8, 7.8, 1.2, 1.2); ^{13}C NMR 154.8, 146.0, 145.5, 142.1, 133.6, 132.0, 128.8 (2 C), 128.5 (2 C), 129.3, 128.1, 127.8 (2 C), 126.7, 126.4, 124.2, 122.3 (2 C), 119.4; IR (KBr) 1682, 1626, 1595, 1575.

***N*-(2-(1-Methylethyl)-4*H*-3,1-benzoxazin-4-ylidene)benzenamine (2c)** was prepared analogously from diamide (**1c**) (282 mg, 1.0 mmol). The reaction mixture was refluxed for 1.5 h, and concentrated. The dark residue was shaken with anhydrous benzene (10 mL) and the triethylamine hydrobromide was filtered off. The solution was concentrated and the resulting dark residue was purified by flash chromatography on silica gel (6:1 hexane/EtOAc containing 2% Et_3N) to give 206 mg (78%) of **2c** as a white solid: mp 53-54 °C; ^{1}H NMR 8.25 (br d, 1H, *J* = 8.0), 7.60 (ddd, 1H, *J* = 7.6,7.6, 1.6), 7.42 (dd, 2H, *J* = 8.0, 1.6), 7.36 (dd, 2H, *J* = 8.0, 8.0), 7.10-7.20 (m, 3H), 2.35 (hept, 1H, *J* = 6.8), 1.23 (d, 6H, *J* = 6.8); ^{13}C NMR 165.4, 147.4, 146.5, 143.7, 134.6, 129.7 (2 C), 129.0, 127.4, 127.3, 125.1, 123.7 (2 C), 120.5, 35.1, 20.6 (2 C); IR (KBr) 1674, 1644, 1606, 1593.

***N*-(2-Phenyl-4*H*-3,1-benzoxazin-4-ylidene)methanamine (2d)** was prepared analogously from diamide (**1d**) (254 mg, 1.0 mmol). Flash chromatography on silica gel (5:1 hexane/EtOAc containing 2% Et_3N) gave 168 mg (78%) of a mixture of **2d** and **1d** (23:1) as a colorless oil. The data for **2d** were determined from the mixture: ^{1}H NMR 8.19 (dd, 2H, *J* = 7.7, 1.2), 8.12 (br d, 1H, *J* = 8.1), 7.43-7.57 (m, 5H), 7.32 (ddd, 1H, *J* = 8.0, 8.0, 1.2), 3.32 (s, 3H); ^{13}C NMR 155.8, 148.6, 143.0, 133.7, 132.1, 132.1, 129.5 (2 C), 128.8, 128.7 (2 C), 127.6, 126.3, 120.7, 34.2.

***N*-[2-(4-Nitrophenyl)-4*H*-3,1-benzoxazin-4-ylidene]methanamine (2e)** was prepared analogously from diamide (**1e**) (300 mg, 1.0 mmol). Flash chromatography on silica gel (7:1 CH_2Cl_2/EtOAc containing 2% Et_3N) gave 232 mg (78%) of a 2.1:1 mixture of **2e** and **1e** as a light yellow solid. The data for **2e** were determined from the mixture: ^{1}H NMR 8.41 (d, 2H, *J* = 8.9), 8.36 (d, 2H, *J* = 8.9), 8.09 (d, 1H, *J* = 8.7), 7.51-7.58 (m, 2H), 7.42 (ddd, 1H, *J* = 7.5, 7.5, 1.3), 3.37 (s, 3H); ^{13}C NMR 153.9, 150.8, 147.7, 142.4, 138.0, 134.1, 130.0, 129.7 (2 C), 128.1, 126.7, 124.7 (2 C), 121.0, 34.4.

