AN EFFECTIVE METHOD FOR FORMYLATION OF WEAKLY NUCLEOPHILIC ANILINES AND INDOLE

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Abstract — In the presence of a catalytic amount of active titanium(IV) salt or $Yb(OTf)_3$, weakly nucleophilic anilines and indole react under mild conditions with formic acid or aqueous formic acid to afford respectively the corresponding formanilides and indole-3-carboxaldehyde in excellent yields using 4-trifluoromethylbenzoic anhydride as a coreagent.

The acylation of amines using acyl halides or carboxylic anhydrides is one of the most fundamental reactions for the preparation of carboxamides.[1] In the case of formylation of amines, acetic formic anhydride generated in situ has generally been used because formyl chloride is unstable. The synthesis of formanilides derived from weakly nucleophilic anilines such as nitroanilines or trihaloanilines has also been carried out under limited conditions.[2] In the course of our investigations to develop catalytic condensation reactions, an effective method was reported for the synthesis of carboxylic acid derivatives from nearly equimolar amounts of silyl carboxylates (or free carboxylic acids) and corresponding silyl nucleophiles (or free alcohols) using 4-trifluoromethylbenzoic anhydride and several acidic catalysts.[3] Recently, it was presented that the above reagents were also effective for the synthesis of carboxanilides derived from weakly nucleophilic anilines.[4] Based on these results, a new and efficient method for the synthesis of formanilides derived from weakly nucleophilic anilines by using formic acid or aqueous formic acid in the presence of 4-trifluoromethylbenzoic anhydride and a catalytic amount of active titanium(IV) salt or $Yb(OTf)_3$ was studied.

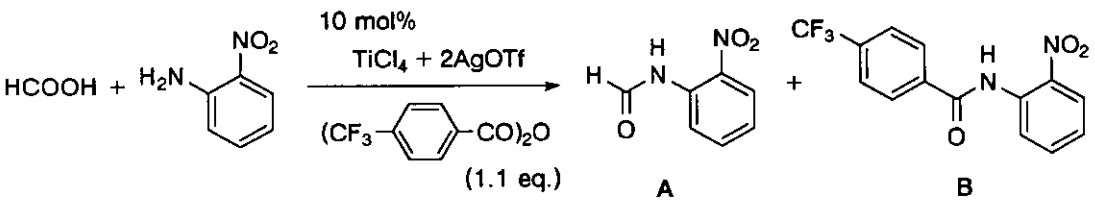
Dedicated to Professor Rolf Huisgen on the occasion of his 75th birthday.

In the first place, the condensation of formic acid with 2-nitroaniline was attempted in the presence of 4-trifluoromethylbenzoic anhydride and a catalytic amount of active titanium(IV) salt generated in situ from 1 mol of $TiCl_4$ and 2 mol of AgOTf. However, the reaction was not completed and the desired formanilide was formed in 23% yield along with a small amount of a by-product derived from 4-trifluoromethylbenzoic anhydride. In order to improve the yield and chemoselectivity, several reaction conditions were examined concerning solvents and an additive such as molecular sieves. Then, it was revealed that the combined use of a mixture of dichloromethane and hexamethyldisiloxane as solvent together with MS-5Å was quite effective in the above formylation (Table 1, Entry 4). It can be pointed out that hexamethyldisiloxane works as silylating reagent of the starting materials, alcohols and carboxylic acids,[5] as well as suitable solvent.[6] Several examples of the present formylation of weakly nucleophilic anilines are listed in Table 2. In every case, the reaction proceeds smoothly at room temperature to give the corresponding formanilides in excellent yields.

A typical experimental procedure is described for the reaction of formic acid and 2-nitroaniline in the presence of a catalytic amount of active titanium(IV) salt: To a suspension of AgOTf (0.06 mmol), $TiCl_4$ (0.03 mmol) and MS-5Å (58.6 mg) in hexamethyldisiloxane (2.0 ml) were added successively a mixture of 4-trifluoromethylbenzoic anhydride (0.33 mmol) and formic acid (0.54 mmol) in dichloromethane (1.0 ml) and a solution of 2-nitroaniline (0.3 mmol) in dichloromethane (1.0 ml). The reaction mixture was kept stirring for an additional 20 h at room temperature, and then quenched with aq. sat. $NaHCO_3$. After the usual work up, the crude product was purified by preparative tlc on silica gel to afford 2'-nitroformanilide (96% yield).

