Quantitative Cascade Condensations between *o*-Phenylenediamines and 1,2-Dicarbonyl Compounds without Production of Wastes

Gerd Kaupp*[a] and M. Reza Naimi-Jamal[a]

Keywords: Cascade reactions / Green chemistry / Heterocycles / Ketones / Solid-state reactions / Waste prevention

o-Phenylenediamines **1** underwent a series of cascade condensations with 1,2-dicarbonyl compounds to afford quantitative yields (eight cases) of heterocycles in solid-state syntheses that avoided waste formation. The products were produced in pure form and did not require purifying workup. The components were ball-milled in stoichiometric ratio, or in exceptional cases they were melted together and heated in the absence of solvents (some of them giving quantitative yields). Benzils and 2-hydroxy-1,4-naphthoquinone afforded quinoxaline derivatives **3** and **5**, 2-oxoglutaric acid gave a 3-oxodihydroquinoxaline **7**, and oxalic acid afforded the dihydroquinoxaline-2,3-dione **9**. This last condensed with **1a** in the melt, to afford a mixture of bis(benzimidazolyl) **10** and fluoflavin **11**. Alloxane hydrate provided a 100% yield of the 3-oxodihydroquinoxaline-2-carbonylureas **15/16** at room temperature. Parabanic acid required a melt reaction providing a 78% yield of 3-oxodihydroquinoxalinyl-2-urea **22** and side products. Despite numerous reaction steps, most of these uncatalyzed stoichiometric reactions proceeded quantitatively in the solid state to give only one product (plus water), with unsurpassed atom economy. If catalysis with HCl was tried, the results were inferior. If melt reactions were required it appeared to be advantageous to have the products crystallize directly at the reaction temperature. The synthetic results have been interpreted mechanistically and compared to some similar solution reactions that do not exhibit the benefits of the solid-state techniques.

Introduction

Cascade reactions, with their high atom economy, are particularly benign if they proceed quantitatively from stoichiometric mixtures of the reagents. Most suitable for that purpose are solid-state techniques, with their favorable kinetics,[1] but melt reactions should also be favorable if the product crystallizes during reaction. We report here on various cascade condensations between *o*-phenylenediamines and 1,2-dicarbonyl compounds that ran with 100% yields, variously in the solid state, or both in the solid state and in the melt at higher temperatures, or only in the melt upon heating.

Results and Discussion

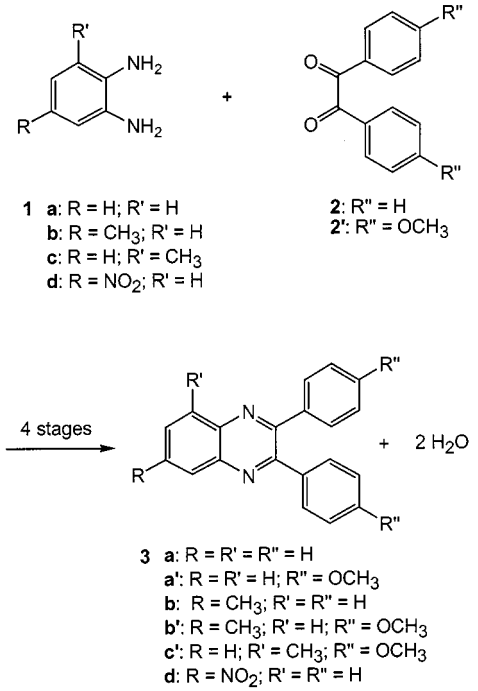
Condensation between *o*-Phenylenediamines and Benzils

Condensation between *o*-phenylenediamine **1a** and benzil **2** in refluxing ethanol gave the quinoxaline **3a** in 62%[2] or 87% yields[3] (Scheme 1). Our previous solid-state cascades of **1** with ninhydrin[4] prompt us to report improvements of the synthesis of quinoxaline and of numerous substituted quinoxalines to give 100% yields. These reactions may appear common and simple; from the point of view of sustainable chemistry, however, it is extremely useful to perform them in stoichiometric 1:1 reactant ratio without production of wastes in order to avoid the necessity for workup with solvent (Scheme 1).

It is highly remarkable that we obtained three different quinoxalines − **3a**, **3a′**, and **3b′** − in quantitative yields in the solid state, even though a 4-cascade (addition twice, and elimination twice) was required. They were prepared by grinding the appropriate starting materials together in a ball-mill for up to 1 h. If solid-state techniques were not applicable due to low melting eutectica, it was still better to perform stoichiometric melt reactions rather than solution reactions with acid catalysis.[2]

It turned out that our stoichiometric cascade reactions in the melt were also quantitative and complete, because the products crystallized directly from the melts (Table 1). The water of reaction in all of these condensations was easily removed from the product crystals by heating under vacuum. No further workup was necessary, as the products were pure. In the previous solution reactions (AcOH, EtOH), the yields were much lower (62−87% for **3a**,[2,3] 85% for **3a′**[3]), and additional waste was produced by the auxiliaries and by the necessary workup in solvents. The products **3b**, **3c′**, and **3d** could only be prepared in stoichiometric melt reactions at 100 °C, 80 °C, and 160 °C, as the

[a] University of Oldenburg, FB Chemie, Organische Chemie I
Postfach 2503, 26111 Oldenburg, Germany
Fax: (internat.) + 49-(0)441/798-3409
E-mail: kaupp@kaupp.chemie.uni-oldenburg.de



Scheme 1. Quantitative synthesis of quinoxaline derivatives

first two mixtures became sticky at room temperature and the third did not react in the solid state, probably for crystallographic reasons.

