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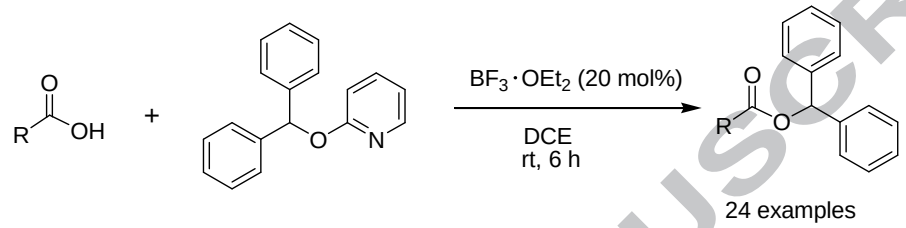

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Facile Synthesis of Diphenylmethyl Esters from 2-Diphenylmethoxypyridine using Catalytic Boron Trifluoride·Diethyl Etherate

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ABSTRACT

A practical method for the direct preparation of diphenylmethyl (DPM) esters from 2-diphenylmethoxypyridine is described. The reaction was readily performed in the presence of a catalytic amount of boron trifluoride-diethyl etherate at room temperature. Using this reaction protocol, various carboxylic acids were converted to DPM esters with high yields. This method is highly effective for the protection of carboxylic acids and the synthesis of DPM esters, and offers a promising approach for facile esterification of a variety of carboxylic acids.

1. Introduction

Protection and deprotection of carboxylic acids is one of the most popular methodologies in organic synthesis. The diphenylmethyl (DPM) group is one of the commonly used protecting groups for carboxylic acids and hydroxyl groups. The cleavage of DPM ester is known to be readily achieved under acidic condition using acetic acid, trifluoroacetic acid, and hydrofluoric acid, in the presence of hydrazine, or $AlCl_3$ or by hydrogenation with Pd.[1-7] These various options for removal of a DPM group provide an advantage in multistep synthesis. Thus, the DPM group has been used in a wide range of organic reactions and the syntheses of various compounds including enzyme inhibitors, antibacterial agents, leukotriene receptor antagonists, and amphiphilic chelators.[8-11]

Several synthetic methods for DPM ester have been reported. The preparation of DPM esters can be performed by the treatment of benzophenone hydrazine in the presence of iodine and acetic acid, in the presence of $PhI(OAc)_2$,[12] or in the presence of peracetic acid.[13] DPM esters was also produced from diazodiphenylmethane in acetone.[14] The employment of $(Ph_2CHO)_3PO$ and trifluoroacetic acid has also been shown to protect esters with DPM groups.[15] However, these conditions use expensive reagents and require strong acidic conditions which can restrict the scope of the esterification. In addition, metal catalyst-mediated methods using 5 mol% MoO_2Cl_2 (molybdenum(VI) dichloride dioxide) in the presence of benzoic anhydride have been reported for synthesis of DMP ester, but the reaction took more than one day to complete.[16]

Thus, the discovery of a novel efficient synthetic method using inexpensive starting materials under mild conditions for DMP ester formation is still a challenge. Dudley and co-workers reported a reaction protocol using 2-benzyloxy-1-methylpyridine to prepare benzyl esters.[17] In this method, 2-benzyloxy-1-methylpyridine was converted to 2-benzyloxy-1-methylpyridinium triflate salt by MeOTf. In the reaction mechanism, the oxypyridinium salt serves as a key intermediate to produce benzyl esters. However, this method required two steps and reaction temperatures as high as 83 °C. Moreover it took one day to complete the reaction. However, from the reactions using 2-benzyloxy-1-methylpyridine, we hypothesized that 2-diphenyloxy-1-methylpyridine, which contains groups more bulky than the benzyl group, can be used as a starting material for the preparation of DPM esters with the employment of novel catalytic reagents. To the best of our knowledge, a synthetic method for the direct preparation of DPM ester from 2-diphenylmethoxypyridine has not been reported. We predicted that a Lewis acid reagent could serve as a key reagent for DPM esterification because of the versatility of Lewis acids as catalysts in several organic reaction.[18-20] Here, we report the novel facile synthesis of DPM esters from 2-diphenylmethoxypyridine and various carboxylic acids using a catalytic amount of Lewis acid.