Another approach to develop a convenient method for the synthesis of formanilides was tried by using a catalytic amount of $Yb(OTf)_3$ in the above reaction with a certain amount of water because $Yb(OTf)_3$ is known as an unique Lewis acid catalyst which works in aqueous media.[7] After several screening of reaction conditions concerning solvents, amount of water and an additive, it was revealed that formylation of weakly nucleophilic anilines proceeds smoothly by using aqueous formic acid in the presence of 4-trifluoromethylbenzoic anhydride and a catalytic amount of $Yb(OTf)_3$ (Table 3, Entry 1). Several examples of the present formylation are shown in Table 4. In every case, the reaction proceeds smoothly at refluxing temperature of dichloromethane to give the corresponding formanilides in excellent yields.

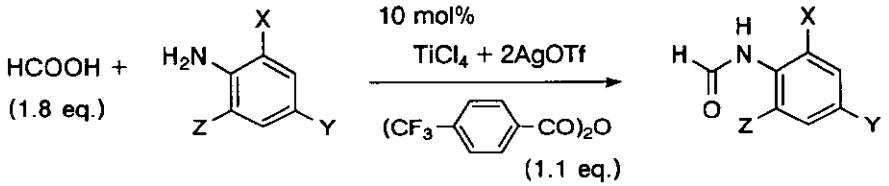
Table 1. Effect of Solvents and MS-5Å



Entry	HCOOH / eq.	Solvent	Additive	Yield / %[a] A	Yield / %[a] B
1	1.1	CH_2Cl_2	None	23	2.3
2	1.8	CH_2Cl_2	MS-5Å	58	Trace
3	1.5	CH_2Cl_2 + TMS_2O	None	70	0
4	1.8	CH_2Cl_2 + TMS_2O	MS-5Å	96	0
5	3.0	CH_2Cl_2 + TMS_2O	None	56	Trace

a) Isolated yield.

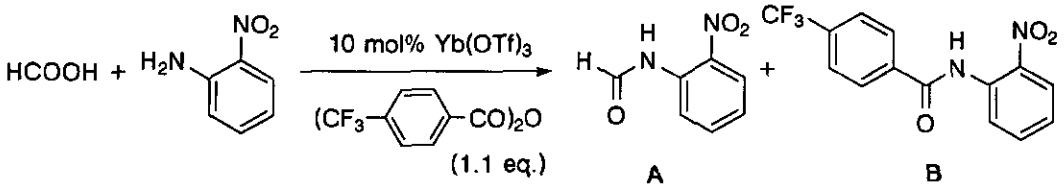
Table 2. Synthesis of Formanilides



Entry	X	Y	Z	Yield / %[a]
1	NO_2	H	H	96
2	NO_2	Cl	H	96
3	Cl	NO_2	H	90
4	Cl	Cl	Cl	99

a) Isolated yield.

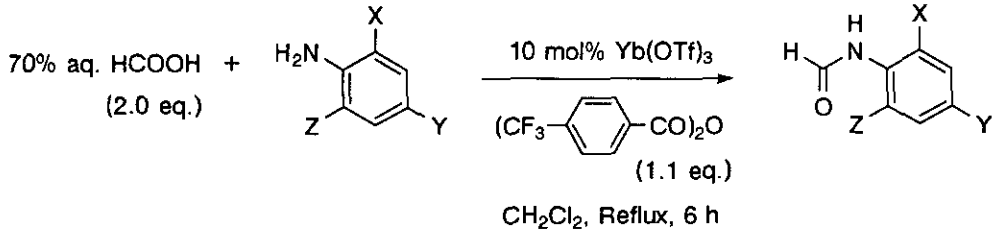
Table 3. Effect of Reaction Conditions by Using $Yb(OTf)_3$



Entry	HCOOH / eq.	Solvent	H_2O / eq.	Temp. /°C	Yield / %[a] A	Yield / %[a] B
1	1.8	CH_2Cl_2	2.3	Reflux	95	Trace
2	1.8	CH_2Cl_2	187	Reflux	0	0
3	1.6	CH_3CN	1.6	50	47	Trace
4	1.8	CH_3CN	26	50	5	0
5	1.7	CH_3CN	235	50	0	0

a) Isolated yield.

Table 4. Synthesis of Formanilides



Entry	X	Y	Z	Yield / %[a]
1	NO_2	H	H	98
2	NO_2	Cl	H	95
3	Cl	NO_2	H	95
4	Cl	Cl	Cl	92

a) Isolated yield.