Table 1. Yields of **3** from stoichiometric **1** + **2** mixtures under various reaction conditions

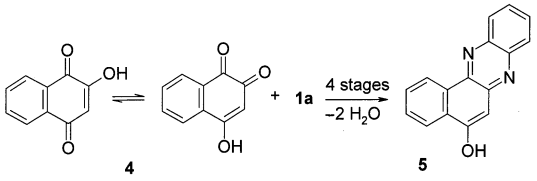
3	*T* [°C]	Phase	Yield (%)	Yield (%) in solution	M.p. [°C]	Ref. m.p. [°C]
a	25	solid	100	62[2]	123	121[2]
	100	melt	100	87[3]		
a′	75	solid	100	85[3]	146−147	145.5−146[3]
	130	melt	100			
b	100	melt	100	68[5]	109−110	111[6]
b′	80	solid	100	−	123−125	−
	130	melt	100			
c′	80	melt	100	−	156−158	−
d	160	melt	100	57[7]	186.5−187.5	187.5−187.9[7]

Substituted quinoxalines are known for their varied biological activities. For example, **3a** had a high antimicrobial activity towards *Staphylococcus aureus*[8] and it had some inhibiting action on platelet-derived growth factor receptor (PDGFR) kinase.[2]

The versatility of the solid-solid reactions is remarkable, as various crystalline reagents, most probably with different crystal packings, fulfill the necessary requirements to undergo phase rebuilding, phase transformation, and thereafter crystal disintegration.[1] It might therefore be expected that this 4-cascade type may be extendable to related condensations.

Condensation between *o*-Phenylenediamine and 2-Hydroxy-1,4-naphthoquinone

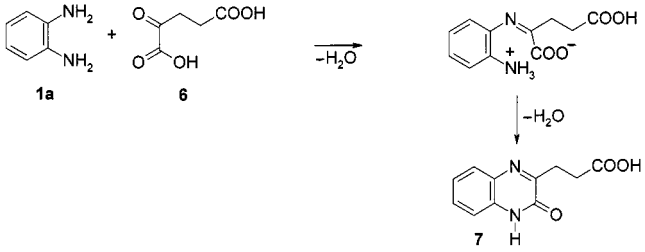
2-Hydroxy-1,4-naphthoquinone **4** and **1a** gave **5** in 100% yield in solid-state 1:1 runs in 15 min at 70 °C (Scheme 2). If the same reaction was performed as a melt (30 min at 120 °C), a 100% yield was also obtained. The same product was reported from a synthesis in refluxing acetic acid, but in 77% yield after a complicated workup.[9] This reaction resembles that of benzils, if **4** is formulated as its *o*-quinone tautomer.



Scheme 2. Quantitative synthesis of benzo[*a*]phenazin-5-ol (**5**)

Condensation between *o*-Phenylenediamine and 2-Oxoglutaric Acid

If 1:1 mixtures of the α-oxo acid **6** and **1a** were ground together, salt formation and cyclization to give **7** took place (Scheme 3). Ball-milling for 10 min at room temperature gave a 90% yield of **7**, which could not be increased by further milling for 1 h. However, if the previously milled mixture was heated to 120−125 °C for 30 min, a quantitative yield of **7** was obtained without intermediate melting. Furthermore, it sufficed to cogrind 1:1 mixtures of **1a** and **6** in a mortar and heat to 120−125 °C in a vacuum for 30 min to obtain a 100% yield. This compared favorably with the 95%[10] or 82−100% yields[11] obtained under neutral or acidic solution conditions. It would be expected that the reaction would start by condensation of the oxo group. The amide formation might be hindered by some salt formation with the unconjugated carboxylic acid group, so that the last 10% of conversion would require heating of the crystalline mixture. Compound **7** is a useful building block[10] and a strong fluorescent agent.[11]

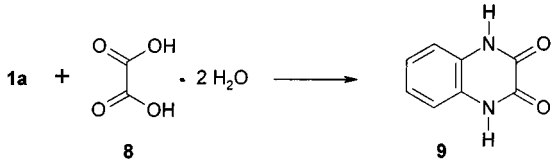


Scheme 3. Quantitative condensation between *o*-phenylenediamine and 2-oxoglutaric acid

Condensation between *o*-Phenylenediamine and Oxalic Acid

It is of considerable interest that even oxalic acid (**8**), which formed a high-melting salt (m.p. > 300 °C) upon cogrinding with **1a**, reacted quantitatively, though at higher temperature (150 °C, 8 h or 180 °C, 20 min), to give a 100%

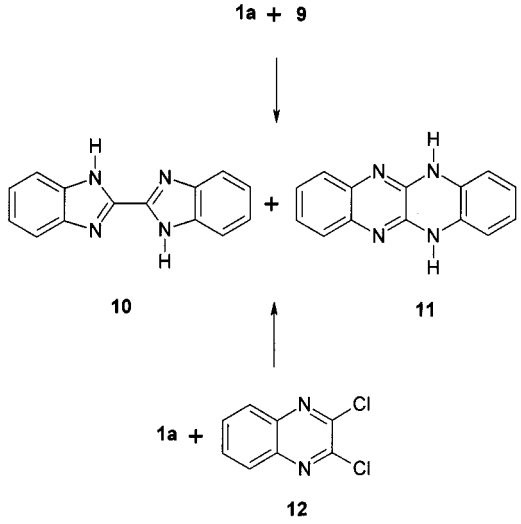
yield of 1,4-dihydroquinoxaline-2,3-dione (**9**) in a solid-state cascade condensation (Scheme 4). It was possible to start either with oxalic acid dihydrate or with the dehydrated acid.



