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Formanilide and carbanilide from aniline and carbon dioxide

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Abstract—Earlier syntheses of formamides from the catalytic hydrogenation of CO_2 in the presence of amines were only successful for the preparation of dialkylformamides. After an analysis of the reason for the failure of the reaction using aniline as a starting material, formanilide has been prepared, for the first time, from CO_2, H_2 and aniline with the use of 1,8-diazabicyclo[5.4.0]undec-7-ene. Omission of the H_2 reductant causes the selectivity to switch to the production of carbanilide (1,3-diphenylurea). © 2003 Elsevier Science Ltd. All rights reserved.

Carbon dioxide, by virtue of its great abundance, has attracted continuing attention as a useful C1 building block.[1] There have been many reports describing the conversion of CO_2 to a small range of useful chemicals with the help of homogeneous catalysts.[2–5] However, further work is required to extend the range. For example, highly efficient homogeneous catalysts have been identified for the synthesis of dialkylformamides from CO_2 and amines,[6–8] but no catalysts have been found for the preparation of formanilides from CO_2 and anilines (Eq. (1)). We have now observed the homogeneously catalyzed conversion of aniline, CO_2, and H_2 into formanilide with high selectivity. In the absence of H_2, carbanilide is formed (Eq. (2)).

$$PhNH_2 + CO_2 + H_2 \longrightarrow PhHN-\overset{\overset{O}{\|}}{C}-H + H_2O \quad (1)$$

$$2PhNH_2 + CO_2 \longrightarrow PhHN-\overset{\overset{O}{\|}}{C}-NHPh + H_2O \quad (2)$$

Synthetic methods for the preparation of formamide derivatives via hydrogenation of CO_2 in the presence of ammonia, a primary amine, or a secondary amine were first developed in 1935.[9] However, the method has so far been essentially restricted to the preparation of *N*,*N*-dimethylformamide (from dimethylamine) and other simple formamides from mono- or dialkylamines of similar basicity and with very small alkyl groups. Haynes et al.[10] reported that the conversion of pyrrolidine and piperidine using $RhCl(PPh_3)_3$ could be achieved at 125°C but no yields were given and the reaction was 'not fast'. Supercritical pressures of CO_2, combined with *trans*-$RuCl_2(PMe_3)_4$ catalyst, were found to be highly effective for the conversion of CO_2 and dialkylamines to dialkylformamides.[6–8,11–14] Unfortunately, even the supercritical CO_2 protocol was unable to prepare a significant yield of formanilide from aniline. Although formanilides, which are used as antioxidants and in the pharmaceutical industry,[15] represent an important class of formamides, their preparation by CO_2 hydrogenation in the presence of anilines has not been reported.

The *N*,*N*-dialkylformamide synthesis with *trans*-$RuCl_2(PMe_3)_4$ catalyst precursor is known[6,7] to proceed by Ru-catalyzed and alcohol-cocatalyzed hydrogenation of CO_2 to the ammonium formate salt, which is then thermally dehydrated in situ to the corresponding formamide (Eq. (3)). The failure of less basic amines such as aniline to be converted to formamides is a result of their inability to promote the hydrogenation of CO_2 in the first step, not any inability of the formate salt to be dehydrated to the formamide. This was confirmed by heating a 1:1 mixture of formic acid and aniline to 100°C for 10 h (in the absence of solvent or catalyst); 76% of the aniline was found to be converted to formanilide. Therefore, the reason for the poor yield of formamide from CO_2, with these more difficult amines, must lie in the hydrogenation step of Eq. (3).

$$R_2NH + CO_2 + H_2 \xrightarrow{Ru} [H_2NR_2][O_2CH] \xrightarrow{\Delta} HC(O)NR_2 + H_2O \quad (3)$$

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Table 1. The reactions of aniline with CO_2 and H_2[a]

Base	Alcohol	Formanilide (mol%)	Carbanilide (mol%)
None	None	5	0
None	MeOH	2	0.3
None	C_6F_5OH	14	0
Barton's	None	1	0
DBU	None	35	0
DBU[b]	None	85	0
DBU	C_6F_5OH	35	6

[a] All experiments with 3 μmol $RuCl_2(PMe_3)_4$, 120 bar CO_2, 80 bar H_2, 0.1 mmol alcohol (where used), 5 mmol base (where used), 5 mmol aniline, 31 mL stainless steel vessel at 100°C for 10 h.
[b] 10 mmol DBU, 23 h.

More efficient conversion of these amines into formamides by the hydrogenation of CO_2 therefore requires an increase in the rate of the hydrogenation step. We recently discovered that use of particularly acidic alcohols has a favorable effect on the rate of that step.[16] In the presence of weakly basic amines such as aniline derivatives, the rate of CO_2 hydrogenation is increased by the use of C_6F_5OH rather than methanol or water as the cocatalyst. We found in the present system that addition of C_6F_5OH did indeed increase the yield of formanilide (Table 1). However, adding a stoichiometric amount of the base DBU (1,8-diazabicyclo-[5.4.0]undec-7-ene) increases the yield by an order of magnitude, probably because DBU is a better base than aniline and therefore is better able to stabilize the formate salt intermediate in Eq. (3). DBU is used in stoichiometric quantities because the rate of the hydrogenation step is known to be proportional to base concentration, at least at lower base concentrations.[7] Adding both C_6F_5OH and DBU simultaneously does not further increase the yield. The greatest spectroscopic yield of formanilide was 85% (1,400 TON), obtained by increasing both the reaction time and the amount of DBU. The product was isolated by washing the vessel contents with 5% HCl, extracting three times from the acid washes with ether, combining the ether extracts with the organic residue from the vessel, drying with $MgSO_4$, filtering and removing volatiles in vacuo. The formanilide product was obtained as white crystals in 72% isolated yield.