***N*-(2-Phenyl-4*H*-3,1-benzoxazin-4-ylidene)-2-propanamine (2f)** was prepared analogously to **2b** from diamide (**1f**) (1.12 g, 4.0 mmol). Flash chromatography on silica gel (5:1 hexane/EtOAc containing 2% Et_3N) gave 852 mg (81%) of **2f** as a white solid: mp 130.5-131.5 ºC; ^{1}H NMR 8.21 (ddd, 2H, *J* = 6.8, 1.6, 1.2), 8.12 (br d, 1H, *J* = 7.6, 1.2), 7.45-7.59 (m, 5H), 7.33 (ddd, 1H, *J* = 8.0, 8.0, 1.2), 4.38 (hept, 1H, *J* =

6.8), 1.31 (d, 6H, *J* = 6.4); ^{13}C NMR 156.2, 145.8, 143.3, 133.8, 133.0, 1325, 129.7 (2 C), 128.8 (3 C), 127.6, 126.9, 121.1, 47.5, 24.7 (2 C); IR (KBr) 1679, 1628, 1602, 1573.

***N*-[2-(4-Nitrophenyl)-4*H*-3,1-benzoxazin-4-ylidene]-2-propanamine (2g)** was prepared analogously to **2c** from diamide (**1g**) (0.33 g, 1.0 mmol). Recrystallization from CH_2Cl_2 gave 160 mg (52%) of **2g** as a white solid: mp 198-199 ^{o}C; ^{1}H NMR 8.31-8.41 (m, 4), 8.14 (d, 1H, *J* = 8.0), 7.59 (dd, 1H, *J* = 8.0, 8.0), 7.51 (d, 1H, *J* = 8.0), 7.40 (dd, 1H, *J* = 8.0, 8.0), 4.36 (hept, 1H, *J* = 6.7), 1.31 (br d, 6H, *J* = 6.7); ^{13}C NMR 154.1, 150.7, 144.7, 142.2, 138.1, 133.9, 129.8, 129.6 (2 C), 127.9, 127.1, 124.8 (2 C), 121.2, 47.6,24.5 (2 C); IR (KBr) 1681, 1654, 1626, 1595, 1524, 1346.

***N*-(2-(1-Methylethyl)-4*H*-3,1-benzoxazin-4-ylidene)-2-propanamine (2h)** was prepared analogously from diamide (**1h**) (248 mg, 1.0 mmol). The mixture was refluxed under N_2 for 1.5 h, and concentrated. Flash chromatography on silica gel (5:1 hexane/EtOAc containing 2% Et_3N) gave 186 mg (81%) of an 8:1 mixture of **2h** and **1h** as a colorless oil. The data for **2h** were determined from the mixture: ^{1}H NMR 8.06 (dd, 1H, *J* = 7.6, 1.2), 7.49 (ddd, 1H, *J* = 7.6, 7.6,1.6), 7.27-7.35 (m, 2H), 4.17 (hept, 1H, *J* = 6.8), 2.41 (hept, 1H, *J* = 6.8), 1.33 (d, 6H, *J* = 6.8), 1.22 (d, 6H, *J* = 6.0); ^{13}C NMR 164.6, 145.1, 141.9, 132.1, 127.4, 125.9, 125.6, 119.9, 46.1, 34.3, 23.6 (2 C), 19.6 (2 C).