Scheme 4. Quantitative condensation between *o*-phenylenediamine and oxalic acid

Previously, this reaction had been performed with excess **8** at 160 °C, but no yield had been reported and the product had to be separated from the excess oxalic acid.[12] Compound **9** is known as the pharmacophore for the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor antagonists in the treatment of neurodegenerative disorders.[13]

Compound **9** did not condense with a second molecule of **1a** at 180 °C, but did so slowly in a melt reaction at 200 °C (incomplete after 20 h). However, heating of a 1:1 mixture of **1a** and **9** to 240 °C for 12 h gave complete reaction, to provide **10** and its isomer fluoflavin (**11**)[14] in 96% and 4% yields (Scheme 5). Almost the same product ratio (95:5) was obtained at 355 °C (1 h). Only a slight change in the product ratio (80% **10** and 20% **11**) was obtained when equimolar quantities of **1a**·2HCl and **9** were heated to 240 °C in a vacuum for 6 h. Interestingly, the product ratio was reversed in the synthesis of fluoflavin (**11**) from **1a** and 2,3-dichloroquinoxaline (**12**) at 150 °C for 30 min in a 1:1 melt. The product mixture contained **11** and **10** in the ratio of 7.6:1. The structures of **10** and **11** were clearly distinguishable by their ^{1}H NMR and ^{13}C NMR signals, and were unequivocally assigned by an X-ray structure determination of **10**.[15] The tautomerism of **11** was determined by DFT calculations at the B3LYP/6-31G* level, which indicated that the mirror-symmetric tautomer was 1.74 kcal·mol^{-1} more stable than the centro-symmetric one. Furthermore, **10** was found to be 3.38 kcal·mol^{-1} more stable than **11** by the same technique. However, no thermal rearrangement of **11** into **10** (or the reverse) could be detected on heating to 340 °C for 90 min in a vacuum.



Scheme 5. Solvent-free syntheses of mixtures of the compounds **10** and fluoflavin (**11**)

Condensation between *o*-Phenylenediamine and Alloxane Hydrate

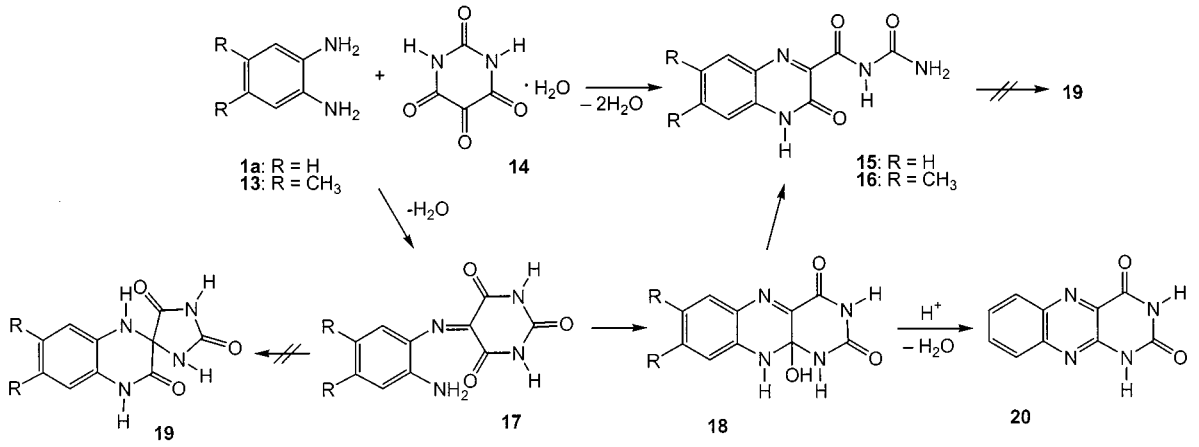
Alloxane hydrate (**14**) reacted quantitatively with *o*-phenylenediamines **1a** or **13** at room temperature in the solid state (Scheme 6) to give the products **15** or **16**, obviously in 4-cascades consisting of substitution, elimination, cyclization, and ring-opening. Conversely, a stoichiometric solid-state run with **1a**·2HCl and **14** provided a mixture of **15** (30%) and alloxazine (**20**, 68%) at room temperature. The corresponding reactions between **1a** and **14** in boiling 1-pentanol or boiling pyridine gave mixtures of **15** (23%) and **20** (13%),[16] but almost quantitatively **20** when the reaction was performed in acidic solution (or with the dihydrochloride of **1a**), and **15** in a solution of sodium acetate (yield not reported).[17] The structure of **15** had already been suggested by Hinsberg[12] for the product of the reaction between alloxane hydrate (**14**) and **1a** in neutral aqueous solution. We repeated this solution reaction and obtained the same product **15**, though in only 75% yield. The superiority of the uncatalyzed solid-state synthesis of **15** was also clearly established by comparison with the melt reaction at 120−130 °C, which was incomplete and yielded 47% of **15** in addition to 14% of alloxazine (**20**). The neutral solid-state reaction makes compounds **15** and **16** very easily available in pure forms.

