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Carbonylation of nitrobenzene to *N*-methyl phenylcarbamate catalyzed by palladium–phenanthroline complexes Bifunctional activation by anthranilic acid

Michela Gasperini, Fabio Ragaini*, Sergio Cenini, Emma Gallo

Dipartimento di Chimica Inorganica, Metallorganica e Analitica and ISTM-CNR, via Venezian 21, 20133 Milan, Italy

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Dedicated to Professor Renato Ugo on the occasion of his 65th birthday

Abstract

The palladium–phenanthroline catalyzed carbonylation reaction of nitrobenzene to methyl phenylcarbamate is known to be accelerated by both the addition of aniline and a carboxylic acid. Here, we report that combining the acidic and amino function in the same molecule, 2-$NH_2C_6H_4COOH$, anthranilic acid, an higher activity is observed with respect to the use of simple benzoic acid. The 4-amino isomer does not show the same increased activity.

Keywords: Nitrobenzene; Carbonylation; Palladium; Urethanes; Carboxylic acids

1. Introduction

The carbonylation of organic nitro compounds is a process with a high potential synthetic and industrial interest, since many products can be obtained from nitro compounds and CO, including isocyanates, carbamates and ureas [1–3]. Ureas and carbamates are important final products and intermediates in the synthesis of pesticides and fertilizers and mono- and diisocyanates are important intermediates in the manufacturing of pesticides, polyurethane foams plastics, synthetic leather, adhesives, and coatings.

The classical method for the production of isocyanates requires the intermediate reduction of the nitro compound to amine, followed by reaction with phosgene. However, phosgene is a very toxic and corrosive material and an enormous effort has been applied to the development of phosgene-free routes to isocyanates. Among these, the carbonylation of nitro compounds, particularly of aromatic ones, represents one of the most interesting alternatives, but the direct carbonylation of nitro compounds to the corresponding isocyanates has proved to be a difficult reaction [1–3]. However, in the presence of an alcohol, carbamates can be obtained more easily and with a high selectivity (Eq. (1)):

$$ArNO_2 + ROH + 3CO \rightarrow ArNHCOOR + 2CO_2 \quad (1)$$

If the isocyanate is the desired product, this can be obtained by thermal cracking of the carbamate (Eq. (2)):

$$ArNHCOOR \xrightarrow{\Delta} ArNCO + ROH \quad (2)$$

Despite an intense effort both in industrial and academic laboratories, no process has been developed

* Corresponding author. Fax: +39-02-5031-4405.
E-mail address: fabio.ragaini@unimi.it (F. Ragaini).

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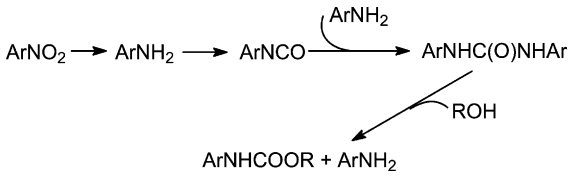


Scheme 1.

up to now, which may compete from an economical point of view with the established technology employing phosgene. This is mostly due to the insufficient turnover numbers (generally in the hundreds or even less) that even the most efficient catalysts can achieve, making catalyst recycle too expensive. In recent years, the catalytic system based on palladium–phenanthroline complexes has emerged as the most active and promising for a possible industrial application [4–30]. Several groups have reported that the addition of acidic co-catalysts (carboxylic acids [11,12,15,18] or phenanthrolinium salts [20–22,24]) markedly improves both rate and selectivity of the carbonylation of nitroarenes to give isocyanates or carbamates. Independent research in our laboratories showed that aniline is an intermediate in the main reaction pathway towards methyl phenylcarbamate [31]. Nitrobenzene is first reduced to aniline, which is in turn carbonylated to phenylisocyanate, this step being the rate determining one. The isocyanate so formed reacts first with excess aniline to afford diphenylurea and only in the end is this product alcoholyzed by methanol, used as solvent, to generate methyl phenylcarbamate and aniline, which reenters the cycle (Scheme 1). As the reaction of aniline is rate determining, addition of a small amount of this amine from the beginning of the reaction increases the reaction rate.