1-[2-(*N*-Phenylcarboxamido)phenylimino(phenyl)methyl]pyrrolidine (11b). A solution of iminobenzoxazine (**2b**) (298 mg, 1.0 mmol) and pyrrolidine (0.17 mL, 2 mmol) in EtOAc (0.4 mL) was heated to 80 °C and stirred for 19 h. The mixture was cooled, diluted with EtOAc (5.0 mL), and concentrated to give 375 mg (>100%) of crude **11b** as a light brown oil. The residue was triturated with Et_2O (1.0 mL), and the resulting crystals were filtered and washed with additional ether (3 × 1.0 mL) to give 203 mg (54%) of pure amidine carboxamide **11b** as a white solid: mp 129.5-130.5°C; ^{1}H NMR 8.17 (dd, 1H, *J* = 7.6, 1.6), 7.75 (dd, 2H, *J* = 8.4, 1.2), 7.38 (dd, 2H, *J* = 8.0, 8.0), 7.20-7.30 (m, 3H), 7.08-7.17 (m, 3H), 6.94 (ddd, 1H, *J* = 7.6, 7.6, 1.2), 6.87 (ddd, 1H, *J* = 8.0, 8.0, 1.6), 6.25 (dd, 1H, *J* = 8.0, 1.2), 3.87 (br, 2H), 3.23 (br, 2H), 2.05 (br, 2H), 1.90 (br, 2H); ^{13}C NMR 165.3, 159.8, 149.3, 139.0, 133.9, 131.0, 130.4, 129.0 (2 C), 128.9, 128.4 (2 C), 128.3 (2 C), 125.6, 124.5, 123.4, 121.4., 120.2 (2 C), 49.5, 47.7, 25.7, 24.8; IR (KBr) 1665, 1598, 1582, 1568, 1536.

A similar reaction of **2b** (300 mg, 1.0 mmol) in neat pyrrolidine (0.5 mL, 6 mmol) was complete in 2 h at 80 °C and gave 360 mg (97%) of **11b**.

2,3-Diphenyl-4(3*H*)-quinazolinone (3b). A solution of oily crude **11b** (from 1.0 mmol of **2b**) in 99:1 MeCN/AcOH (5 mL) was stirred for 2 h at 80 °C. The reaction mixture was concentrated, and the residue was purified by flash chromatography on silica gel (2:1 hexane/EtOAc) to give 275 mg (92% from **2b**) of **3b** as a white solid: mp 156-157 °C (lit.,[6] mp 157 °C); ^{1}H NMR 8.37 (ddd, 1H, *J* = 8.0, 1.2, 1.2), 7.78-7.86 (m, 2H), 7.55 (ddd, 1H, *J* = 8.0, 5.2, 2.2), 7.18-7.36 (m, 8H), 7.15 (ddd, 2H, *J* = 7.0, 1.6, 1.6); ^{13}C NMR 162.2, 155.1, 147.4, 137.6, 135.4, 134.7, 129.2, 129.0 (2 C), 128.9 (4 C), 128.3, 127.9 (2 C), 127.7, 127.2, 127.1, 120.9; IR (KBr) 1684, 1603, 1583, 1553.

1-[2-(*N*-Phenylcarboxamido)phenylimino(phenyl)methyl]pyrrolidine (11c). A solution of iminobenzoxazine (**2c**) (66 mg, 0.25 mmol) and pyrrolidine (0.045 mL, 0.5 mmol) in EtOAc (0.15 mL) was heated to 80 °C and stirred for 12 h. The mixture was cooled, diluted with EtOAc (5.0 mL), and concentrated to give 80 mg (99%) of a 7:1 mixture of **11c** and **1c** as a colorless sticky oil.

A similar reaction of **2c** (264 mg, 1.0 mmol) in neat pyrrolidine (0.5 mL, 6 mmol) was complete in 2 h at 80 °C and gave 321 mg (99%) of a 5:1 mixture of **11c** and **1c** as a colorless sticky oil.

The data for **11c** were determined from the mixture: ^{1}H NMR 11.20 (br, 1H, NH), 8.22 (dd, 1H, *J* = 7.6, 1.2), 7.66 (ddd, 2H, *J* = 8.4, 1.2, 1.2), 7.25-7.37 (m, 3H), 7.09 (dddd, 1H, *J* = 7.6, 7.6, 1.2, 1.2), 7.03 (ddd, 1H, *J* = 8.4, 8.4, 1.2), 6.61 (dd, 1H, *J* = 8.0, 1.2), 3.42 (br, 4H), 2.16 (hept, 1H, *J* = 6.8), 1.88 (br, 4H), 1.22 (br d, 6H, *J* = 6.8); ^{13}C NMR 165.2, 163.4, 149.7, 138.8, 131.2, 130.8, 128.8 (2 C), 124.2, 123.4, 132.0, 121.1, 120.2 (2 C), 48.9 (br, 2 C), 31.6, 25.1 (br, 2 C), 20.0 (2 C).