The structures of **15** and **16** were supported by the ^{1}H and ^{13}C NMR spectra of the products. Compounds **17** were ruled out by the occurrence of three carbonyl-^{13}C signals, while the spiro compounds **19** could also be discounted, since there were no suitable signals for the spiro-C in the ^{13}C NMR spectra.[18]

The mechanistic interpretation is given in Scheme 6. While **17** is an obvious primary intermediate, the presumed second intermediate **18** may ring-open to give **15/16** and eliminate water to give **20**. Obviously, the latter reaction requires acid catalysis, which is not operative in the quantitative solid-state syntheses of **15** and **16**. In water or in acidic media, however, **20** may be formed. Compound **15** does not seem to be an intermediate in the synthesis of **20**, as it could not be transformed into **20** by heating it to 250 °C, nor in the presence of HCl gas (24 h), nor by heating it under reflux in aqueous HCl solution.

Condensation between *o*-Phenylenediamine and Parabanic Acid

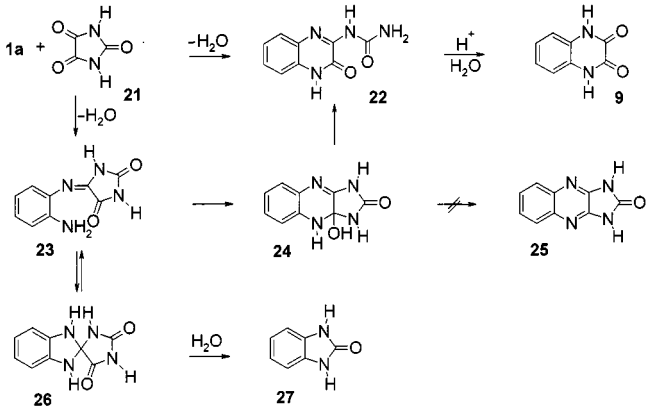
Parabanic acid (**21**, m.p. 103−105 °C) could not be induced to react with **1a** in the solid state. However, a 70% yield of **22** could be achieved in a stoichiometric melt at 130−140 °C.



Scheme 6. The solid-state reaction between *o*-phenylenediamines **1a/13** and alloxane hydrate (**14**) to give **15/16** (and in the presence of acid also **20**)

This product could be hydrolyzed with aqueous HCl to give **9**. Neither the tricyclic product **25** nor the spiro compound **26** could be detected. However, production of **25** had been claimed[19] for the aqueous reaction. We repeated that reaction (25−100 °C) but did not obtain the reported product with m.p. 237 °C. Compounds **9** and **27** were formed instead, in a 1.4:1 ratio at 100 °C. The benefit of the solvent-free techniques is clearly evident.

The structure of **22** was established by its NMR and MS data and its clean hydrolysis to give **9**. The course of the reaction is depicted in Scheme 7. Compound **22** was obtained in reasonable yield from the non-acidic melt, and the water of reaction did not significantly hydrolyze the "amidine" moiety of **22**. No **23** could be detected, but it is a reasonable intermediate for both **24** and **26**. While **24** appears to provide the isolated product **22** in the melt, the situation differs in aqueous solution: **24** gives **22**, which hydrolyzes to **9**, and **26** (which should equilibrate with **23**) hydrolyzes to the now obtainable **27**. Unlike in the case of **18**, no elimination of water from **24** was observed, and the compound **25** has to be prepared by different paths.[20]



Scheme 7. Reaction between *o*-phenylenediamine (**1a**) and parabanic acid (**21**)

Experimental Section

General Methods: Melting points were determined with a Gallenkamp melting point apparatus and are uncorrected. Infrared (IR) spectra were recorded with a Perkin−Elmer 1720-X FT-IR spectrometer with potassium bromide pellets. All NMR spectra were taken with a Bruker WP 300 at 300 MHz (^{1}H) or 75 MHz (^{13}C). $CDCl_3$/[D_6]DMSO and $CDCl_3$/CF_3COOH mixtures contained up to 25% [D_6]DMSO or CF_3COOH, respectively. All δ values refer to TMS as internal standard. Mass spectra were obtained with a Finnigan MAT 212 System. The ball-mill was a Retsch MM 2000 swing mill with a 10-mL stainless steel, double-walled beaker with fittings for circulating coolants. Two stainless steel balls of 12 mm diameter were used. Ball-milling was performed at 20−25 Hz frequency, usually at room temperature (without circulating liquid the temperature did not rise above 30 °C). Water or methanol of the appropriate temperature was circulated for heating or cooling. Completeness of the solid-state reactions was checked by IR spectroscopy in KBr, product purity by m.p. and ^{1}H NMR spectroscopy. B3LYP (basis set 6-31G*) calculations with full geometry optimization were performed with the program TITAN, version 1.01, from Wavefunction, Inc., Irvine, USA.

2,3-Diphenylquinoxaline (3a)

a) In the Solid State: *o*-Phenylenediamine (**1a**, 108 mg, 1.00 mmol) and benzil (**2**, 210 mg, 1.00 mmol) were ball-milled for 1 h at room temperature. Pure **3a** (282 mg, 100%) was obtained after drying at 80 °C in a vacuum, m.p. 123 °C (121 °C[2]). ^{1}H NMR ($CDCl_3$): δ = 7.30 (m, 6 H), 7.50 (m, 4 H), 7.73 (pseudo-d, 2 H), 8.18 (pseudo-d, 2 H). ^{13}C NMR ($CDCl_3$): δ = 128.2 (4 C), 128.8 (2 C), 129.2 (2 C), 129.8 (4 C), 129.9 (2 C), 139.1 (2 C), 141.2 (2 C), 153.5 (2 C).

b) Reaction in the Melt: Compounds **1a** (108 mg, 1.00 mmol) and **2** (210 mg, 1.00 mmol) were heated to 100 °C for 20 min in an evacuated 5-mL flask. Compound **3a** (282 mg, 100%) was obtained after drying in a vacuum at 80 °C.