Since carboxylic acids apparently accelerate the reaction of aniline with an intermediate complex, we thought it was feasible to improve the catalytic efficiency by combining the amino and acid functions in the same molecule and the results of our efforts are described here.

2. Results and discussion

The results of the catalytic reactions performed are reported in Table 1.

It should be noted that very high catalytic ratios were employed in order to provide better evidence of the different promoting abilities of the acids employed. These ratios are up to 10 times higher than the ratio reported by van Leeuwen in his original paper in which the promoting efficiency of carboxylic acids on the carbonylation reaction of nitrobenzene was reported [15]. The phenanthroline/palladium and the acid/palladium mol ratios have been kept constant to values optimized in our group for a wider range of promoters. A small amount of 2,2-dimethoxypropane was always added as an internal drying agent, since this was found to have a beneficial effect on the selectivity, in accord with the data reported in the literature [20–24].

As it is evident from a comparison of entries 1–3, 2-aminobenzoic acid (anthranilic acid) has a promoting effect on the reaction rate which is much stronger than the one of simple benzoic acid, but its 4-amino analogue shows no special effect. However, both amino-substituted acids give lower selectivities in the desired carbamate. Since the addition of aniline accelerates the reaction, it may be possible that the observed promoting effect of the addition of anthranilic acid is only due to the fact that more amino groups are added when it is the promoter with respect to the case of benzoic acid. However, this should also be the case of 4-aminobenzoic acid, which shows a different behavior. Moreover, when aniline was added in a larger amount (882:1 aniline/Pd mol ratio) with benzoic acid as a promoter (entry 4), so that the total amount of amino groups is the same as in entry 2, a rate increase was indeed observed with respect to entry 1, but the conversion remained anyway quite lower than the one obtained with anthranilic acid. It is also instructive to compare the absolute amounts of methyl phenylcarbamate formed, which are 2.36, 4.83, 1.52, and 3.44 mmol for entries 1–4, respectively, in the table. These results show unequivocally that the presence of an amino group on the acid can markedly increase its promoting activity and that an *ortho* disposition of the carboxylic and amino group is essential to observe the effect.

Unfortunately, if the reaction time is increased (entry 5), the conversion increases, but not linearly, indicating that the catalytic system is deactivating (independent measurements show that with palladium–phenanthroline catalysts and in the absence

Table 1
Effect of benzoic and aminobenzoic acids as promoters for the $[Pd(Phen)_2][BF_4]_2$ catalyzed carbonylation of nitrobenzene to methyl phenylcarbamate[a]

Entry	$PhNO_2$/Pd mol ratio	$PhNH_2$/Pd mol ratio	Promoter	t (h)	$PhNO_2$ conversion (%)[b,c]	$PhNH_2$ conversion (%)[c,d]	$PhNHCO_2Me$ selectivity (%)[c,e]	PhNHC(O)NHPh selectivity (%)[e,f]	PhN=NPh selectivity (%)[c,g]	PhN(O)=NPh selectivity (%)[c,g]
1	7500	200	PhCOOH	2.5	17.9	86.1	70.9	2.1	<0.5	20.0
2	7500	200	2-$NH_2C_6H_4COOH$	2.5	49.4	22.4	59.0	2.8	1.0	22.5
3	7500	200	4-$NH_2C_6H_4COOH$	2.5	20.1	37.1	44.1	–	<0.5	48.1
4	7500	882	PhCOOH	2.5	32.0	70.8	51.6	4.0	1.0	32.3
5	7500	200	2-$NH_2C_6H_4COOH$	6	67.7	77.0	60.6	1.0	1.0	27.4
6	3750	200	PhCOOH	2.5	52.8	79.3	82.2	1.8	0.5	13.7
7	3750	200	2-$NH_2C_6H_4COOH$	2.5	95.1	–[h]	72.7	4.2	0.9	5.8
8	3750	200	4-$NH_2C_6H_4COOH$	2.5	27.9	24.3	56.9	3.9	0.6	36.4