Omitting H_2 gas from the reaction mixture during the formanilide preparation completely reverses the selectivity to carbanilide, rather than formanilide, synthesis (Table 2). Carbanilides, which are used as antimicrobials and dyes,[17–19] are traditionally prepared from aniline and either phosgene or arylisocyanates, both highly toxic. Uncatalyzed syntheses from aniline and CO_2 include the use of unusual drying agents such as $[BuP(OPh)_3]Br$[20] or $SO_3{\cdot}NMe_3$,[21] usually in conjunction with organic bases such as DBU. Of course, in the absence of a strong dehydrating agent, it is difficult to obtain a high yield of carbanilide. Although the extent of conversion, after 10 h at 100°C, is low, the selectivity is very high; no formanilide or other aromatic products are detected by ^1H NMR spectroscopy. The synthesis requires DBU, does not require the Ru complex, and is inhibited by the addition of an acidic alcohol. Decreasing the amount of DBU 5-fold caused the yield of carbanilide to drop by half. Decreasing the CO_2 pressure to only 10 bar CO_2 caused only a small decrease in the yield of carbanilide. Attempts to obtain a greater

Table 2. The reactions of aniline with CO_2 in the absence of H_2[a]

DBU (mmol)	Additive	T (°C)	Formanilide (mol%)	Carbanilide (% of theoretical yield)
0	None	100	0	0
0	C_6F_5OH	100	0	0
1	None	100	0	10
5	None	60	0	0
5	None	100	0	18
5	Mol. sieve	100	0	15
5[c]	DMSO	100	0	11
5[c]	DMSO & mol. sieve	100	0	20
5[d]	None	100	0	13
5[c,e]	None	100	0	17
5[b]	None	100	0	17
5[c]	$[bmim]BF_4$	100	0	15
5	C_6F_5OH	100	0	4
10[c,e]	None	100	0	17
10[f]	None	100	0	46
10[c,e]	None	120	0	39[g]
10[c]	C_6F_5OH	100	0	23

[a] Conditions: 120 bar CO_2, 5 mmol aniline, 0.1 mmol C_6F_5OH (where used), 3–4 mL DMSO (where used), 1.5 mL 1,3-butylmethylimidazolium tetrafluoroborate (where used), 3 μmol $RuCl_2(PMe_3)_4$, 31 mL stainless steel vessel at 100°C for 10 h.
[b] No $RuCl_2(PMe_3)_4$ added.
[c] 18–22 h.
[d] Only 10 bar CO_2.
[e] 9 μmol $RuCl_2(PMe_3)_4$.
[f] 48 h.
[g] Other unidentified products also observed.

yield of carbanilide, by adding molecular sieves, more DBU, or a solvent (DMSO or *N*,*N*-butylmethylimidazolium tetrafluoroborate) were unsuccessful. Raising the temperature to 120°C more than doubled the yield of carbanilide but unidentified other products were also observed. The reaction did not proceed appreciably at 60°C. The greatest yield (46% of theoretical yield) was obtained at 100°C with a 48 h reaction time and using aniline distilled immediately before use.

The existence of a significant back-reaction at 100°C was demonstrated by reacting carbanilide and water in the presence of DBU, *trans*-$RuCl_2(PMe_3)_4$, and CO_2 gas; within 10 hours, 20% of the carbanilide had been converted to aniline.

After runs in which DBU had been used, typically half of the unconverted aniline in the product mixture was found to be in the form of the carbamate salt, [DBU][O_2CNHPh] (where $DBUH^+$ is protonated DBU), rather than as free aniline. Although aniline by itself does not react with CO_2 to form a carbamate, it does so in the presence of DBU[21] or a guanidine base (Eq. (4)).[22] Reaction of the carbamate salt with a dehydrating or deoxygenating agent is known to give diarylurea,[21] presumably by dehydration to the isocyanate followed by coupling with aniline. A similar mechanism is presumed to be operating here.

$$PhNH_2 + CO_2 + B \longrightarrow [BH][O_2CNHPh] \quad (4)$$

The reaction is not likely to proceed via production of formamide followed by Ru-catalyzed reaction of the formamide with the aniline,[23,24] because that mechanism would require a Ru(II) catalyst and a reductant while the present carbanilide synthesis requires neither.

An attempt to convert diethylamine to tetraethylurea by this method produced a mixture of the formamide, the urea, and an unidentified product.

In conclusion, we have discovered that the combination of a catalytic amount of $RuCl_2(PMe_3)_4$ and a stoichiometric amount of DBU allows the synthesis of formanilide from aniline, H_2 and CO_2 with excellent selectivity. Omission of the H_2 under otherwise identical conditions gives carbanilide instead.

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