2,3-Bis(4-methoxyphenyl)quinoxaline (3a′)

a) In the Solid State: *o*-Phenylenediamine (**1a**, 108 mg, 1.00 mmol) and 4,4′-dimethoxybenzil (**2′**, 270 mg, 1.00 mmol) were ball-milled for 1 h at 75 °C. Pure **3a′** (342 mg, 100%) was obtained after drying at 80 °C in a vacuum, m.p 146−147 °C (148−149 °C[3]). ^{1}H NMR

($CDCl_3$): δ = 3.83 (s, 6 H), 6.87 (pseudo-d, 4 H), 7.50 (pseudo-d, 4 H), 7.72 (pseudo-d, 2 H), 8.13 (pseudo-d, 2 H). ^{13}C NMR ($CDCl_3$): δ = 55.3 (2 C), 113.8 (4 C), 129.0 (2 C), 129.5 (2 C), 131.3 (4 C), 131.8 (2 C), 141.1 (2 C), 153.0 (2 C), 160.2 (2 C).

b) Reaction in the Melt: Compounds **1a** (108 mg, 1.00 mmol) and **2′** (270 mg, 1.00 mmol) were heated to 130 °C for 30 min in an evacuated 5-mL flask. Pure **3a′** (342 mg, 100%) was obtained after drying in a vacuum at 80 °C.

2,3-Diphenyl-6-methylquinoxaline (3b): 4-Methyl-*o*-phenylenediamine (**1b**, 122 mg, 1.00 mmol) and **2** (210 mg, 1.00 mmol) were coground in a mortar and heated to 100 °C for 15 min under vacuum. Pure **3b** (296 mg, 100%) was obtained, m.p. 109−110 °C (111 °C[7]). ^1H NMR ($CDCl_3$): δ = 2.60 (s, 3 H), 7.32 (m, 6 H), 7.50 (m, 4 H), 7.60 (m, 1 H), 8.00 (m, 1 H), 8.10 (m, 1 H). ^{13}C NMR ($CDCl_3$): δ = 21.8, 128.0, 128.2 (4 C), 128.6 (2 C), 129.8 (4 C), 132.3, 134.8, 139.2 (2 C), 139.7, 140.4, 141.2, 152.5, 153.3.

2,3-Bis(4-methoxyphenyl)-6-methylquinoxaline (3b′)

a) In the Solid State: 4-Methyl-*o*-phenylenediamine (**1b**, 122 mg, 1.00 mmol) and 4,4′-dimethoxybenzil (**2′**, 270 mg, 1.00 mmol) were ball-milled at 80 °C for 1 h and then dried at 80 °C in a vacuum for 1 h. Pure **3b′** (356 mg, 100%) was obtained, m.p. 123−125 °C. ^1H NMR ($CDCl_3$): δ = 2.59 (s, 3 H), 3.82 (s, 6 H), 6.86 (AA′BB′, 4 H), 7.47 (BB′AA′, 4 H), 7.54 (m, 1 H), 7.89 (m, 1 H), 8.00 (m, 1 H). ^{13}C NMR ($CDCl_3$): δ = 21.8, 55.2 (2 C), 113.7 (4 C), 127.8, 128.5, 131.2 (4 C), 131.8, 131.9, 139.5, 139.9 (2 C), 141.1, 152.1, 152.8, 160.0 (2 C). HRMS (EI) calcd. for $C_{23}H_{20}N_2O_2$ 356.1525; found 356.1509.

b) Reaction in the Melt: Compounds **1b** (122 mg, 1.00 mmol) and **2′** (270 mg, 1.00 mmol) were heated to 130 °C for 30 min in an evacuated 5-mL flask. Pure **3c** (356 mg, 100%) was obtained after drying in a vacuum at 80 °C.

2,3-Bis(4-methoxyphenyl)-5-methylquinoxaline (3c′): 3-Methyl-*o*-phenylenediamine (**1c**, 122 mg, 1.00 mmol) and 4,4′-dimethoxybenzil (**2′**, 270 mg, 1.00 mmol) were ball-milled for 30 min at 75 °C and dried in a vacuum at 80 °C for 1 h. Pure **3c′** (356 mg, 100%) was obtained, m.p. 156−158 °C. ^1H NMR ($CDCl_3$): δ = 2.83 (s, 3 H), 3.82 (s, 6 H), 6.80−6.90 (m, 4 H), 7.45−7.65 (m, 6 H), 7.94 (m, 1 H). ^{13}C NMR ($CDCl_3$): δ = 17.0, 55.3 (2 C), 113.6 (2 C), 113.8 (2 C), 126.7, 129.2, 129.4, 131.1 (2 C), 131.4 (2 C), 132.0, 137.3 (2 C), 140.2, 140.9, 151.3, 152.3, 160.1 (2 C). HRMS (CI) calcd. for $C_{23}H_{20}N_2O_2$ + H 357.1603; found 357.1602.