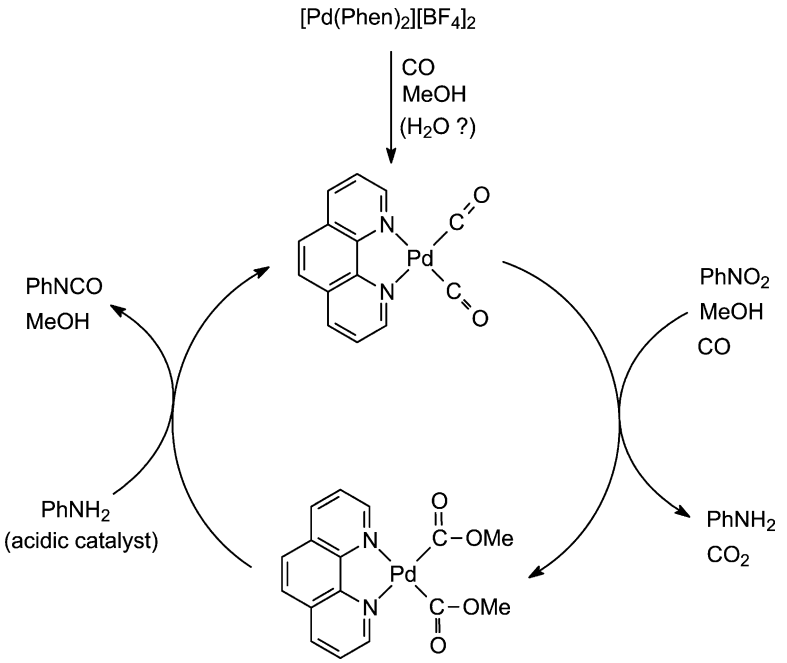
[a] Experimental conditions: $[Pd(Phen)_2][BF_4]_2$ = 1.4 mg, 2.19×10^{-3} mmol, mol ratio Pd/Phen/acid = 1:100:682, P_{CO} 60 bar, T = 175 °C, in methanol (15 ml). 2,2′-Dimethoxypropane (0.5 ml) was also added to the reaction mixture.
[b] Calculated with respect to the starting $PhNO_2$.
[c] Measured by GC.
[d] Calculated with respect to the starting aniline.
[e] Calculated with respect to the sum of reacted nitrobenzene and aniline.
[f] Measured by HPLC.
[g] Calculated with respect to the converted $PhNO_2$.
[h] More aniline (1.6% with respect to the reacted nitrobenzene) was present at the end of the reaction with respect to the initially added one.

of deactivation, the reaction is zero order in nitrobenzene up to close to its complete consumption). However, no metallic palladium was observed at the end of the reaction, indicating that decomposition of the catalyst to inactive metal is not responsible for the loss of activity. Conversely, if the catalytic ratio is halved (entries 6–8), conversions increase and the results obtained with the three promoters parallel those obtained with the higher nitrobenzene amount.

