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The dilemma between acid and base catalysis in the synthesis of benzimidazole from *o*-phenylenediamine and carbon dioxide†‡

Martin Hulla, Simon Nussbaum, Alexy R. Bonnin and Paul J. Dyson *

The tandem synthesis of benzimidazole and other azoles can be achived by the *N*-formylation of *ortho*-substituted anilines followed by a cyclization reaction. However, CO_2-based *N*-formylations with hydrosilane reducing agents are base catalyzed whereas the cyclization reaction is acid catalyzed. The mismatch in catalytic conditions means that only one of the steps can be catalyzed in a single pot reaction. While the *N*-formylation reaction is frequently the target of catalyst development, the cyclization reaction requires comparably much harsher reaction conditions. Identification of these difficulties lead us to the development of a one-pot, two-step synthesis of benzimidazole under mild reaction conditions employing acid catalysts.

Carbon dioxide is an attractive C1 building block for chemical synthesis.[1–4] However, its inherent thermodynamic stability[5] limits the reactions of CO_2 to those involving high energy substrates,[6,7] strong nucleophiles[8–11] or equally strong reducing agents.[12–14] For all other applications catalysts are required with catalysts for reductive C–N bond forming reactions of amines with CO_2 having advanced considerably.[15–18] The *N*-formylation reaction with hydrosilane reducing agents, in particular, has reached the stage where it can be performed with organic[19,20] or simple salt catalysts[21–24] under ambient conditions (Fig. 1a).

In addition, the *N*-formylation reaction with N-heterocyclic carbene (NHC) catalysts has been extended to the tandem synthesis of benzimidazole and related cyclic compounds (Fig. 1b).[25] Subsequently, the synthesis of various azoles prepared using this methodology have been reported with a number of *N*-formylation catalysts including 1-butyl-3-methylimidazolium acetate ([BMIm][OAc]),[26] 1,5-diazabicyclo[4.3.0]non-5-ene (DBN)[27] and $B(C_6F_5)_3$.[28] However, unlike the *N*-formylation reaction, temperatures of 60–150 °C and elevated pressures up to 50 bars are required. In addition, excess hydrosilane is required in all cases.[25–28] Hence, we decided to study the tandem *N*-formylation and cyclization reaction in order to identify why such harsh reaction conditions are necessary. The synthesis of benzimidazole from *o*-phenylenediamine and CO_2 was selected as the model reaction and studied by *in situ* ^{1}H NMR spectroscopy as well as synthetic methods.

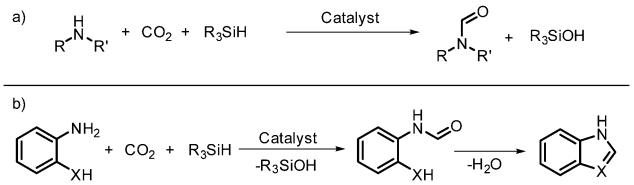


Fig. 1 (a) *N*-formylation of amines with CO_2 and hydrosilane reducing agents. (b) Cascade synthesis of benzimidazole, oxazole and thiazole, where X = NH, O or S respectively.

The reaction was proposed to proceed by the *N*-formylation of *o*-phenylenediamine to *N*-(2-aminophenyl)formamide, followed by its cyclization to benzimidazole, accompanied by the elimination of water (Fig. 1b).[25–28] Monitoring the reaction *in situ* by ^{1}H NMR spectroscopy in DMSO-d_6 showed that even at 25 °C and in the absence of a catalyst *o*-phenylenediamine rapidly *N*-formylates to *N*-(2-aminophenyl)formamide. However, the subsequent cyclization reaction is slow (Fig. 2). Addition of an *N*-formylation catalyst, such as tetra-*n*-butylammonium acetate ([TBA][OAc]),[29] slightly accelerates the *N*-formylation reaction but has no significant effect on the cyclization of *N*-(2-aminophenyl)formamide to benzimidazole, its yield remained below 10% even after 13 h.