6-Nitro-2,3-diphenylquinoxaline (3d): 4-Nitro-*o*-phenylenediamine (**1d**, 153 mg, 1.00 mmol) and **2** (210 mg, 1.00 mmol) were coground in a mortar and heated to 160 °C under vacuum for 15 min. Pure **3d** (327 mg, 100%) was obtained, m.p. 186.5−187.5 °C (187.5−187.9 °C[5]). ^1H NMR ($CDCl_3$): δ = 7.40 (m, 6 H), 7.56 (m, 4 H), 8.29 (m, 1 H), 8.52 (m, 1 H), 9.07 (m, 1 H). ^{13}C NMR ($CDCl_3$): δ = 123.3 (2 C), 125.6 (2 C), 128.4 (2 C), 129.6 (2 C), 129.8 (2 C), 129.9 (2 C), 130.7 (2 C), 138.1, 140.0, 143.6, 147.9, 155.7, 156.3.

Benzo[*a*]phenazin-5-ol (5)

a) In the Solid State: *o*-Phenylenediamine (**1a**, 108 mg, 1.00 mmol) and 2-hydroxy-1,4-naphthoquinone (**4**, 174 mg, 1.00 mmol) were ball-milled for 15 min at 70 °C. Pure **5** (246 mg, 100%) was obtained, m.p. > 300 °C (> 300 °C[9]). ^1H NMR ($CDCl_3/CF_3COOH$): δ = 7.35 (s, 1 H), 7.85−8.18 (m, 5 H), 8.43 (m, 1 H), 8.50 (m, 1 H), 9.26 (m, 1 H). ^{13}C NMR ($CDCl_3/CF_3COOH$): δ = 96.0, 118.6, 125.2, 126.0, 127.8, 129.1, 130.8, 131.1, 131.4, 132.8, 132.9, 136.3, 137.6, 140.7, 144.0, 168.7.

b) Reaction in the Melt: Compounds **1a** (216 mg, 2.00 mmol) and **4** (348 mg, 2.00 mmol) were heated to 110 °C for 30 min in an evacuated 5-mL flask. Pure **5** (492 mg, 100%) was obtained after drying in a vacuum at 80 °C.

3-(3-Oxo-3,4-dihydroquinoxalin-2-yl)propionic Acid (7): 2-Oxoglutaric acid (**6**, 292 mg, 2.00 mmol) and **1a** (216 mg, 2.00 mmol) were coground in a mortar and heated to 120−125 °C for 30 min in a vacuum. Pure **7** (472 mg, 100%) was obtained, m.p. 252−254 °C (255−257 °C[21]). ^1H NMR ([D_6]DMSO): δ = 2.70 (t, *J* = 7.0 Hz, 2 H), 3.00 (t, *J* = 7 Hz, 2 H), 7.22−7.28 (m, 2 H), 7.45 (m, 1 H), 7.67 (m, 1 H), 12.26 (br. peak, 2 NH). ^{13}C NMR ([D_6]DMSO): δ = 27.6, 29.6, 115.2, 123.0, 128.0, 129.4, 131.4, 131.6, 154.5, 160.2, 173.8.

1,4-Dihydroquinoxaline-2,3-dione (9): Compound **1a** (108 mg, 1.00 mmol) and oxalic acid dihydrate (**8**, 126 mg, 1.00 mmol) were coground in a mortar and heated to 150 °C for 8 h, or to 180 °C for 30 min, or to 210−220 °C for 10 min under vacuum. Pure **9** (162 mg, 100%) was obtained in all cases, m.p. > 300 °C (365−367 °C[22]). ^1H NMR ([D_6]DMSO): δ = 6.85 (m, 2 H), 6.70 (m, 2 H). ^{13}C NMR ([D_6]DMSO): δ = 117.0 (2 C), 119.6 (2 C), 132.6 (2 C), 162.7 (2 C).

1*H*,1′*H*-[2,2′]Bis(benzimidazolyl) (10) and 5,12-Dihydroquinoxalino[2,3-*b*]quinoxaline (11)

a) From 1a and 9: Compounds **1a** (54 mg, 0.50 mmol) and **9** (81 mg, 0.50 mmol) were heated to 240 °C for 12 h under vacuum. The conversion was quantitative and **10** and **11** (117 mg, 100%) were obtained in a ratio of 94:6 according to ^1H NMR analysis.

b) From 1a·2HCl and 9: Compounds **1a**·2HCl (45 mg, 0.25 mmol) and **9** (40 mg, 0.25 mmol) were sealed under vacuum in a glass tube and heated to 140 °C for 6 h. After treatment of the solid with 1 N NaOH and four washings with water, a quantitative yield of an 80:20 mixture of **10** and **11** was obtained.

c) From 1a and 12: Compounds **1a** (108 mg, 1.00 mmol) and 2,3-dichloroquinoxaline (**12**, 199 mg, 1.00 mmol) were heated to 150 °C in a vacuum for 30 min. The crude mixture contained **1a**·2HCl (39%), **10** (7%), and **11** (53%) according to ^1H NMR analysis. It was treated with 1 N NaOH, filtered, and washed with water and cold ethanol (20 mL). The residue contained **11** and **10** in a 93:7 ratio. Pure **11** was obtained by heating the mixture with 5 mL of ethanol, hot filtration, and washing of the crystals three times with 3 mL of hot ethanol.

Compound 10: M.p. > 300 °C (470 °C[23]). ^1H NMR ([D_6]DMSO):[24] δ = 7.40 (pseudo-d, 4 H), 7.72 (pseudo-d, 2 H), 7.85 (pseudo-d, 2 H), 13.70 (br. s, 2 NH). ^{13}C NMR ([D_6]DMSO): δ = 112.1 (2 C), 119.2 (2 C), 122.2 (2 C), 123.6 (2 C), 134.8 (2 C), 143.6 (2 C), 143.8 (2 C).

