New Route to *N*-Formylation of Primary Amines with Amino Acids as a Source of CO Using Polyaniline Catalyst

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The treatment of primary amines with amino acids as a CO source in the presence of polyaniline emeraldine salts bring about *N*-formylation to give the corresponding formamides. This route to *N*-formylation methodology of primary amine represents the first reported example of a CO-transfer *via* radical mechanism by highly nanoporous polyaniline emeraldine salts catalyst.

Key Words: *N*-Formylation, CO generation, Amino acid, Polyaniline emeraldine salt

Introduction

The formylation reactions of aromatic compounds with acid catalysts and CO are well known as Gattermann-Koch reaction.[1] Olah *et al*. reported that the Koch type carbonylation as well as a distinctly different direct formylation to give C-formylation take place.[2,3] In most cases, these formylations have been carried out under high pressure CO and strong superacids. There is continuing interest in the formylation with CO under milder conditions. A carbonylation reaction without the use of highly poisonous CO would make reactions such as these desirable. In addition, a variety of literature methods for *N*-formylation were examined,[4] it continues to attract considerable attention due to its potential use in biosynthetic application. For example, glycinamide ribonucleotide transferase (GAR Tfase) catalyzes the first of two formyl transfer reactions in the de novo biosynthetic pathway of purine and kynurenine pathway.[5]

Recently, Wittmann *et al*. proposed the competitive generation of CO and CO_2 from carboxylic acid system such as a malonic acid in the presence of an radical species by dehydration and decarboxylation pathway.[6] Among the conducting polymers, polyaniline (PANI) having a radical species is unique conjugated polymer in that it can be tailored for specific applications through a non-redox acid/base doping process.[7,8] In 1993, Hirao *et al*. reported that the use of catalytic system for dehydrogenative oxidation of benzylamine based on solid supported PANI has received attention.[9] In this reaction, the formylated product of benzylamine was obtained as a by-product which was not well characterized, and their related mechanisms have not been defined. Recently, Lee *et al*. report a synthetic method and true metallic nature of nanoporous PANI.[10] The use of nanostructured PANI such as nanoparticles could greatly improve diffusion, since the PANI have much greater exposed surface area, as well as much greater penetration depth relative to their bulk counterparts.[11,12] In particular, the nanoporous PANI-emeraldine salt (ES) form having a radical cation species serves as an insoluble solid-supported catalyst for the efficient dehydrogenative oxidation of benzylamines in the presence of molecular oxygen by radical mechanism.[13] One of the significant advantages based nanoporous PANI conducting particles is that appropriate design combined with CO generation could allow efficient control of the formylation and oxidation process. If CO species were generated from amino acid compounds by PANI-ES, it would be reacted with amine species to afford the desired *N*-formylated products for potential biosynthetic application. We now report new route to *N*-formylation procedure using new formylation reagents such as a phenylglycine amino acids in the presence of nanoporous PANI-ES (Fig. 1). This study provides, to our knowledge, the first example of *N*-formylation route using amino acid as a CO source. We have extended this method as a general procedure which accommodates functionality. The method can also be carried out under heterogeneous phase conditions, impressing that the nanoporous PANI is reusable.

Experimental

Aniline (1 mmol) used for polymerization of PANI was purified by distillation in an all-glass distillation unit. The PANI-ES was synthesized by the SSDP method using the ammonium persulfare (1 mmol) as an oxidant for high surface area. This molar ratio (aniline : ammonium persulfate = 1 : 1) is different from the earlier experiment (aniline : ammonium persulfate = 1 : 0.25).[10] All reagents and solvent were purchased from Sigma-Aldrich and used as received. ^{1}H-NMR spectra were recorded on

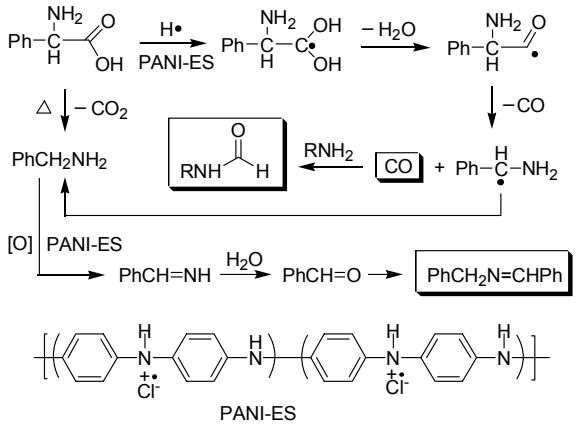


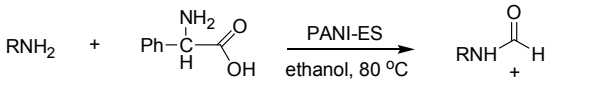
Figure 1. Working hypothesis for *N*-formylation and dehydrogenative oxidation process by the competititive CO and CO_2 generation from an amino acid in the presence of PANI-ES.

a Bruker AM-300 (MHz) spectrometer with TMS as an internal standard. UV absorption spectra were recorded using a Varian Carry-100 spectrophotometer. FT-IR spectra were recorded using a Thermo Mattson Satellite spectrometer.