2. Result and Discussion

The overall equation for the preparation of DPM ester from diphenylmethyl alcohol is shown in Scheme 1. In the first step, 2-diphenylmethoxypyridine was prepared using a modification of the previously reported method.[21] The reaction of diphenylmethyl

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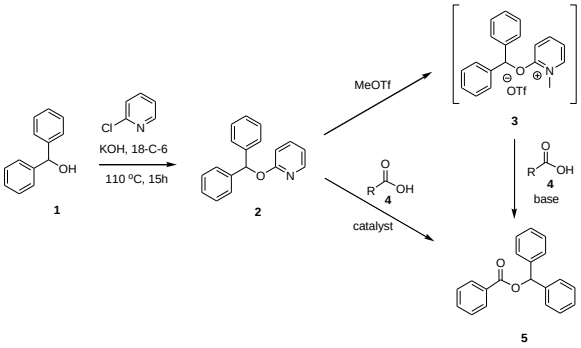
alcohol with 2-chloropyridine in the presence of potassium hydroxide and 18-crown-6 produced 2-diphenylmethoxypyridine (compound **2**) with 93% yield. In the initial study, we used the previously reported synthetic method using oxypyridinium salt to prepare DPM ester. Compound **2** was treated with MeOTf to induce alkylation yielding 2-diphenylmethoxy-1-methylpyridinium triflate, which can be used in situ for reaction with carboxylic acids. Several reagents including K_2CO_3, and Et_3N were employed for the reaction of 2-diphenylmethoxy-1-methylpyridinium triflate, according to the previous reported procedure.[22] However, no advantage was observed during the reaction (17 % for K_2CO_3 and 18% for Et_3N).



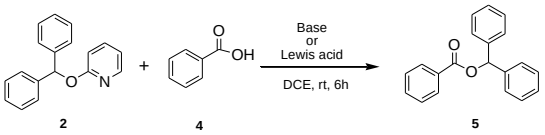
Scheme 1. Synthetic route to diphenylmethyl esters.

Thus, a novel reaction protocol for the treatment of carboxylic acids with 2-diphenylmethoxypyridine was explored to achieve better direct transformation of carboxylic acids to DPM esters without the formation of oxypyridinium salt. Benzoic acid was used as the substrate to select the initial optimal reaction condition for the synthesis of DPM ester. The screening of reaction condition was carried out with a series of organic reagents, including bases and Lewis acids to find a better catalytic reagent for DPM ester formation. In this study, the esterification reaction of benzoic acid was performed in the presence of 1.0 equiv. of compound **2**, 1.0 equiv. of benzoic acid and 0.2 equiv. of either Lewis acid or base in dichloroethane (DCE). After reaction for 6 h, the effect of each reagent on esterification was measured. Our initial screening results suggest that the catalytic activities of the organic reagents varied significantly according to catalyst type, as shown in Table 1. The catalytic activities of the bases K_2CO_3, Et_3N, $NaHCO_3$, and DBU were very low (0-5% yield). Addition of Lewis acids such as $TiCl_4$, $AlCl_3$, and $SnCl_4$, resulted in a small increase in DPM esterification, but yield remained less than 10%. Finally, the screening reaction experiment with $BF_3{\cdot}OEt_2$ was investigated. Unexpectedly, the conversion yield for the desired product was enhanced to 95%, suggesting that direct *in situ* reaction with $BF_3{\cdot}OEt_2$ is the most effective for DPM esterification.

Next, the effect of solvent choice on the reaction was explored. Reactions performed with $BF_3{\cdot}OEt_2$ in solution with THF, MeCN, 1,4-dioxane, and toluene led to low yield synthesis of DPM ester. When the reaction was carried out in toluene, the conversion yield for the desired product increased to 58%, but still unsatisfactory. However, when chlorinated solvents such as dichloromethane (DCM) and dichloroethane (DCE) were employed in the reaction, the yield of the desired DMP ester increase significantly (92% for dichloromethane, and 95% for dichloroethane; Table 2). The solvent screening results suggest that DCE is the most suitable solvent for the reaction.