Compound 11: M.p. > 300 °C (> 360 °C[14]). ^1H NMR ($CDCl_3/CF_3COOH$): δ = 7.38 (m, 4 H), 7.48 (m, 4 H). ^{13}C NMR ($CDCl_3/CF_3COOH$): δ = 118.9 (4 C), 125.9 (4 C), 130.4 (4 C), 142.8 (2 C).

***N*-[(3-Oxo-3,4-dihydroquinoxalin-2-yl)carbonyl]urea (15)**

a) Solid-Solid Reaction: Compound **1a** (108 mg, 1.00 mmol) and alloxane hydrate (**14**, 160 mg, 1.00 mmol) were ball-milled for 1 h at room temperature. Pure **15** (232 mg, 100%) was obtained, m.p. 254−256 °C (250 °C[12]; 238−239 °C[17]). ^1H NMR ($CDCl_3/CF_3COOH$): δ = 7.30 (br. s, 1 NH), 7.50 (pseudo-d, 1 H), 7.68 (m,

1 H), 7.90 (m, 1 H), 8.20 (pseudo-d, 1 H), 8.85 (br. s, 1 NH). ^{13}C NMR ($CDCl_3$/CF_3COOH): δ = 116.6, 128.1, 131.3, 132.0, 133.2, 137.0, 140.0, 156.3, 157.1, 163.0.

b) Reaction in the Melt: Compounds **1a** (108 mg, 1.00 mmol) and **14** (160 mg, 1.00 mmol) were heated in an evacuated flask to 130−140 °C for 30 min. The mixture was dissolved in hot acetic acid (20 mL), at which point the alloxazine (**20**)[16,17] (30 mg, 14%) remained undissolved and was filtered from the hot solution. Compound **15** (100 mg, 47%) separated from the cold mother liquor. The mother liquor contained unchanged **1a** and **14**.

Compound 20: M.p. > 300 °C (dec. 330 °C[16]). IR (KBr): $\tilde{\nu}$ = 3196, 3091, 2844, 1738, 1703, 1584, 1392, 1365, 1336, 1274, 781 cm^{-1}. ^{1}H NMR ($CDCl_3$/CF_3COOH): δ = 8.08 (m, 1 H), 8.21 (m, 1 H), 8.40 (m, 1 H), 10.75 (br. s, 2 NH). ^{13}C NMR ($CDCl_3$/CF_3COOH): δ = 125.7, 129.4, 130.6, 132.8, 138.4, 141.2, 142.4, 145.3, 151.8, 162.7.

c) Reaction in Water: *o*-Phenylenediamine **1a** (216 mg, 2.00) was dissolved in water (20 mL) and added to an aqueous solution of alloxane (320 mg, 2.00 mmol in 20 mL). A yellow powder precipitated immediately. After the mixture had been heated at 80 °C for 1 h the raw material was filtered and washed with hot water (3 × 20 mL). Compound **15** (350 mg, 75%) was obtained.

d) Solid-Solid Reaction with *o*-Phenylenediamine Dihydrochloride: Compound **1a**·2HCl (181 mg, 1.00 mmol) and alloxane hydrate (**14**, 160 mg, 1.00 mmol) were ball-milled at room temperature for 1 h. The yellow powder was extracted with hot water and the solid residue was dried to give alloxazine (**20**, 100 mg). The filtrate deposited another crop of **20** (45 mg, total yield 145 mg, 68%). The residual solution contained **15** (70 mg, 30%).

***N*-[(6,7-Dimethyl-3-oxo-3,4-dihydroquinoxalin-2-yl)carbonyl]urea (16):** 4,5-Dimethyl-*o*-phenylenediamine (**13**, 136 mg, 1.00 mmol) and alloxane hydrate (**8**, 160 mg, 1.00 mmol) were ball-milled for 1 h at room temperature. Pure **16** (260 mg, 100%) was obtained, m.p. 270−272 °C (274−275 °C[25]). ^{1}H NMR ($CDCl_3$/CF_3COOH): δ = 2.49 (s, 3 H), 2.56 (s, 3 H), 7.20 (br. s, 1 NH), 7.38 (s, 1 H), 7.93 (s, 1 H), 8.70 (br. s, 1 NH). ^{13}C NMR ($CDCl_3$/CF_3COOH): δ = 19.7, 21.1, 116.7, 130.6, 130.7, 132.8, 137.7, 139.3, 150.7, 156.6, 157.5, 163.7.

***N*-(3-Oxo-3,4-dihydroquinoxalin-2-yl)urea (22):** A melt of **1a** (216 mg, 2.00 mmol) and parabanic acid (**21**, 228 mg, 2.00 mmol) was heated to 130−140 °C for 30 min under vacuum. The raw material contained **22** (78%), **9** (7%), and unchanged **1a** (11%). It was washed with cold 50% AcOH (10 mL), and the residue was recrystallized from acetic acid to yield **22** as a white powder (286 mg, 70%), m.p. > 300 °C. IR (KBr): $\tilde{\nu}$ = 3334, 3170, 1715, 1666, 1395 cm^{-1}. ^{1}H NMR ([D$_6$]DMSO): δ = 7.38 (m, 2 H), 7.46 (m, 1 H), 7.60 (br. peak, 1 NH), 7.75 (d, *J* = 7.9 Hz, 1 H), 8.38 (s, 1 NH), 8.66 (br. peak, 1 NH), 12.75 (br. peak, 1 NH). ^{13}C NMR ([D$_6$]DMSO): δ = 115.4, 123.7, 126.0, 126.8, 129.0, 130.2, 146.2, 150.5, 153.2. HRMS (EI) calcd. for $C_9H_8N_4O_2$ 204.0647, found 204.0637. Hydrolysis of **22** (40 mg) to give **9** was achieved by heating under reflux in 1 N HCl (10 mL) for 2 h, filtration after cooling, washing with water, and drying. Compound **9** was characterized by comparison with the authentic sample.