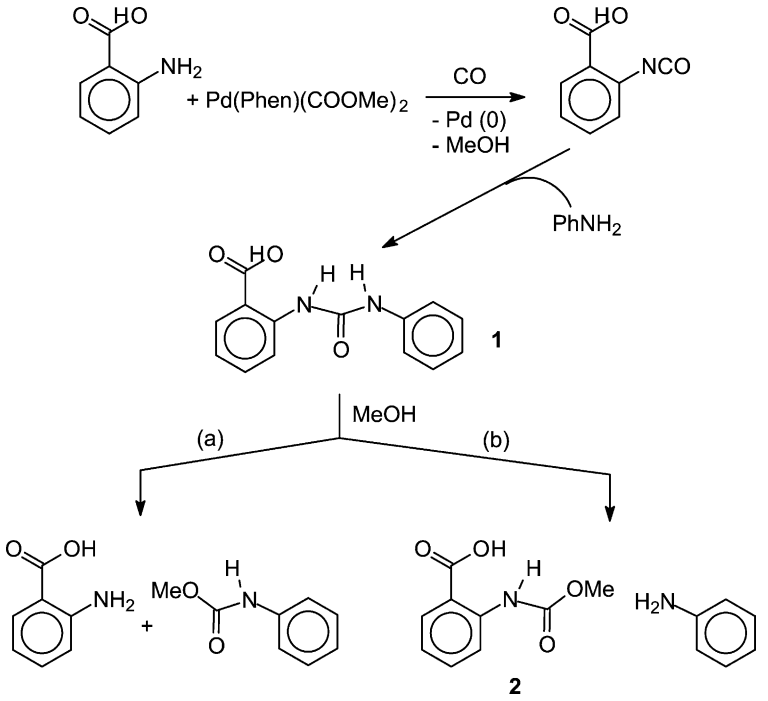
We now come to the problem of the mode of action of anthranilic acid. A mechanistic study is in progress in our laboratories on the palladium–phenanthroline catalyzed carbonylation reaction of nitroarenes. The results obtained till now support the previous proposal [1,19] of a cycle involving the reaction of a palladium(0) complex with nitrobenzene, CO and methanol, to give aniline and a palladium(II) complex that is probably Pd(Phen)$(COOMe)_2$. The latter then reacts with aniline to initially afford phenylisocyanate, which is immediately trapped by excess aniline to give diphenylurea (Scheme 2), in accord with the general mechanism reported in Scheme 1.

During the mechanistic study in our group, we have verified that the reaction of Pd(Phen)$(COOMe)_2$ with aniline is indeed accelerated by carboxylic or other acids, although the original explanation that the role of the acid is to protonate a methoxy group and generate a cationic carbonyl complex is surely not correct [32]. Diphenylurea is the only observable organic product at moderate temperatures when aniline is the substrate, but the initially formed isocyanate could be detected when the sterically hindered 2,6-diisopropylaniline was employed as substrate. In this case, formation of the urea would require the coming in close proximity of four isopropyl groups and is disfavored [32]. We initially supposed that anthranilic acid may enter the cycle at the stage of the reaction with Pd(Phen)$(COOMe)_2$, to afford in a sequence 2-$(HO_2C)C_6H_4NCO$ and the mixed urea 2-$(HO_2C)C_6H_4NHC(O)NHPh$ (**1**) (Scheme 3). Alcoholysis can now occur in two different ways.

Under the assumption that this is the role of anthranilic acid, for the success of the catalytic reaction it is essential that path (a) in Scheme 3 is strongly favored with respect to path (b). Indeed, the latter does

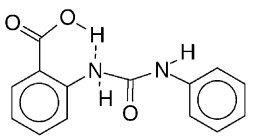


Scheme 2.



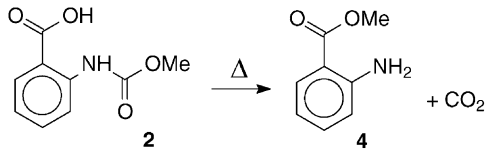
Scheme 3.

not generate the desired product and leads to a sterically hindered benzoic acid, which is expected to have only a low promoting efficiency on the catalytic reaction. Before starting this project, we surmised that path (a) may be favored because the acid group may form an intramolecular hydrogen bond with the vicinal amino group, as shown below, and this interaction may facilitate the expulsion of the amino group on that side.



For the sake of completeness, we must also mention that the intermediately formed $(HOOC)C_6H_4NCO$ may also be trapped by a second molecule of anthranilic acid, acting as an amine, rather than an aniline one. This reaction will generate the symmetric urea (**3**) with two carboxylic groups. Alcoholysis of this urea would give the carbamate containing the carboxylic group in any case.