Since, monitoring of the reaction by ^{1}H NMR spectrscopy *in situ* requires a slightly elevated CO_2 pressure (5 bars), which promote the *N*-formylation reaction and may hinder the cyclization, we performed a series of *ex situ* experiments with the reported *N*-formylation catalysts [TBA][OAc],[29] Cs_2CO_3,[22] 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD)[30] and $B(C_6F_5)_3$[28] under ambient conditions (Table 1).

The *ex situ* experiments performed under ambient conditions confirm the trend from the *in situ* ^{1}H NMR spectroscopic study at 5 bar of CO_2 and concur with earlier studies.[22,29–31] The *N*-formylation reaction proceeds catalyst free in DMSO[31]

Institute of Chemistry and Chemical Engineering, École Polytechnique Fédérale de Lausanne (EPFL), CH-1015 Lausanne, Switzerland. E-mail: pjd@epfl.ch

† Dedicated to Prof. Robin Perutz on the occasion of his 70th birthday.

‡ Electronic supplementary information (ESI) available: NMR spectra and synthetic procedures. See DOI: 10.1039/c9cc06156h

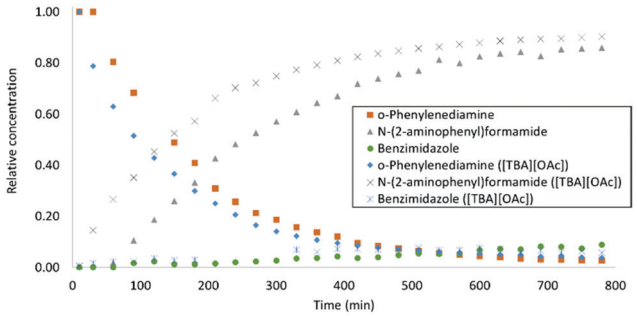
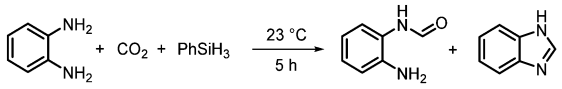


Fig. 2 *In situ* ^{1}H NMR spectroscopic monitoring of the *N*-formylation and cyclization of *o*-phenylenediamine to *N*-(2-aminophenyl)formamide and benzimidazole respectively. Reaction conditions: *o*-phenylenediamine (0.25 mmol), phenylsilane (0.25 mmol), [TBA][OAc] catalyst (0.025 mmol), CO_2 (5 bar), DMSO-d_6 (1.5 mL), 25 °C, 13 h.

Table 1 *N*-formylation of *o*-phenylenediamine to *N*-(2-aminophenyl)-formamide and its cyclization to benzimidazole



Entry	Catalyst	Solvent	Yield 2 (%)	Yield 3 (%)
1	—	DMSO	58	4
2	[TBA][OAc]	DMSO	83[a]	12
3	Cs_2CO_3	DMSO	83[a]	5
4	TBD	DMSO	84[a]	10
5	$B(C_6F_5)_3$	DMSO	19	1
6	—	THF	0	0
7	[TBA][OAc]	THF	84	13
8	Cs_2CO_3[b]	THF	0	0
9	TBD	THF	10	0
10	$B(C_6F_5)_3$	THF	0	0

Reaction conditions: *o*-phenylenediamine (0.25 mmol), phenylsilane (0.25 mmol), catalysts (0.025 mmol), CO_2 (1 bar), DMSO or THF (0.5 mL), 23 °C, 5 h. The reaction yields were determined by ^{1}H NMR spectroscopy using dibromomethane as an internal standard. An average of two runs is reported. [a] Additionally ~5% of *o*-phenylenediformamide was obtained. [b] Not fully soluble *i.e.* <10 mol% of catalyst in solution.

