DOI 10.5012/bkcs.2010.31.5.1424

Convenient *N*-Formylation of Amines in Dimethylformamide with Methyl Benzoate under Microwave Irradiation

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Received January 13, 2010, Accepted March 23, 2010

Key Words: *N*-Formylation, Formamide, Dimethylformamide (DMF), Methyl benzoate, Microwave irradiation

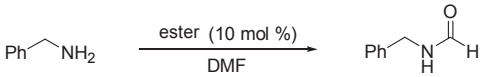
Formylation of amines is a very useful process in synthetic organic chemistry. Formamides are a class of important intermediates that have been widely used in synthesis of pharmaceutically important compounds.[1] In addition, formamides have been also extensively employed in organic synthesis as protecting group of amines,[2] precursor for formamidines[3] and isocyanide[4] preparation, an intermediate for mono methylated amines from primary amines,[5] and Lewis base catalyst for allylation or hydrosilylation of carbonyl compounds.[6]

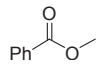
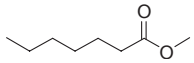
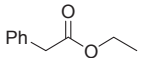
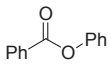
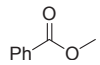
A number of formylating methods and formylating agents such as chloral,[7] acetic formic anhydride,[8] formic acid using Dean-Stark trap,[9] zinc oxide as a catalyst,[10] or polyethylene glycol,[11] formic acid under microwave irradiation,[12] activated formic acid using DCC,[13] EDCI,[14] or 2-chloro-4,6-dimethoxy [1,3,5]triazine (CDMT),[15] activated formic acid ester,[16] solid-supported formic acid,[17] ammonium formate,[18] *N*-formylbenzotriazole,[19] and chloroform with KF-Al_2O_3[20] have been reported. Interestingly, in recent days we discovered that the corresponding formamide could be successfully prepared from benzylamine when we used *N*,*N*-dimethylformamide (DMF) with methyl benzoate as a promoter under microwave irradiation. Although DMF as a formylating source has been employed for the formylation reaction with 2,3-dihydro-1,4-phthalazinedione as a promoter, it needed long reaction time of more than 40 hours and was limited to the formylation of primary amines.[21] Herein we report the convenient and efficient formylation of various primary and secondary amines using DMF with methyl benzoate as a promoter under microwave irradiation.

Initially, the reaction of benzylamine without an ester in DMF at 200 °C under microwave irradiation[22] provided the corresponding formamide only in 9% yield (entry 1 in Table 1). When a catalytic amount (10 mol %) of methyl benzoate was used, however, the yield was dramatically increased to 92% (entry 2).[23] In order to examine the effect of ester in the formylation using DMF, the reaction of benzylamine as a model compound in DMF was performed with various esters as a reaction promoter under the same reaction condition. As shown in Table 1, when methyl heptanoate was used, the reaction gave the desired formamide in 33% yield (entry 3). The formylation of benzylamine in DMF with ethyl phenylacetate, phenyl benzoate, and phenyl acetate afforded the same product in 43%, 50%, and 67% yields, respectively (entries 4, 5, and 6). On the other hand, when the reaction temperature was reduced to 150 °C, the formylation reaction with methyl benzoate gave the formamide in 32% yield (entry 7). This result clearly indicates that an ester is working as a promoter in the formylation reaction using DMF. Particularly, methyl benzoate was operated as the best promoter out of the esters used.

Next, the generality of the effect of methyl benzoate as a promoter in the formylation of amines was investigated. A variety of primary and secondary amines were treated with a catalytic amount of methyl benzoate in DMF under microwave irradiation. All substrates investigated gave the corresponding formamides in excellent yields (Table 2). The formylation reaction of primary amines such as 3-phenylpropylamine and octylamine at 200 °C for 5 min afforded the desired formamides in 93% and 92% yields, respectively (entries 1 and 2). The reaction of primary amines with hydroxyl group such as 2-hydroxyethylamine, 5-hydroxypentylamine, and 4-(2-aminoethyl)phenol also provided the desired products formylated only to amino group in excellent yields (entries 3-5). The same reaction of ethylenediamine gave the bis-formylated product in 72% yield (entry 6).

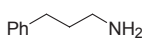
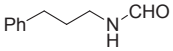
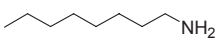
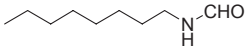
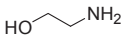
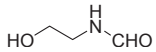
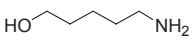
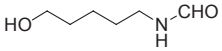
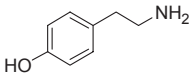
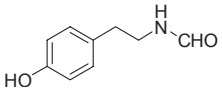
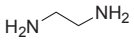
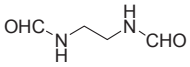
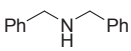
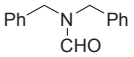
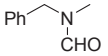
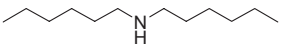
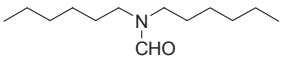
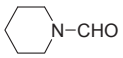
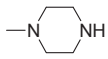
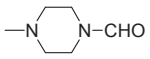
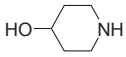
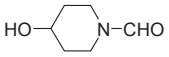
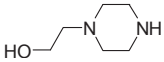
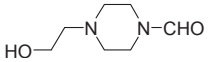
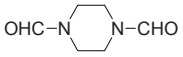
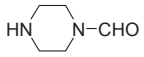
Table 1. Formylation of benzylamine using DMF with various esters as a promoter.