3-(1-Methylethyl)-2-phenyl-4(3*H*)-quinazolinone (3c). A solution of the oily 7:1 mixture of **11c** and **1c** (from 1.0 mmol of **2c**) in 99:1 MeCN/AcOH (5.0 mL) was stirred for 2 h at reflux. The reaction mixture was concentrated, and the residue was purified by flash chromatography on silica gel (3:1 hexane/EtOAc) to give 241 mg (91% from **11c**) of **3c** as a white solid: mp 143-144 °C (lit.,[7] mp 136-137 ºC); ^{1}H NMR 8.27 (br d, 1H, *J* = 8.0), 7.70-7.80 (m, 2H), 7.48-7.60 (m, 3H), 7.45 (ddd, 1H, *J* = 8.0, 6.4, 1.6), 7.27 (dd, 2H, *J* = 7.2, 1.6), 2.29 (hept, 1H, *J* = 6.8), 1.22 (br d, 6H, *J* = 6.8); ^{13}C NMR 162.3, 161.5, 147.7, 137.4, 134.3, 129.8 (2 C), 129.1, 128.3 (2 C), 127.2, 126.9, 126.4, 120.7, 32.3, 21.2 (2 C); IR (KBr) 1676, 1602, 1589, 1571.

3-Methyl-2-phenyl-4(3*H*)-quinazolinone (3d) and 2-(Benzoylamino)-pyrrolidinylbenzamide (14d). A solution of Br_2 (194 mg, 1.2 mmol) in CH_2Cl_2 (2 mL) was added dropwise to a solution of Ph_3P (315 mg, 1.2 mmol) in CH_2Cl_2 (7.5 mL) under N_2. The solution was stirred for 10 min, and Et_3N (0.42 mL, 3.0 mmol) and diamide (**1d**) (254 mg, 1.0 mmol) were added. The reaction mixture was refluxed under N_2 for 2 h, cooled and concentrated. The residue was taken up in cold benzene (10 mL), and triethylamine hydrobromide was filtered off. The filtrate was concentrated and the resulting dark crude **2d** was dissolved in a solution of pyrrolidine (0.17 mL, 2 mmol) in EtOAc (0.6 mL), and stirred for 16 h at 80 °C. The mixture was cooled, and excess pyrrolidine was removed under reduced pressure. The resulting dark residue was purified by flash chromatography on silica gel (2:1 hexane/EtOAc containing 2% Et_3N) to give 83 mg (50%) of **3d** as a white solid followed by 157 mg (48%) of a 20:1mixture of **14d** and **1d** as a colorless oil.

The data for **3d**: mp 133-134 °C (lit.,[8] mp 133 °C); ^{1}H NMR 8.35 (d, 1H, *J* = 8.0), 7.72-7.81(m, 2H), 7.49-7.61 (m, 6H), 3.51 (s, 3H); ^{13}C NMR 163.7, 157.1, 148.3, 136.4, 135.3, 131.0, 129.9 (2 C), 129.0 (2 C), 128.5, 127.8, 127.7, 121.5, 35.2; IR (KBr) 1680, 1609, 1589, 1563.

The data for **14d** were determined from the mixture:[9] ^{1}H NMR 10.8 (br, 1H, NH), 8.56 (br d, 1H, *J* = 7.9), 7.99 (d, 2H, *J* = 8.0), 7.40-7.59 (m, 5H), 7.13 (dd, 1H, *J* = 8.0, 8.0), 3.67 (t, 2H, *J* = 6.7), 3.55 (t, 2H, *J* = 6.7), 1.93-2.04 (m, 2H), 1.81-1.93 (m, 2H); ^{13}C NMR 170.0, 166.1, 138.7, 135.5, 132.4, 132.2, 129.7 (2 C), 128.8, 128.3 (2 C), 125.0, 123.6, 123.0, 51.4, 47.5, 27.4, 25.2; IR 3460 (br), 1673, 1621, 1591, 1521.