Based on our primary results, we further tested the use of $BF_3{\cdot}OEt_2$ in different amounts (0.05 equiv, 0.1 equiv and 1.0 equiv) in DPM esterification. Reactions performed using 1.0 equiv of $BF_3{\cdot}OEt_2$ resulted in synthesis of the desired DPM ester with 95% yield in 30 min, while 0.05 equiv and 0.1 equiv of $BF_3{\cdot}OEt_2$ resulted in synthetic yields of 41% and 78%, respectively, after performing the reaction for 24 h (Table 2, entries 7, 8 and 9). These results suggest that the loading amount of $BF_3{\cdot}OEt_2$ significantly influences the synthetic yield of the DPM ester compounds. Based on these conversion yields, a

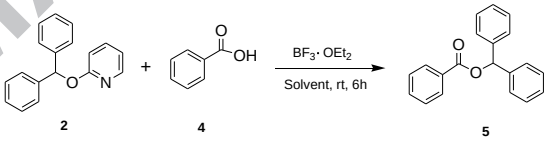
Table 1. Screening of catalysts for DMP esterification[a]



Entry	Base or Lewis acid	time	Temp.	Yield[b] (%)
1	K_2CO_3	6	r.t.	4
2	Triethylamine	6	r.t.	3
3	$NaHCO_3$	6	r.t.	NR[c]
4	DBU	6	r.t.	NR[c]
5	$TiCl_4$	6	r.t.	8
6	$AlCl_3$	6	r.t.	7
7	$SnCl_4$	6	r.t.	9
8	$BF_3{\cdot}OEt_2$	6	r.t.	95
9	None	6	r.t.	NR[c]

[a] Reaction conditions: compound **2** (1.5 mmol), carboxylic acid (1.0 mmol), Bases or Lewis acids (0.2 mmol), DCE (4 mL), 6 h
[b] Isolated yield after purification of flash column chromatography.
[c] No reaction.

Table 2. Screening of solvent for in situ esterification [a]



Entry	Lewis acids (equiv)	Solvent	Temp.	Yield[b] (%)
1	$BF_3{\cdot}OEt_2$ (0.2)	THF	r.t.	21
2	$BF_3{\cdot}OEt_2$ (0.2)	MeCN	r.t	27
3	$BF_3{\cdot}OEt_2$ (0.2)	1,4-dioxane	r.t.	NR[c]
4	$BF_3{\cdot}OEt_2$ (0.2)	Toluene	r.t.	58
5	$BF_3{\cdot}OEt_2$ (0.2)	CH_2Cl_2	r.t.	92
6	$BF_3{\cdot}OEt_2$ (0.2)	DCE	r.t.	95
7[d]	$BF_3{\cdot}OEt_2$ (0.05)	DCE	r.t.	41
8[d]	$BF_3{\cdot}OEt_2$ (0.1)	DCE	r.t.	95
9[e]	$BF_3{\cdot}OEt_2$ (1.0)	DCE	r.t.	78

[a] Reaction conditions: compound **2** (1.5 mmol), carboxylic acid (1.0 mmol), Lewis acids (0.2 mmol), solvent (4 mL), 6 h
[b] Isolated yield after purification of flash column chromatography.
[c] No reaction.
[d] Reaction conducted for 24 h.
[e] Reaction conducted for 30 min.

catalytic amount of $BF_3{\cdot}OEt_2$ of 0.2 equiv (20 mol%) was selected for the subsequent studies of the DPM ester synthesis, although reactions containing 1.0 equiv of $BF_3{\cdot}OEt_2$ resulted in a sufficient yield of the desired product in short time.

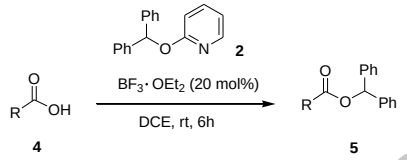
The suitability and scope of the optimized reaction conditions for the preparation of various other DPM esters were examined (Table 3). These reactions were performed by mixing 1.0 equiv. of carboxylic acid substrates with 1.5 equiv. of 2-diphenylmethoxypyridine in the presence of 20 mol% of $BF_3{\cdot}OEt_2$ in anhydrous DCE at room temperature. All DPM esterification yields of benzoic acids were evaluated for 6 h. First, benzoic acids containing electron-donating and electron-withdrawing groups were used for the preparation of DPM esters. Reactions of benzoic acids with electron-donating group generated the corresponding DPM ester in high yield ranging from 94% to 96% (Table 3, entries 2 and 3). Similarly, benzoic acids with electron-withdrawing group were esterified with good yield under the same conditions (Table 3, entries 4-8). This result indicates that the reactions using catalytic amounts of $BF_3{\cdot}OEt_2$ work well with aromatic carboxylic acids to produce the corresponding DPM ester with good yield.