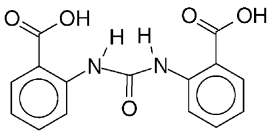
GC–MS analysis of the products of the reactions in which anthranilic acid was added showed, in addition to the compounds listed in Table 1, the presence of $2\text{-}NH_2C_6H_4COOMe$ (**4**). It has already been reported in the literature that the anthranilic acid derived carbamate, $2\text{-}(HOOC)C_6H_4NHCOOMe$ (**2**) decomposes by an intramolecular reaction under conditions very similar (150–170 °C, 5–7 h) to those employed by us to afford **4** (Eq. (3)) [33].



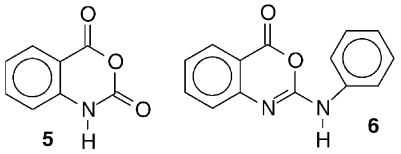
(3)

Quantitative analysis of the ester **4** showed that 37.1, 43.7, and 45.4%, respectively, of the initial anthranilic acid had been converted to this ester during the reactions in entries 2, 7, and 5, respectively, of the table. This data shows that part of the anthranilic acid has indeed been converted to an inactive byproduct, thus explaining the loss of activity of the system with increasing reaction time.

Very small amounts of isatoic anhydride (**5**), and *N*-phenyl-2-amino-4*H*-3,1-benzoxazin-4-one (**6**) were also detected in the GC–MS spectrum. It should be noted that GC–MS analysis cannot detect compounds containing a free carboxylic group or which are heavy enough not to exit the column. However, the mass spectrum of the solid residue after evaporating the solution after the catalytic reaction in entry 2 showed, in addition to the previously mentioned products, peaks attributable to the unrearranged **2**, the mixed urea **1** and the symmetric urea containing two carboxylic groups **3**.



3



5 **6**

Both **5** and **6** can derive from intramolecular reactions of mixed urea or of the intermediately formed isocyanate. All of the peaks corresponding to these products are of low intensity, although they contribute to explaining the missing mass balance in the products shown in Table 1.

The secondary products of the reactions with 4-aminobenzoic acid have not been investigated in such a detail, but it is obvious from the results in the table that this acid suffers from a similar and even worse problem of selectivity and even no acceleration of the reaction is observed, due to the *para* disposition of the two functional groups, which prevents any cooperative effect.

In order to check if the formation of the mixed urea **1** and a limited selectivity in the alcoholysis were responsible respectively for the rate increase and the lower selectivity of the system containing anthranilic acid, we synthesized **1** by reaction of anthranilic acid with phenylisocyanate and investigated its methanolysis reaction at 175 °C. The result was unexpected. GC and GC–MS analysis of the solution after the reaction showed the exclusive formation of aniline and **4**. No methyl phenylcarbamate was detectable. The mass spectrum of the solid after solvent evaporation again showed the presence of small amounts of **2**, **5**, **6**, and unreacted **1**. When 2,2-dimetoxypropane was also added, the same products were obtained, with the addition of isopropylidene-phenylamine, the imine formed by the condensation between aniline and acetone, produced by the reaction between 2,2-dimetoxypropane and water. This imine was identified by GC–MS but not quantified.

The results of the these reactions clearly show that, contrary to our expectations, **1** is alcoholyzed on the undesired side only. Thus, the formation of **1** cannot explain the rate acceleration and the higher amounts of methyl phenylcarbamate formed in the presence of anthranilic acid, although it is clearly responsible both for the lower selectivity and the loss of activity of the catalytic system. The accelerating effect must thus depend on the mutual *ortho* orientation of the amino and carboxylic groups, but without the amino group being directly involved in the formation of the isocyanate. No further details can be given at the moment. We are now developing other promoters that may show increased activity without showing the disadvantage of being consumed during the reaction.