3-Methyl-2-(4-nitrophenyl)-4(3*H*)-quinazolinone (3e) and 2-(4-Nitrobenzoylamino)pyrrolidinylbenzamide (14e). A solution of Br_2 (0.063 mL, 1.2 mmol) in CH_2Cl_2 (2. mL) was added dropwise to a solution of Ph_3P (315 mg, 1.2 mmol) in CH_2Cl_2 (7.5 mL) under N_2. The solution was stirred for 10 min, and Et_3N (0.42 mL, 3.0 mmol) and diamide (**1e**) (254 mg, 1.0 mmol) were added. The reaction mixture was refluxed under N_2 for 2 h, cooled and concentrated. The residue was taken up in benzene (20 mL), and triethylamine hydrobromide was filtered off. The filtrate was concentrated and the resulting dark **2e** was dissolved in a solution of pyrrolidine (0.17 mL, 2 mmol) in EtOAc (0.8 mL), and stirred for 24 h at 80 °C.

The mixture was cooled down, and excess pyrrolidine was removed under lowered pressure. The resulting dark residue was purified by flash chromatography on silica gel (1:1 hexane/EtOAc containing 2% Et_3N) to give 221 mg (79%) of **3e** as a white solid followed by 23 mg (8%) of a 2.1:1 mixture of **14e** and **1e** as a light yellow solid.

Data for **3e**:[10] mp 190-191 °C; ^{1}H NMR 8.42 (d, 2H, *J* = 8.5), 8.36 (d, 1H, *J* = 7.9), 7.81 (d, 2H, *J* = 8.5), 7.80 (dd, 1H, *J* = 8.5, 6.8), 7.74 (d, 1H, *J* = 8.5), 7.56 (dd, 1H, *J* = 7.9, 6.8), 3.51 (s, 3H); ^{13}C NMR 163.3, 154.8, 149.6, 147.9, 142.1, 135.6, 130.4 (2 C), 128.7, 128.6, 127.8, 125.1 (2 C), 121.6, 35.1; IR (KBr) 1682, 1605, 1583, 1566, 1516, 1348.

The data for **14e** were determined from the mixture: ^{1}H NMR 11.30 (br, 1H, NH), 8.56 (br d, 1H, *J* = 8.6), 8.34 (br d, 2H, *J* = 9), 8.15 (br d, 2H, *J* = 9), 7.45-7.54 (m, 2H), 7.17 (dd, 1H, *J* = 8.0, 8.0), 3.68 (t, 2H, *J* = 6.8), 3.60 (t, 2H, *J* = 6.4), 1.95-2.07 (m, 2H), 1.84-1.95 (m, 2H); ^{13}C NMR 169.9, 163.9, 141.1, 138.5, 134.0, 132.1, 129.5 (2 C), 129.1, 124.9 (2 C), 124.6, 124.2, 122.4, 51.6, 47.7, 27.5, 25.2.