1,3-Dihydro-2*H*-benzimidazol-2-one (27): Compounds **1a** (216 mg, 2.00 mmol) and **21** (228 mg, 2.00 mmol) were heated under reflux in water (20 mL) for 17 h. After evaporation of the solvent, the pink residue contained **1a** (57%), **9** (25%), and **27** (18%) according to the ^{1}H NMR analysis. The solid mixture was washed with dichloromethane (2 × 20 mL) for removal of **1a** and **27**. The latter was isolated by chromatography at SiO_2 with EtOAc (91 mg, 34%).

Compound 27: M.p. 311−312 °C (316 °C[26]). ^{1}H NMR ($CDCl_3$/[D$_6$]DMSO): δ = 6.88−6.98 (AA′BB′, 4 H), 10.43 (br. peak, 2 NH). ^{13}C NMR ($CDCl_3$/[D$_6$]DMSO): δ = 107.7 (2 C), 119.4 (2 C), 128.6 (2 C), 154.7.

Acknowledgments

This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie. We thank Mrs. Ludmila Hermann for her skillful help in the synthetic work.

[1] G. Kaupp, in: *Comprehensive Supramolecular Chemistry*, vol. 8 (Ed.: J. E. D. Davies), Elsevier, Oxford **1996**, pp. 381−423 + 21 color plates.
[2] A. Gazit, H. App, G. McMahon, J. Chen, A. Levitzki, F. D. Bohmer, *J. Med. Chem.* **1996**, *39*, 2170−2177.
[3] R. W. Bost, E. E. Towell, *J. Am. Chem. Soc.* **1948**, *70*, 903−905.
[4] G. Kaupp, M. R. Naimi-Jamal, J. Schmeyers, *Chem. Eur. J.* **2002**, *8*, 594−600.
[5] A. E. Siegrist, *Helv. Chem. Acta* **1967**, *50*, 909−957.
[6] O. Hinsberg, *Justus Liebigs Ann. Chem.* **1887**, *237*, 339.
[7] F. B. Mallory, C. S. Wood, B. M. Hurwitz, *J. Org. Chem.* **1964**, *29*, 2605−2609.
[8] J. Metzner, E. Lippmann, F. G. Weber, G. Westphal, *Pharmazie* **1981**, *36*, 368−370.
[9] G. M. Rehberg, J. L. Rutherford, *J. Heterocycl. Chem.* **1995**, *32*, 1643−1644.
[10] E. C. Taylor, A. McKillop, R. E. Ross, *J. Am. Chem. Soc.* **1965**, *87*, 1990−1995.
[11] J. Mowbray, J. H. Ottaway, *Biochem. J.* **1970**, *120*, 171−175.
[12] O. Hinsberg, *Justus Liebigs Ann. Chem.* **1896**, *292*, 247.
[13] J. Ohmori, H. Kubota, M. Shimizu-Sasamata, M. Okada, S. Sakamoto, *J. Med. Chem.* **1996**, *39*, 1331−1338.
[14] O. Hinsberg, J. Pollak, *Ber. Dtsch. Chem. Ges.* **1896**, *29*, 784−785.
[15] T. Akutagawa, G. Saito, T. Nakamura, K. Sakaguchi, M. Kusunoki, *Mol. Cryst. Liq. Cryst. Sci. Technol. Sect. A.* **1996**, *276*, 257−266.
[16] H. Rudy, *Ber. Dtsch. Chem. Ges.* **1938**, *71*, 847−857.
[17] W. Bednarezyk, L. Marchlewski, *Biochem. Z.* **1938/1939**, *300*, 46−55.
[18] T. Harayama, Y. Tezuka, F. Yoneda, *J. Chem. Soc., Perkin Trans. 1* **1987**, 75−83.
[19] I. G. Farbenind., DE 634036, **1935**; *Chem. Zentralbl.* **1936**, *II*, 3705.
[20] C. A. Obafenri, W. Pfleiderer, *Helv. Chim. Acta* **1994**, *77*, 1549−1556, and references cited therein.
[21] F. Weygand, K. Burger, *Chem. Ber.* **1966**, *99*, 2880−2884.
[22] P. A. Petyunin, A. M. Choudry, *Chem. Heterocycl. Compd. (Engl. Transl.)* **1982**, 519−521; *Khim. Geterotsikl. Soedin.* **1982**, *18*, 684−686.
[23] M. C. Rezende, C. A. Marques, E. L. Dall'Oglio, C. Zucco, *Liebigs Ann./Recueil* **1997**, 925−929.
[24] C. Zucco, E. L. Dall'Oglio, G. V. Salmória, H. Gallardo, A. Neves, M. C. Rezende, *J. Phys. Org. Chem.* **1998**, *11*, 411−418.
[25] E. E. Haley, J. P. Lambooy, *J. Am. Chem. Soc.* **1954**, *76*, 2926−2929.
[26] K. E. Schwiebert, D. N. Chin, J. C. MacDonald, G. M. Whitesides, *J. Am. Chem. Soc.* **1996**, *118*, 4018−4029.

Received October 26, 2001
[O01522]