Results and Disucssion

Nanoporous PANI-ES was similarly prepared by the SSDP method with a honey-comb like nanostructure in the presence of aniline (1 equiv) and initiator (1 equiv).[10,13] The obtained PANI-ES has high surface area and porosity (50.1 m^2/g) with small diameters (< 100 nm), on which chemical and/or physical modifications can be easily performed, compared with the porosity (30.5 m^2/g) of previously synthesized PANI catalyst. To test our hypothesis, we targeted *N*-formylation and dehydrogenative oxidation of amino acids in the presence of benzylamine. Although the dehydrogenative oxidations of benzylamine and decarboxylations of phenylglycine have been developed for the formation of imine structure,[9,13] it continues to attract considerable attention due to its related mechanism for the *N*-formylation process. Our initial studies examined the feasibility of PANI-ES catalyzed CO-transfer from amino acid to primary amine, because PANI supported catalyst are known not only to conducting properties but also to catalyze the oxidation of alcohol, aldehyde, ketone.[14,15] and C-N bond formation.[16] The reaction mixture of benzylamine (1.0 mmol) and phenylglycine (2.0 mmol) in the presence of nanoporous PANI-ES (10 mol%) in ethanol was sonificated to lead well dispersed PANI nanoparticles, and then the resulting solution was reacted at 80 °C for 12 hr to afford the desired formylated product, *N*-benzylformamide in 21% isolated yield, along with 52% of dehydrogenative oxidation product, *N*-benzylidenebenzylamine (PhCH = NCH_2Ph) as shown in Table 1 (entry 1). This shows that amino acid can be used as a carbon monoxide equivalent and that its CO moiety is incorporated into *N*-benzylformamide. At the early stage, the amount of *N*-benzylidenebenzylamine was much greater than

Table 1. *N*-formylation of primary amines with phenylglycine as a source of CO in the presence of PANI-ES.



(R = Ph, $PhCH_2$) $PhCH_2N$ = CHPh

Entry	Substrate (equiv)	Condition	Yield (%)
1	Benzylamine (1)	- / 12 h	21 (52)[a]
2	Aniline (1)	- / 12 h	32 (64)[b]
3	Butylamine (1)	- / 12 h	31 (65)[b]
4	4-Nitroaniline	- / 24 h	No rea.
5	Methyl benzylamine	- / 24 h	No rea.
6	Phenol	- / 24 h	No rea.
7	Benzylamine (1)	O_2 / 12 h	37 (45)
8	Aniline (1)	O_2 / 12 h	41 (53)[a]
9	Anil. (3): Phenylgl. (1)	O_2 / 12 h	25 (69)[b]
10	Anil. (1): Phenylgl. (3)	O_2 / 12 h	45 (42)[b]

[a]Values in parentheses are yields of *N*-benzylidenebenzylamine recovered. [b]Values in parentheses are yields of amines recovered.