1-[2-(*N*-1-Methylethylcarboxamido)phenylimino(phenyl)methyl]pyrrolidine (11f). A solution of iminobenzoxazine (**2f**) (70 mg, 0.26 mmol) and pyrrolidine (0.045 mL, 0.52 mmol) in EtOAc (0.2 mL) was heated to 80 °C and stirred for 18 h. The mixture was cooled, and concentrated under lowered pressure to give 90 mg (100%) of **11f** as a white solid: mp 139-140 °C; ^{1}H NMR 9.41 (br d, 1H, NH, *J* = 7.6), 8.07 (dd, 1H, *J* = 7.6, 1.6), 7.14-7.26 (m, 3H), 7.04-7.10 (m, 2H), 6.91 (ddd, 1H, *J* = 7.6, 7.6, 1.2), 6.82 (ddd, 1H, *J* = 7.2, 7.2, 1.2), 6.23 (dd, 1H, *J* = 8.0, 1.2), 4.29-4.43 (m, 1H), 3.78 (br, 2H), 3.22 (br, 2H), 2.05 (br, 2H), 1.93 (br, 2H), 1.29 (br d, 6H, *J* = 6.4); ^{13}C NMR 166.2, 159.2, 149.5, 134.2, 130.5, 130.3, 128.9, 128.3 (2 C), 128.1 (2 C), 125.7, 124.3, 121.5, 49.5 (br), 47.4 (br), 41.2, 26.0 (br), 25.0 (br), 23.3 (2 C); IR (KBr) 3182 (br), 1643, 1584, 1566, 1520.

A similar reaction of **2f** (264 mg, 1.0 mmol) in neat pyrrolidine (0.5 mL, 6 mmol) was complete in 2 h at 80 °C and gave 335 mg of **11f** (99%).

1-[2-(*N*-1-Methylethylcarboxamido)phenylimino(4-nitrophenyl)methyl]pyrrolidine (11g). A solution of iminobenzoxazine (**2g**) (160 mg, 0.50 mmol) and pyrrolidine (0.090 mL, 1.0 mmol) in EtOAc (1.0 mL) was heated to 70 °C and stirred for 24 h. The mixture was cooled, and concentrated under reduced pressure to give 190 mg (100%) of **11g** as a yellow solid: mp 195-196 °C; ^{1}H NMR 8.91 (br, 1H, NH), 8.10 (br d, 2H, *J* = 9), 8.02 (dd, 1H, *J* = 7.3, 1.2), 7.27 (br d, 2H, *J* = 9), 6.94 (ddd, 1H, *J* = 7.3, 7.3, 1.7), 6.87 (dd, 1H, *J* = 7.3, 7.3), 6.21 (br d, 1H, *J* = 7.9), 4.30-4.41 (m, 1H), 3.79, (br, 2H), 3.18 (br, 2H), 2.08 (br, 2H), 1.96 (br, 2H), 1.29 (br d, 6H, *J* = 6.7); ^{13}C NMR 166.9, 157.7, 149.3, 148.7, 141.6, 131.8, 131.6, 130.1 (2 C), 127.1, 124.9, 124.7 (2 C), 123.2, 50.4 (br), 48.5 (br), 42.3, 27.0 (br), 25.8 (br), 24.2 (2 C); IR (KBr) 3230, 1734, 1646, 1577, 1520, 1350.

3-(1-Methylethyl)-2-(4-nitrophenyl)-4(3*H*)-quinazolinone (3g). A solution of **11g** (114 mg, 0.30 mmol) in 99:1 MeCN/AcOH (5.0 mL) was stirred for 50 h at 90 °C. The reaction mixture was concentrated, and the residue was purified by flash chromatography on silica gel (2:1 hexane/EtOAc, containing 2% Et_3N) to give 45 mg (18%) of recovered **11g** followed by 41 mg (64%) of **3g** as a white solid: mp 223-224 °C; ^{1}H NMR 8.41 (br d, 2H, *J* = 8.5), 8.32 (br d, 1H, *J* = 7.9), 7.72-7.82 (m, 3H), 7.69 (br d, 1H, *J* = 7.9), 7.54 (dd, 1H, *J* = 7.9, 7.9), 4.19 (hept, 1H, *J* = 6.7), 1.62 (br d, 6H, *J* = 6.8); ^{13}C NMR 163.1, 155.3, 149.4, 147.4, 143.3, 135.5, 129.7 (2 C), 128.6, 128.3,127.6, 125.2 (2 C), 123.2, 55.4, 20.7 (2 C); IR (KBr) 1669, 1608,

1589, 1573, 1517 ,1350; HRMS (EI) *m/z* 309.1110 (calcd for $C_{17}H_{15}N_3O_3$, M^+, 309.1113).