(Table 1, entry 1) and is accelerated by basic catalysts (Table 1, entries 2–4).[22,29,30,32] However, the effect of the basic *N*-formylation catalysts on the cyclization reaction is minimal and the increased concentration of benzimidazole can be attributed to the increased concentration of the *N*-(2-aminophenyl)formamide intermediate rather than a true catalytic effect towards the cyclization reaction. Contrary to a previous hypothesis, the acid catalyst $B(C_6F_5)_3$[28] appears to hinder the *N*-formylation reaction (Table 1, entry 5), at least under the ambient conditions in DMSO employed here. In addition, no reaction occurred in THF, where a base catalyst is necessary (Table 1, entries 6, 7 and 9). Hence, it would appear, at least in DMSO, that the synthesis of benzimidazole from *o*-phenylenediamine and CO_2 is limited by the cyclization reaction and not by the *N*-formylation of the starting material, which tends to be the target of catalysis.[25–27]

The cyclization reaction is promoted at elevated reaction temperatures.[25] However, elevated reaction temperatures also promote the sequential reduction of CO_2 with hydrosilanes to

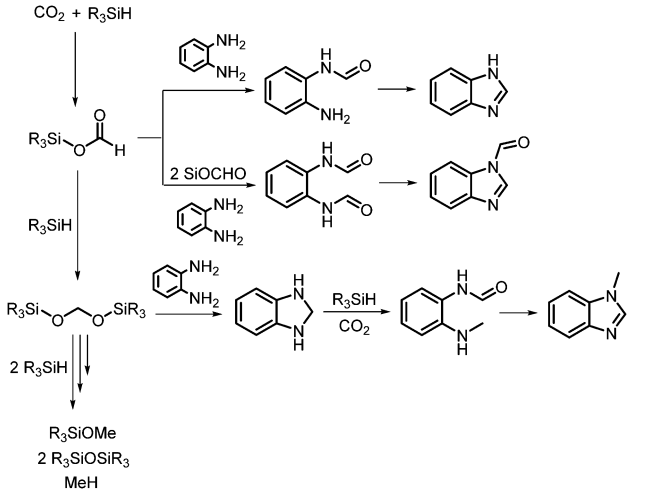


Fig. 3 Sequential reduction of CO_2 with hydrosilanes and possible products resulting from reactions at elevated temperatures with one equivalent of *o*-phenylenediamine.

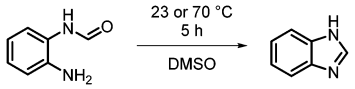
formoxysilanes, silylacetals, methoxysilanes and eventually to silylethers and methane in the presence of basic catalysts (Fig. 3).[33,34] While formoxysilanes are necessary intermediates along the *N*-formylation pathway,[29,35,36] silylacetals lead to the undesirable formation of aminals and *N*-methylamines (Fig. 3).[37–39] Furthermore, such sequential reductions decrease the quantity of available hydrosilane potentially leading to the need for having it in excess. These side reactions can be suppressed at elevated reaction pressures,[39] leading to the elevated reaction temperatures and pressures frequently observed in the synthesis of benzimidazole.

Alternatively, the sequential reduction of CO_2 appears to be suppressed by the use of less reactive hydrosilanes such as polymethylhydrosiloxane (PMHS).[25] Using DMSO instead of a base catalyst, which accelerates not only the *N*-formylation reaction but the entire sequence of CO_2 reductions, leads to good yields and *N*-formylation selectivity even at elevated reaction temperatures. In DMSO complete *N*-formylation of *o*-phenylenediamine can be achieved under ambient reaction conditions in 24 h or at 70 °C in 6 h with partial cyclization to benzimidazole (Fig. 4). If only one equivalent of phenylsilane is used no undesirable side reactions are observed. The cyclization reaction should then be the priority for catalyst development, which would enable an efficient tandem synthesis of benzimidazole and other azols under mild reaction conditions.

In order to test the cyclization reaction we prepared the *N*-(2-aminophenyl)formamide intermediate and attempted to cyclize

Fig. 4 Tandem *N*-formylation and cyclization of *o*-phenylenediamine. Reaction conditions: *o*-phenylenediamine (0.25 mmol), phenylsilane (0.25 mmol), CO_2 (1 bar), DMSO (0.5 mL), 70 °C, 6 h. The reaction yields were determined by ^{1}H NMR spectroscopy using dibromomethane as an internal standard.