N-benzylformamide, indicating that the decarboxylation and dehydrogenative oxidation process of phenylglycine was kinetically favored in dehydration process. The imine double bond of *N*-benzylidenebenzylamine (PhCH = NCH_2Ph) obtained by the oxidation process is thermodynamically unstable in acidic or high temperature conditions and, is cleaved into benzylamine and benzaldehyde adducts. Therefore, the *N*-formylated was suppressed due to the dominant decarboxylation process. Reaction with primary amines (entries 2 and 3) such as aniline and butylamine resulted in moderate higher yields of the desired formanilide (32%) and butylformamide (31%), respectively. ^{1}H NMR spectra of the formylated products, such as *N*-benzylformamide, formanilide and butylformamide, were identical with that of the corresponding commercially available products. However, no fomylated product was obtained when 4-nitroaniline, secondary amine as an *N*-methyl benzylamine, and phenol were used (entries 4-6). It is clear that an electron withdrawing group as nitro moiety, bulky secondary amine, or hydroxyl group cannot be formylated in the same manner as a primary amine group. Thus, these imply that the fromylation reactions are suppressed by the corresponding electronic effect, steric hindrance, or weak nucleophilicity of phenol. To improve the efficiency of *N*-formylation, the similar reactions of benzylamine and aniline were examined under molecular oxygen (Table 1, entries 7 and 8). The reaction yields were increased compared with that of entries 1 and 2. Oxygen is essential for the *N*-formylation of primary amines since dehydration process of phenylglycine were promoted by molecular oxygen to give the CO species followed by PANI-ES-catalyzed CO transfer yielding the observed *N*-formylated products. The excess amounts of aniline (3 equiv with respect to phenylglycine) had a deleterious effect on the formylation (entry 9), whereas the excess amounts of phenylglycine (3 equiv) had a useful (entry 10). The exact role played by molecular oxygen is not clear; it could be that the interactions between oxygen and PANI-ES to give the formation of radical species promote the activity of PANI-ES catalysts.

Meanwhile, the PANI-ES (green) is well known to a conducting polymer due to a polaron band (≥ 780 nm) in the radical cation species. PANI is also known to interconvert among various oxidation states such as the blue color of leucoemeraldine (LB, fully reduced form), emeraldine base (EB, half-reduced form) and pernigraniline base (PB, fully oxidized form) which permit construction of a reversible redox cycle.[7,8] After our formylation reaction, the observed color change (green at 780 nm → blue at 610 nm) means that the doped form of PANI-ES is changed into the de-doped PANI structure, and IR spectral change data were similar trends compared with that of previous study.[13] Based upon the experimental results here, these finding could also be involved with radical mechanism. Under molecular oxygen, our proposed mechanism (Fig. 1) is considered to involve hydrogen atom abstraction process of carboxylic acid group from the protonated PANI-ES forming α-carbon radical structure, which under the acidic condition converts into an acylinium radical structure. The acylinium radical intermediate lead to the formation of carbon monoxide (CO) and benzylamine compounds *via* a stable benzyl radical intermediate. Finally, the CO intermediate can be easily trapped by primary amine to give the corresponding *N*-formylated products. On the other

Table 2. *N*-formylation of primary amines with various amino acids or benzoic acid as a source of CO in the presence of PANI-ES.

Entry	Substrate (equiv)	Time	Yield (%)
1	Aniline (1): *N*-Ac-PhA (1)	12 h	52 (38)[a]
2	Aniline (1): *N*-Ac-PhA (1)	24 h	58 (13)[a]
3	Aniline (1): *N*-Ac-PhA (3)	24 h	65 (25)[a]
4	Aniline (1): PhA (3)	24 h	32 (58)[a]
5	BAm. (1): *N*-Ac-PhA (3)	24 h	52 (27)[b]
6	BAm. (1): PhA (3)	24 h	23 (53)[b]
7	Aniline (1): Glutamine (3)	12 h	No rea.
8	Aniline (1): GlutA (3)	12 h	No rea.
9	Aniline (1): BA (3)	12 h	53 (35)[a]
10	Aniline (1): BA (3)[c]	12 h	58 (34)[a,c]
11	BAm. (1): BA (3)	12 h	48 (41)[b]

[a]Values in parentheses are yields of the recovered aniline monomer. [b]Values in parentheses are yields of the *N*-benzylidenebenzylamine. [c]Reaction was carried out in dioxane.

Table 3. Reuse of PANI.[a]

No. of uses	Recovery of PANI (%)	Yield (%)
1	95	52
2	93	49
3	92	47

[a]Reaction conditions is similar with that of Table 2 (entry 1).

hand, the competitive decarboxylation process lead to the formation of benzylamine adduct and *N*-benzylidenebenzylamine product by the sequential dehydrogenative oxidation process. Therefore, the resulting two products such as formanilide and *N*-benzylidenebenzylamine could also be produced competitively.