3. Experimental

3.1. General procedure

Unless otherwise specified, all the preparations were conducted under a dinitrogen atmosphere, using solvents dried by standard procedures, but manipulations of the solutions for the analysis were conducted in the air. The catalyst $[Pd(Phen)_2][BF_4]_2$ was prepared by either of two published procedures [7,34]. *N*-(2-Carboxyphenyl),*N*′-phenylurea (**1**) was synthesized by a slight modification of the published procedure [35]. The products of the reactions were quantified by GC or HPLC, using the internal standard method. The following instruments were employed: NMR spectra, Brucker AC-300 spectrometer; IR spectra, Bio-Rad FTS-7 spectrophotometer, GC analysis, Dani 8620 gas chromatograph, equipped with a PSS 255 column; GC–MS spectra, Shimadzu series 5000 instrument. Mass spectra and elemental analyses were performed in the analytical laboratories of Milan University.

3.2. Catalytic reactions

In a typical catalytic reaction, the catalyst, Phen, $PhNO_2$, $PhNH_2$, and the acidic promoter were weighed in a glass liner. The liner was placed inside a Schlenk tube with a wide mouth under dinitrogen and was frozen at −78 °C with dry ice, evacuated and filled with dinitrogen, after which the solvent was added. After the solvent was also frozen, the liner was closed with a screw cap having a glass wool-filled open mouth which allows for gaseous reagents exchange and rapidly transferred to a 200 ml stainless steel autoclave with magnetic stirring. The autoclave was then evacuated and filled with dinitrogen three times. CO was then charged at room temperature at the required pressure and the autoclave was immersed in an oil bath preheated at the required temperature. Other experimental conditions are reported in the captions to the table. At the end of the reaction, the autoclave was cooled with an ice bath, vented and naphthalene was added as an internal standard for the gas chromatographic analysis. A 0.1 ml sample of the solution was withdrawn to this purpose and to the rest of the solution benzophenone was added as an internal standard for HPLC analysis. The results obtained by this last technique have been corrected for the small volume withdrawal preceding the addition of benzophenone.

3.3. Synthesis of 2-methoxycarbonylamino-benzoic acid (**2**)

This compound was obtained by a procedure reported in the literature for other carbamates [36]. Zinc (975 mg, 15 mmol) was suspended in 25 ml of THF, then 3.5 ml (45 mmol) of methyl chloroformate was added. After stirring for 10 min, a solution of anthranilic acid (2.057 g, 15 mmol) in 30 ml of THF was added. After 5 days, the metallic zinc was eliminated by filtration and the collected solution was evaporated to dryness. The solid was dissolved in diisopropyl ether (120 ml) and the solution was washed with a 10% $NaHCO_3$ aqueous solution. Then, the organic layer was washed with water, dried with Na_2SO_4 and evaporated to dryness. The solid obtained was crystallized from methanol (5 ml). Yield was 94.5%. Spectroscopic data and mp are in agreement with the published data [33,37].

3.4. Alcoholysis of N-(2-carboxyphenyl),N′-phenylurea (**1**)

The reaction was performed similar to the catalytic reactions, employing **1** (200 mg, 0.780 mmol) and methanol (15 ml) as the only reactants. The reaction was run at 175 °C for 6 h. A 10 bar N_2 pressure was applied exclusively in order to avoid boiling of the solvent. Analysis of the products showed the formation of (yields with respect to the starting urea in parentheses): aniline (37.1%), diphenylurea (4.7%), 2-aminobenzoic acid methyl ester (33.8%). When the reaction was repeated in the presence of the catalyst and phenanthroline (same amounts as in the catalytic reactions) the results were undistinguishable within the experimental error (selectivities 35.3, 3.3, and 33.8%, respectively, for the three products mentioned above. No methyl phenylcarbamate detected). A mass spectrum of the solid after evaporation of the solvent also showed the presence of peaks attributable to **2**, its methyl ester, and **6**. When 2,2-dimetoxypropane was also added, the analysis showed the presence of: aniline (25.3%), diphenylurea (3.1%), 2-aminobenzoic acid methyl ester (34.7%) and isopropylidene-phenyl-amine, the imine formed by the condensation between aniline and acetone, produced by the reaction between 2,2-dimetoxypropane and water. This imine was identified by GC–MS but not quantified.

Acknowledgements

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