Table 2 Cyclization of *N*-(2-aminophenyl)formamide to benzimidazole



Entry	Catalyst	Temp. (°C)	Yield (%)
1	—	70	3
2	[TBA][OAc]	70	3
3	HCOOH	70	6
4	HCOOH[a]	70	71[a]
5	$AlCl_3$[b]	70	29
6	$Al(OH)_3$[b]	70	5
7	BBr_3	70	100
8	$B(OH)_3$	70	32
9	$B(C_6F_5)_3$	70	78
10	—	23	1
11	[TBA][OAc]	23	3
12	HCOOH	23	2
13	$AlCl_3$[b]	23	3
14	$Al(OH)_3$[b]	23	1
15	BBr_3	23	31
16	$B(OH)_3$	23	1
17	$B(C_6F_5)_3$	23	8

Reaction conditions: *N*-(2-aminophenyl)formamide (0.25 mmol), catalyst (10 mol%), DMSO (0.5 mL), 23–70 °C, 5 h. The reaction yields were determined by ^{1}H NMR spectroscopy using dibromomethane as an internal standard. An average of two runs is reported. [a] 200 mol% of HCOOH. [b] Not fully soluble *i.e.* <10 mol% of catalyst in solution.

it (Table 2). In the absence of a catalyst even at 70 °C the cyclization reaction is slow with benzimidazole obtained in only 3% yield (Table 2, entry 1). Addition of an *N*-formylation catalyst, *e.g.* [TBA][OAc], does not promote the reaction and yield of benzimidazole remains unchanged (Table 2, entry 2), which confirms the limited effect of base catalysts on the cyclization step of the tandem reaction. Notably, the observed benzimidazole yields of 3% are lower than observed under comparable reaction temperatures starting from *o*-phenylenediamine, CO_2 and phenylsilane (Fig. 4). Nevertheless, under the *N*-formylation reaction conditions including CO_2 and phenylsilane only the second *N*-formylation to *o*-phenylenediformamide took place further supporting the preference of *N*-formylation over the cyclization reaction.

Considering that cyclization reactions are frequently acid catalyzed and that formic acid forms as the *N*-formylation reaction side product from the reaction of formoxysilane with water and/or silanol,[29] we decided to test a few acids for their catalytic activity in the synthesis of benzimidazole from *N*-(2-aminophenyl)formamide (Table 2). The presence of formic acid indeed slightly accelerates the cyclization reaction (Table 2, entries 1 and 3). However, large quantities are necessary to have a significant effect on the reaction (Table 2, entry 4). Nevertheless, these results explain the higher benzimidazole yield observed from the *N*-formylation of *o*-phenylenediame in comparison to the cyclization of the *N*-(2-aminophenyl)formamide intermediate. Lewis acids such as $AlCl_3$, $B(C_6F_5)_3$ or BBr_3 were found to be more efficient catalysts with benzimidazole yields of 29, 78 and 100%, respectively (Table 2, entries 5, 7 and 9). Nevertheless, at 23 °C only BBr_3 and $B(C_6F_5)_3$ demonstrated significant catalytic activity (Table 2, entries 15 and 17).

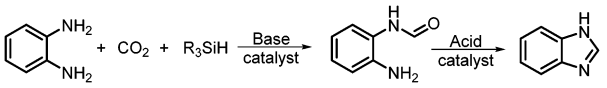


Fig. 5 Catalysts required for the individual steps of benzimidazole synthesis by the tandem *N*-formylation-cyclization reaction of *o*-phenylenediamine with CO_2 and hydrosilanes.

The cyclization of *N*-(2-aminophenyl)formamide is acid catalyzed, whereas its synthesis from *o*-phenylenediamine, CO_2 and a hydrosilane is base catalyzed (Fig. 5).[29,32,35] The mismatch in base and acid catalysts results in the frequently observed harsh reaction conditions for the tandem synthesis of azoles. If base is used to promote the *N*-formylation, elevated reaction temperatures are required for the subsequent cyclization to proceed and elevated CO_2 pressures must also be applied to suppress undesirable side reactions. Acid catalysts accelerate the cyclization, but partly inhibit the *N*-formylation reaction (Table 1, entries 1 and 5), which then requires equally harsh reaction conditions to proceed.