To extend the *N*-formylation method for general procedure, various amino acids as a source of CO were examined with primary amines in the presence of PANI-ES. Primary amines were converted to the corresponding *N*-formylated products under the following optimized reaction conditions: aniline (1.0 mmol), amino acids (3.0 mmol), and ethanol (30 mL) in the presence of PANI-ES (50 mol%) at 80 °C under molecular oxygen. The present reaction is significantly general and high-yielding (Table 2). The use of combination of aniline and *N*-acetylphenylalanine (*N*-Ac-PhA) protected with acetyl group afforded the corresponding formanilide product in a higher yield (52%) than those of phenylglycine (compare the entry 1 of Table 2 and Table 1). When the reaction time of formylation was prolonged (24 h) until all of aniline monomer was consumed, a higher yield (58%) of formanilide was obtained (entry 2). Upon on use of large excess (3 equiv) of *N*-Ac-PhA, best result was observed in the formation of *N*-formylated products (entry 3). To investigate the reactivity of *N*-Ac-PhA, we examined non-protected phenylalanine (PhA). The reaction of *N*-acetylphenylalanine having electron withdrawing group such as acetyl moiety proceeded by more efficiently than non protected phenylalanine (3 equiv) (entry 4). We believed that the advantages of good solubility in ethanol and electronic effects derived from *N*-Ac-PhA could promote the

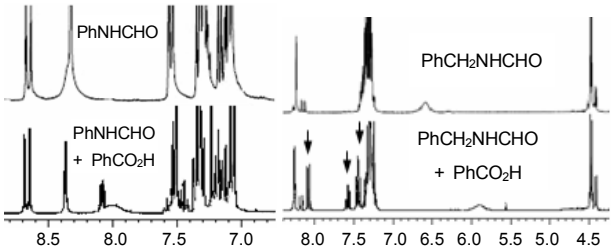


Figure 2. Comparison of ^{1}H NMR spectra for formanilide (left) and *N*-benzylformamide (right) with the corresponding authentic samples.

generation of CO to give the *N*-formylated product. In addition, we think that the CO generation process by dehydration is more dominant than decarboylation process in the competitive generation of CO and CO_2 from *N*-acetylphenylalanine. Therefore, higher yields of formylated products can be produced in the presence of *N*-Ac-PhA. The combination of benzylamine (BAm, 1 equiv) and *N*-Ac-PhA (3 equiv) also afforded *N*-benzylformamide product (52%) in a high yield (entry 5), whereas non-protected PhA afforded *N*-benzylformamide product (23%) in a low yield (entry 6). However, no formylated product was found, and small amount of unknown products were produced when glutamine and glutamic acid (GlutA) were used (entries 7 and 8).

To extend *N*-formylation methodology using other CO source, we next investigated the use of benzoic acid with primary amine in the presence of PANI-ES. The benzoic acid has not only a good solubility in ethanol or dioxane solvent but also different and simple structure compared with that of amino acids system. In this reaction, aniline and benzylamine were also converted to the corresponding *N*-formylated products under the following the reaction conditions: primary amine (1.0 mmol), benzoic acids (3.0 mmol), and ethanol (30 mL) or dioxane in the presence of (50 mol%) at 80 °C under molecular oxygen. Although the formylation carried out in short reaction time for 12 h, the obtained yields were similar with that of entry 1 of Table 2. Upon on use of aniline and ethanol or dioxane solvent, slightly increased yield (58%) was obtained (entry 10) in dioxane compared with that of ethanol solvent. The reaction of benzylamine was also formylated to afford *N*-benzylformamide product (48%) in a moderate yield (entry 11).

This shows that benzoic acid can also be used as a carbon monoxide equivalent. The characteristic signals attributable to a formyl group were observed at 8.35 ppm (s, NH) and 8.68 ppm (d, CHO) in ^{1}H NMR spectra of formanilide (Fig. 2. left). The structure of formanilide was compared with that of the corresponding authentic sample, and confirmed by ^{1}H NMR spectra. The characteristic signals of *N*-benzylformamide were also observed at 8.25 ppm (d, CHO), 8.18 ppm (dd, CHO) and 5.9 ppm (b, NH) in the Fig. 2 (right).

Furthermore, the recovered PANI catalyst was re-doped with HCl treatment, catalytic activity of the resulting PANI-ES was reused. As shown in Table 3, the yields of formanilide after two and three reuses of the catalyst were almost the same as that in the first use. In every case, almost > 90% of PANI was easily recovered from the corresponding reaction mixture by simple washing with ethanol. In this regard, the advantages of this environmentally benign and safe protocol include a simple

reaction setup, not requiring specialized equipment, and mild condition *etc*.

Conclusion

In conclusion, we report on a successful *N*-formylation reaction using amino acids and benzoic acid as a CO source without the need for gaseous CO. This route to *N*-formylation methodology of primary amine represents the first reported example of a CO-transfer *via* radical mechanism by highly nanoporous PANI-ES catalyst. Further studies to address the scope of this new strategy for potential application of formylation in biochemistry are also underway using various amino acids system.

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