Next esterification of alkyl-substituted carboxylic acids was examined. The reactions of alkyl-substituted carboxylic acids with 2-diphenylmethoxypyridine in the presence of catalytic $BF_3{\cdot}OEt_2$ produced the corresponding DPM ester in excellent yields (Table 3, entries 9-13). Cyclohexanecarboxylic acid was also employed as an alicyclic substrate to test the possibility of this application. The desired product was easily obtained with 94% yield from the reaction of cyclohexanecarboxylic acid with 2-diphenylmethoxypyridine (Table 3, entry 14). In additions, both alkenyl and alkynyl-substituted carboxylic acids were used to assess the scope of the novel synthetic method for esterification of unsaturated carboxylic acids. The reaction protocol was proven useful for the synthesis of both alkene-substituted and alkyne-substituted esters. These $BF_3{\cdot}OEt_2$ catalyzed reactions produced DPM esters in high yields with the same method (96% for compound **5o** and 94% for compound **5p**). Interestingly, the result showed that the yields of reactions of alkyl-substituted carboxylic acids were generally higher than those of benzoic acids.

It is known that the steric effect of bulky groups usually influences the reaction yield. Thus, carboxylic acids with more bulky groups were used to explore the application of the new catalytic protocol. When adamantine carboxylic acid containing a hindered bulky group was used, the corresponding ester was formed with 90% yield under the same conditions after 6 h (Table 3, entry 17). The reaction of 3,5-dimethylbenzoic acid also produced the desired product with 93% yield (Table 3, entry 18). Diphenylacetic acid, which contains two bulky benzene groups, was also utilized for DPM esterification, and the reaction yield was not significantly different from those of the other phenyl carboxylic acids (Table 3, entry 19). These results clearly demonstrate the importance of $BF_3{\cdot}OEt_2$ as an efficient catalyst for the conversion of bulky carboxylic acids to DPM esters under mild reaction conditions using 2-diphenylmethoxypyridine.

The scope of utilization of catalytic $BF_3{\cdot}OEt_2$ was extended to a heterocyclic acid compound. For example, the treatment of 2-furoic acid containing oxygen with 2-diphenylmethoxypyridine readily resulted in the successful synthesis of the corresponding DPM ester with 92% yield in 6 h (Table 3, entry 20), demonstrating that heterocyclic DPM compounds can be obtained in high yields in the presence of $BF_3{\cdot}OEt_2$ under mild conditions. In additions, reaction of picolinic acid was performed, and DPM ester with pyridine ring was obtained in high yield (Table 3, entry 21).

Table 3. Scope of DPM esterification using 2-diphenylmethoxypyridine [a]