In DMSO the *N*-formylation reaction proceeds under catalyst-free conditions[31] and the tandem reaction is limited only by the cyclization of the *N*-formylated intermediate. The tandem synthesis of benzimidazole can then be achieved by a two-step procedure in a single pot, where an acid catalyst is added after the completion of the *N*-formylation reaction (Fig. 6a). Optimization of the reaction conditions in DMSO at 70 °C, 1 bar of CO_2 and with phenylsilane as the reducing agent allows full *N*-formylation of *o*-phenylenediamine to be achieved in 6 h without the need of excess reducing agent. The cyclization of the *N*-(2-aminophenyl)formamide intermediate to benzimidazole is then completed in the presence of 10 mol% of BBr_3 in less than 2 h. Under these conditions no significant amounts of side products were observed. In comparison, a single step reaction under acidic conditions with 10 mol% of BBr_3 resulted in almost complete inhibition of the *N*-formylation reaction and the recovery of 98% of *o*-phenylenediamine starting material and benzimidazole yield of only 2%.

In order to demonstrate that the reaction can be extended to the synthesis of other azoles and cyclic products, we have synthesized benzoxazole (82% yield), benzothiazole (73% yield) and dihydroquinazoline (85% yield) from 2-aminophenol, 2-aminothiophenol and 2-aminobenzylamine respectively using the same one-pot, two-step reaction setup and reaction

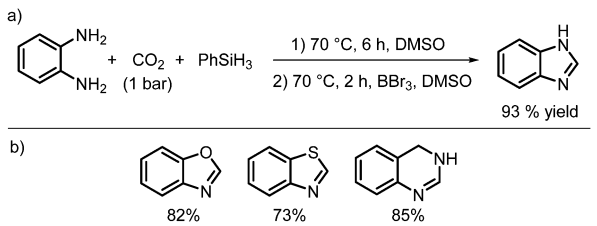


Fig. 6 (a) Two step synthesis of bezimidazole from *o*-phenylenediamine, CO_2 and phenylsilane with BBr_3 acid catalyst (10 mol%) added after 6 h reaction. The reaction yield was determined by ^{1}H NMR spectroscopy using dibromomethane as an internal standard. An average of two runs is reported. (b) Synthesis of benzoxazole, benzothiazole and dihydroquinazoline under the same reaction conditions.

conditions (Fig. 6b). While not optimized for these substrates, the high yields indicate that the process is adaptable to other tandem syntheses of cyclic products *via* amine *N*-formylation followed by acid catalyzed cyclization.

The first *N*-formylation step in the synthesis of benzimidazole from *o*-phenylenediamine, CO_2 and hydrosilane, is base catalyzed. However, base catalysts appear to have no effect on the subsequent cyclization step, which uncatalyzed requires elevated reaction temperatures. Elevation of the reaction temperatures leads to the formation of undesirable side products, which can be suppressed by elevated reaction pressures, the use of less reactive hydrosilanes or by the absence of basic *N*-formylation catalysts (all of which inhibit sequential CO_2 reduction reactions). Nevertheless, this leads to the harsh reaction conditions frequently observed in the tandem synthesis of azoles from *ortho*-substituted anilines. The second cyclization step of the *N*-(2-aminophenyl)-formamide intermediate is acid catalyzed. However, acids such as $B(C_6F_5)_3$ and BBr_3 at least partly inhibit the *N*-formylation reaction, which results in the need for equally harsh reaction conditions. A two-step reaction appears to be the optimal solution, where the *N*-formylation is performed catalyst free in DMSO followed by acidification of the reaction mixture, which promotes the cyclization of the *N*-formylated intermediate. Such a two-step process leads to excellent yields under mild reaction conditions.

We believe that a similar optimization is possible for all tandem syntheses of azole type compounds from *ortho*-substituted anilines.

Conflicts of interest

There are no conflicts to declare.

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