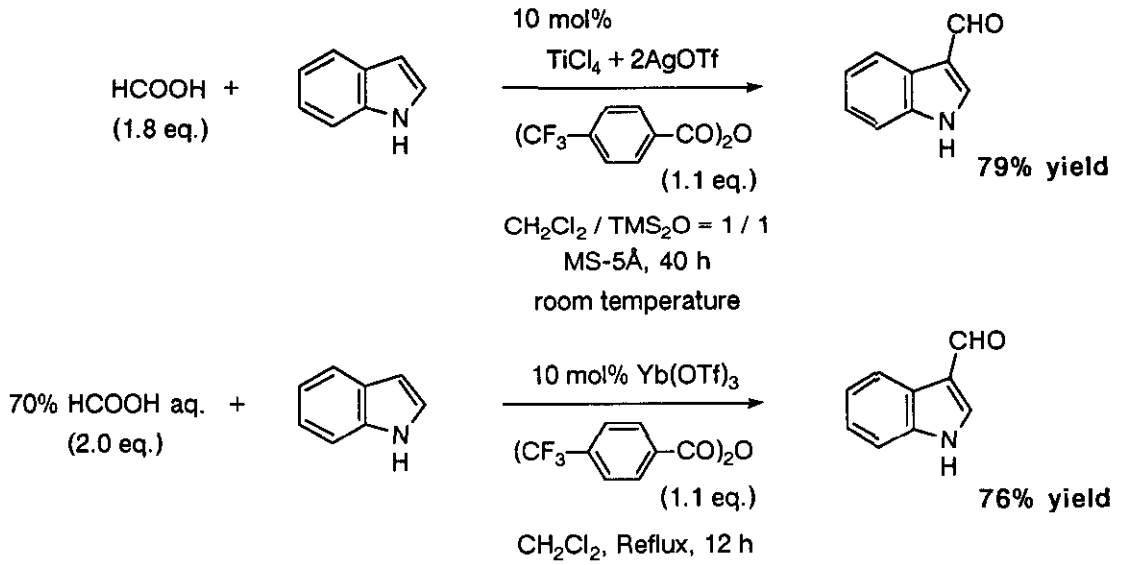
A typical experimental procedure is described for the reaction of formic acid and 2-nitroaniline in the presence of a catalytic amount of $Yb(OTf)_3$: To a suspension of $Yb(OTf)_3$ (0.02 mmol) in dichloromethane (2.0 ml) were added successively a solution of 4-trifluoromethylbenzoic anhydride (0.22 mmol) in dichloromethane (1.0 ml), 70% aqueous formic acid (0.40 ml) and a solution of 2-nitroaniline (0.20 mmol) in dichloromethane (1.0 ml). The reaction mixture was refluxed for 6 h, and then quenched with aq. sat. $NaHCO_3$. After the usual work up, the crude product was purified by preparative tlc on silica gel to afford 2'-nitroformanilide (98% yield).

The formylation of aromatic compounds is one of important methods for the preparation of various aromatic aldehydes, yet there are few methods for the synthesis of aromatic aldehydes according to the generally known Friedel-Crafts acylation reaction because formyl chloride is unstable as mentioned before. Instead of the ordinary Friedel-Crafts acylation reaction, several reactions such as Gattermann-Koch reaction (HCl + CO + $AlCl_3$),[8] Gattermann reaction (HCl + HCN + $ZnCl_2$),[8] Reimer-Tiemann reaction ($CHCl_3$ + KOH) [9] and Vilsmeier-Haack reaction (DMF + $POCl_3$) [10] were developed for the synthesis of aromatic aldehydes. On the other hand, few reports are found on the methods for the formylation of aromatic compounds by use of formic acid as an electrophile. Therefore, it is desired to develop a convenient method for the formylation of aromatic compounds by using formic acid or aqueous formic acid. After screening the reaction conditions, the formylation of indole was successfully carried out according to the above mentioned procedure as shown in scheme 1. In each reaction, indole-3-carboxaldehyde was obtained in good yield under mild conditions similar to the conventional methods.

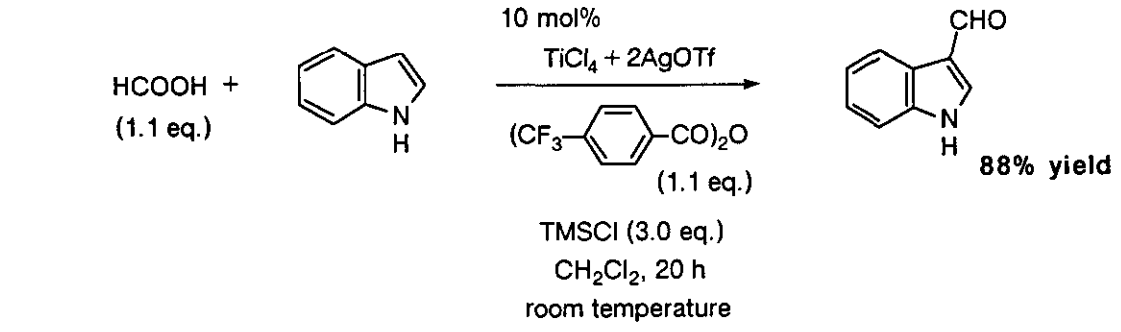
Further, in the presence of a catalytic amount of active titanium(IV) salt together with chlorotrimethylsilane and 4-trifluoromethylbenzoic anhydride, the same formylation of indole also proceeded smoothly to give the corresponding indole-3-carboxaldehyde in 88% yield (Scheme 2). The above reaction conditions were employed quite recently in the esterification reaction between nearly equimolar amounts of free carboxylic acids and alcohols.[3(b)]