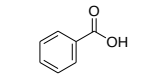
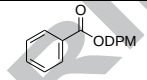
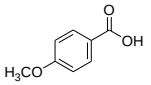
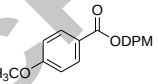
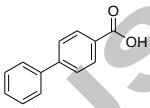
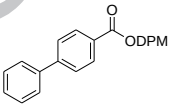
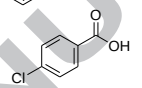
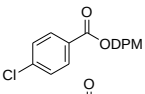
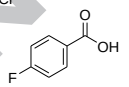
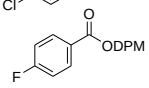
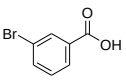
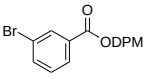
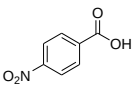
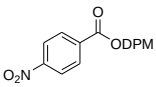
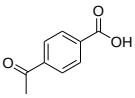
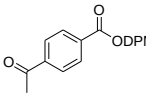
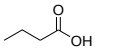
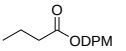
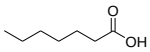
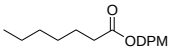
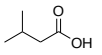
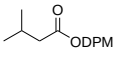
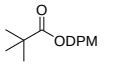
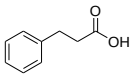
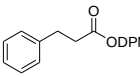
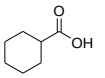
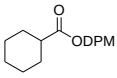
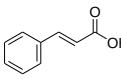
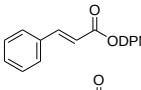
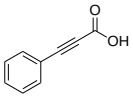
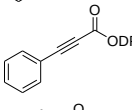
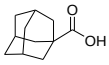
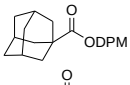
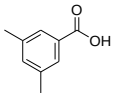
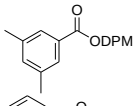
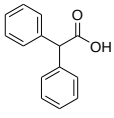
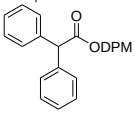
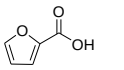
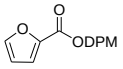
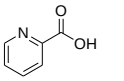
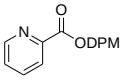
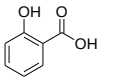
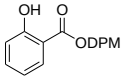
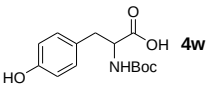
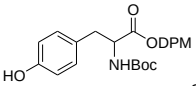
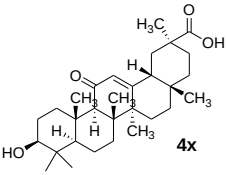
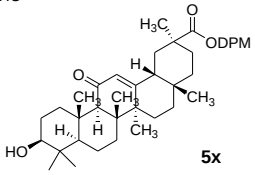
Entry	Carboxylic acid		Product		Yield[b] (%)
1		**4a**		**5a**	95
2		**4b**		**5b**	96
3		**4c**		**5c**	94
4		**4d**		**5d**	82
5		**4e**		**5e**	92
6		**4f**		**5f**	94
7		**4g**		**5g**	91
8		**4h**		**5h**	82
9		**4i**		**5i**	93
10		**4j**		**5j**	81
11		**4k**		**5k**	92
12		**4l**		**5l**	92
13		**4m**		**5m**	93
14		**4n**		**5n**	94
15		**4o**		**5o**	96
16		**4p**		**5p**	94
17		**4q**		**5q**	90
18		**4r**		**5r**	93
19		**4s**		**5s**	91

Table 3. (Contd.)

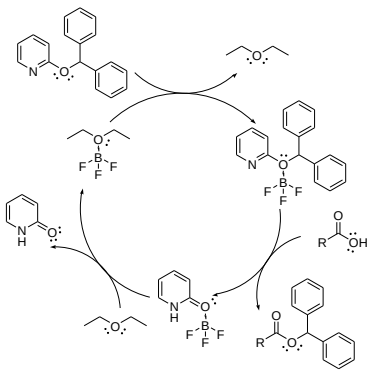
Entry	Carboxylic acid		Product		Yield[b] (%)
20		**4t**		**5t**	92
21		**4u**		**5u**	73
22		**4v**		**5v**	88
23		**4w**		**5w**	40
24		**4x**		**5x**	71

[a] Reaction conditions: Carboxylic acid (1.0 mmol), compound **2** (1.5 mmol), BF_3·OEt_2 (0.2 mmol), DCE (4 mL), rt for 6 h,
[b] Isolated yield after purification of flash column chromatography.

Salicylic acid bearing OH group was employed in our reaction method for the preparation of DPM esters. Reaction of salicylic acid produced desired DPM ester in yield of 88% (Table 3, entry 22). However, reaction of 4-aminobenzoic acid bearing NH_2 group gave DPM protected amine compound instead of DPM ester. The result suggested that the carboxylic group was more reactive to prepare DPM esters than the hydroxyl group, and the amine showed to be the most reactive group which reacted with 2-diphenylmethoxypyridine more rapidly than carboxylic acid. Besides, Boc-protected tyrosine was utilized for DPM esterification, and the corresponding ester was prepared under the same condition (Table 3, entry 23).

Finally, 18*β*-glycyrrhetinic acid, which is more complex biological carboxylic acid, was employed for DPM esterification and the desired product was obtained (Table 3, entry 24).