1-[2-(2-*N*-Methylethylcarboxamido)phenylimino(1-methylethyl)methyl]pyrrolidine (11h). A solution of the 8:1 mixture of **2h** and **1h** (from 0.50 mmol of **1h**) and pyrrolidine (0.085 mL, 1.0 mmol) in EtOAc (0.20 mL) was heated to 80 °C and stirred for 1.5 h. The mixture was cooled, and concentrated to give 148 mg (99%) of a 7:1 mixture of **11h** and **1h** as a light brown sticky residue.

The data for **11h** were determined from the mixture: ^{1}H NMR 8.88 (br d, 1H, NH, *J* = 1.2), 8.13 (dd, 1H, *J* = 8.0, 2.0), 7.25 (ddd, 1H, *J* = 8.0, 8.0, 1.6), 6.98 (ddd, 1H, *J* = 7.6, 7.6, 1.2), 6.57 (dd, 1H, *J* = 8.0, 1.2), 4.27 (m, 1H), 3.42 (br, 4H), 2.12 (hept, 1H, *J* = 7.2), 1.89 (br, 4H), 1.20 (br d, 6H, *J* = 6.8), 1.16 (br d, 6H, *J* = 6.8); ^{13}C NMR 166.0, 162.4, 149.6 (br), 130.7, 130.6, 126.5, 123.0, 121.2, 48.6 (br, 2 C), 41.0, 31.2, 25.2 (br, 2 C), 23.1 (2 C), 19.6 (2 C).

2,3-Bis(1-methylethyl)-4(3*H*)-quinazolinone (3h). A solution of the 7:1 mixture of **11h** and **1h** (150 mg, 0.50 mmol) in MeCN (5 mL) was refluxed for 10 h, the reaction mixture was cooled and concentrated to give crude quinazolinone (**3h**). Flash chromatography on silica gel (2:1 hexane/EtOAc) gave 106 mg (92%) of **3h** as a white solid.

Alternatively, 150 mg (0.50 mmol) of the 7:1 mixture of **11h** and **1h** was dissolved in 99:1 MeCN/HOAc (5 mL). The mixture was stirred at 45 °C for 4 h, cooled, and concentrated to give crude quinazolinone (**3h**). Flash chromatography on silica gel (2:1 hexane/EtOAc) gave 99 mg (86%) of **3h**.

Alternatively, to a solution of the 8:1 mixture of **2h** and **1h** (135 mg, 0.50 mmol) in MeCN (5 mL) was added pyrrolidine (0.085 mL, 1.0 mmol) and AcOH (0.061 mL, 1.0 mL). The reaction mixture was refluxed for 36 h, cooled and concentrated. Flash chromatography on silica gel (2:1 hexane/EtOAc) gave 74 mg (64%) of **3h**: mp 74.5-75.5 °C; ^{1}H NMR 8.21 (dd, 1H, *J* = 8.0, 1.6), 7.68 (br dd, 1H, *J* = 6.8, 7.3), 7.61 (br d, 1H, *J* = 7.3), 7.39 (br dd, 1H, *J* = 8.0, 6.8), 4.70 (br, 1H), 3.21 (hept, 1H, *J* = 6.8), 1.68 (br d, 6H, *J* = 6.8), 1.39 (br d, 6H, *J* = 6.0); ^{13}C NMR 162.1, 161.0 (br), 147.0, 133.6, 126.7, 126.3 (br), 126.0, 121.5(br), 50.2 (br), 32.3, 21.6 (2 C), 19.9 (2 C); IR (KBr) 1664, 1608, 1588, 1571; HRMS (EI) *m/z* 230.1424 (calcd for $C_{14}H_{18}N_2O$, M^+, 230.1419.

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