Entry	Ester	Temp. (°C)	Yield[a] (%)
1	None	200	9
2		200	92
3		200	33
4		200	43
5		200	50
6		200	67
7		150	32

[a]Isolated yields.

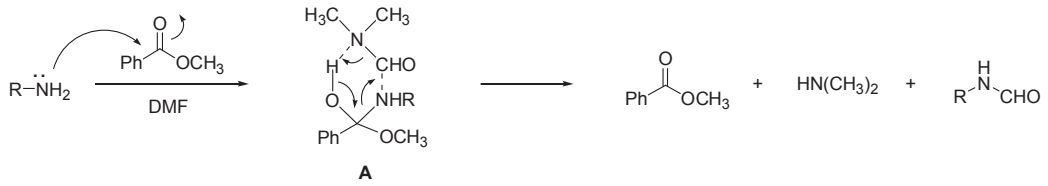
Table 2. Formylation of primary and secondary amines using DMF with methyl benzoate

Entry	Amine	Product	Method[a]	Yield[b] (%)
1			A	93 (95)[c]
2			A	92
3			A	96
4			A	95
5			A	90
6			A	72
7			B	85(N.R.)[c,d]
8			B	96
9			B	92
10			A	85(92)[c]
11			A	86
12			A	99
13			A	91
14			A	80
15			C	76

[a]Method A: MW 200 W, 200 °C. Method B: MW 300 W, 250 °C. Method C: MW 200 W, 160 °C. [b]Isolated yields. [c]Isolated yields at thermal reflux condition (180 °C) for 4 hr. [d]N.R. means no reaction.

However, the same reaction temperature to chain aliphatic secondary amines did not provide the formylated product at all. When the reaction temperature was elevated to 250 °C, the chain aliphatic secondary amines were successfully converted to the desired formylated products in excellent yields. The formylation reaction of dibenzylamine, methylbenzylamine, and dihexylamine afforded the corresponding formamides in 85%, 96%, and 92% yields, respectively (entries 7-9). On the other hand, the reaction of cyclic secondary amines such as piperidine (entry 10), *N*-methylpiperazine (entry 11), 4-hydroxypiperidine (entry 12), and *N*-(hydroxyethyl)piperazine (entry 13) gave the desired products in excellent yields even at 200 °C, like the case of primary amines. The reaction of piperazine at 200 °C afforded the bis-formylated product in 80% yield, whereas the same reaction at 160 °C furnished the mono-formylated product in 76% yield (entries 14 and 15). Clearly, the new reaction condition produced the desired formamides in excellent yields for both primary and secondary amines for short reaction time.

In order to compare with our microwave-assisted *N*-formylation process, several amines were reacted in the classical thermal condition. When the reaction was performed at refluxing condition by heating to 180 °C for 4 hr, 3-phenylpropylamine



Scheme 1. Plausible mechanism of *N*-formylation of amines using methyl benzoate as a promoter in DMF

and piperidine were converted to the corresponding formamides in good yields (entries 1 and 10 in Table 2). The reaction with dibenzylamine, however, did not provide the formylated product at all (entry 7). This result is consistent with the reason that the formylation of chain aliphatic secondary amines needed higher temperature in microwave-assisted process. It results from better nucleophilicity of cyclic secondary amines than chain aliphatic secondary amines to methyl benzoate because nitrogen atom in cyclic secondary amines is more exposed to electrophile in view of steric issue.

Although the role of methyl benzoate in *N*-formylation of amines is not clear definitively, it is speculated that a ternary complex **A** among amine, methyl benzoate, and DMF would be generated in the transition state immediately after amine attacks the carbonyl group in methyl benzoate as shown in Scheme 1. The complex **A** would induce the formyl group in DMF to become more reactive and accelerate the nucleophilic attack by amino group in complex **A** to release the corresponding formamide, dimethylamine, and methyl benzoate.

In conclusion, we have found a highly convenient and efficient protocol for *N*-formylation of primary and secondary amines using DMF with a catalytic amount of methyl benzoate as a promoter under microwave irradiation. Particularly, the chain aliphatic secondary amines were readily formylated in this process, whereas they were not formylated in classical thermal condition. The advantages of this reaction procedure also include neutral reaction condition, simple reaction protocol, short reaction times, high product yields, and selective *N*-formylation in the presence of hydroxyl group.

Acknowledgments. We thank for the support of Korea Research Foundation (KRF) grant funded by the Korean Government (MOEHRD) (No. 2007-331-C00156) and research grant of Kwangwoon University in 2007 for this work.

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22. Discover BenchMate of CEM Corp. was used as microwave reactor.
23. Typical procedure of formylation reaction for benzylamine: A solution of benzylamine (0.20 mL, 1.83 mmol), methyl benzoate (25 mg, 0.18 mmol), and DMF (1.0 mL) in a 10 mL pressurized vial was stirred for 5 min at 200 ^{o}C in microwave reactor. After cooled to room temperature, the reaction mixture was concentrated to remove DMF. The residue was purified by flash column chromatography (hexane/EtOAc, 1:2) to give the desired formamide (228 mg, 92%) as a white solid.