A typical experimental procedure is described for the reaction of formic acid and indole in the presence of a catalytic amount of active titanium(IV) salt: To a suspension of AgOTf (0.046 mmol), $TiCl_4$ (0.023 mmol) and chlorotrimethylsilane (0.69 mmol) in dichloromethane (2.0 ml) were added successively a mixture of 4-

trifluoromethylbenzoic anhydride (0.25 mmol) and formic acid (0.25 mmol) in dichloromethane (1.0 ml) and a solution of indole (0.23 mmol) in dichloromethane (1.0 ml). The reaction mixture was kept stirring for an additional 20 h at room temperature, and then quenched with aq. sat. $NaHCO_3$. After the usual work up, the crude product was purified by preparative tlc on silica gel to afford indole-3-carboxaldehyde (88% yield).



Scheme 1. Formylation of Indole



Scheme 2. Formylation of Indole

Thus, various formanilides derived from weakly nucleophilic anilines and indole-3-carboxaldehyde were successfully prepared in excellent yields by respective reactions of anilines and indole with formic acid or aqueous formic acid in the presence of 4-trifluoromethylbenzoic anhydride and a catalytic amount of active titanium(IV) salt or $Yb(OTf)_3$.

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REFERENCES

1. B. M. Trost and I. Fleming, "Comprehensive Organic Synthesis," ed. by G. Benz, Pergamon Press, Oxford, 1991, Vol. 6, p. 381.
2. C. W. Huffman, *J. Org. Chem.*, 1958, **23**, 727; S. Takahashi and H. Kano¯, *Chem. Pharm. Bull.*, 1964, **12**, 282; S. Krishnamurthy, *Tetrahedron Lett.*, 1982, **23**, 3315; W. K. File and Z. Zhang, *J. Org. Chem.*, 1986, **51**, 3746.
3. (a) Synthesis of esters, thiol esters and macrolactones from silyl carboxylates and silyl nucleophiles, T. Mukaiyama, I. Shiina, and M. Miyashita, *Chem. Lett.*, **1992**, 625; T. Mukaiyama, M. Miyashita, and I. Shiina, *Chem. Lett.*, **1992**, 1747; M. Miyashita, I. Shiina, S. Miyoshi, and T. Mukaiyama, *Bull. Chem. Soc. Jpn.*, 1993, **66**, 1516; T. Mukaiyama, J. Izumi, M. Miyashita, and I. Shiina, *Chem. Lett.*, **1993**, 907. (b) Synthesis of esters and macrolactones from free carboxylic acids and alcohols, I. Shiina, S. Miyoshi, M. Miyashita, and T. Mukaiyama, *Chem. Lett.*, **1994**, 515; I. Shiina and T. Mukaiyama, *Chem. Lett.*, **1994**, 677.
4. M. Miyashita, I. Shiina, and T. Mukaiyama, *Chem. Lett.*, **1993**, 1053; M. Miyashita, I. Shiina, and T. Mukaiyama, *Bull. Chem. Soc. Jpn.*, 1994, **67**, 210.
5. H. W. Pinnick, B. S. Bal, and N. H. Lajis, *Tetrahedron Lett.*, **1978**, 4261; H. Matsumoto, Y. Hoshino, J. Nakabayashi, T. Nakano, and Y. Nagai, *Chem. Lett.*, **1980**, 1475.
6. I. Shiina and T. Mukaiyama, *Chem. Lett.*, **1992**, 2319.
7. S. Kobayashi, I. Hachiya, T. Takahori, M. Araki, and H. Ishitani, *Tetrahedron Lett.*, 1992, **33**, 6815, and references cited therein.

8. B. M. Trost and I. Fleming, "Comprehensive Organic Synthesis," ed. by H. Heaney, Pergamon Press, Oxford, 1991, Vol. 2, p. 749.
9. B. M. Trost and I. Fleming, "Comprehensive Organic Synthesis," ed. by H. Wynberg, Pergamon Press, Oxford, 1991, Vol. 2, p. 769.
10. B. M. Trost and I. Fleming, "Comprehensive Organic Synthesis," ed. by O. Meth-Cohn, Pergamon Press, Oxford, 1991, Vol. 2, p. 777.

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