Based on the present result, a plausible mechanism for this reaction could be proposed, as shown in Scheme 2. In the first step, boron trifluoride diethyl etherate (BF_3·OEt_2) makes a complex with 2-diphenylmethoxypyridine which can easily undergo nucleophilic attack by carboxylic acid to yield the DPM ester product. Then, 2-pyridone was separated from 2-pyridone-BF_3 complex and BF_3·OEt_2 was given back to the reaction and continuously catalyze DPM ester reaction.



Scheme 2. Plausible reaction mechanism.

3. Conclusion

In summary, a novel facile BF_3·OEt_2–catalyzed DPM esterification of various carboxylic acids was developed. Developments of novel reaction methods to generate DPM esters are of particular importance due to their popular use as a protecting group for carboxylic acids. In the present study, BF_3·OEt_2 was used as a catalyst for the reaction of carboxylic acids with 2-diphenylmethoxypyridine for the production of the desired DPM ester compounds with high yield. This method is noteworthy because the formation of DPM esters from carboxylic acid substrates was achieved under mild reaction conditions. Our results suggest that the novel protocol using catalytic BF_3·OEt_2 is efficient and applicable to the protection of a variety of carboxylic acids in a variety of organic syntheses.

Acknowledgments

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References and notes

1. Haslam, R. D.; Haworth, R. D.; Makinson. G. K. *J. Chem. Soc.* **1961**, 5153-5156.

2. Hiskey, R. G.; Smithwick, E. L. *J. Am. Chem. Soc.* **1967**, *89*, 437-441.

3. Stelakatos, G. C.; Paganou, A.; Zervas, L. *J. Chem. Soc. C.* **1966**, 1191-1199.

4. Hills, L. R.; Ronald, R. C. *J. Org. Chem*. **1985**, *50*, 470−473.

5. Hiskey, R. G.; Adams, J. B. *J. Am. Chem. Soc*. **1965**, *87*, 3967-3973.

6. Ohtani, M.; Watanabe, F.; Narisada, M. *J. Org. Chem*. **1984**, *49*, 5271−5272.

7. De Bernardo, S.; Tengi, J. P.; Sasso, G. J.; Weigele, M. *J. Org. Chem*. **1985**, *50*, 3457−3462.

8. Aoyama, Y.; Uenaka, M.; Kii, M.; Tanaka, M.; Konoike, T.; Hayasaki-Kajiwara, Y.; Naya, N.; Nakajima, M. *Bioorg. Med. Chem*. **2001**, *9*, 3065–3075.

9. Yamawaji, K.; Nomura, T.; Yasukata, T.; Uotani, K.; Miwa, H.; Takeda, K.; Nishitani, Y. *Bioorg. Med. Chem*. **2007**, *15*, 6716–6732.

10. Marshall, W. S.; Goodson, T.; Cullinan, G. J.; Swanson-Bean, D.; Haisch, K. D.; Rinkema, L. E.; Fleisch, J. H. *J. Med. Chem*. **1987**, *30*, 682−689.

11. De Sa, A.; Prata, M. I. M. P.; Geraldes, C. F.G.C.; André, J. P.. *J. Inorg. Biochem*. **2010**, *104*, 1051–1062.

12. Bywood, R.; Gallagher, G.; Sharma, G. K.; Walker, D. *J. Chem. Soc.Perkin Trans. 1.* **1975**, 2019-2022.

13. Micetich, R. G.; Malti, S. M.; Spevak, P.; Tanaka, M.;, Yamazaki, T.; Ogawa, K. *Synthesis*. **1986**, *4*, 292-296.

14. Kametani, H.; Sekine, H.; Hondo, T. *Chem. Pharm. Bull*. **1982**, *30*, 4545-4547.

15. Lapatsanis, L. *Tetrahedron Lett.* **1978**, *19*, 4697–4698.

16. Chen, C.-T.; Kuo, J.-H.; Ku, C.-H.; Weng, S,-S,; Liu, C.-Y. *J. Org. Chem*. **2005**, *70*, 1328−1339.

17. Tummatorn, J.; Albiniak, P. A.; Dudley, G. B. *J. Org. Chem*. **2007**, *72*, 8962−8964.

18. Li, Y.; Xiong, Y.; Li, X. M.; Ling, X. G.; Huang, R. F.; Zhang, X. H.; Yang, J. C. *Green Chem*. **2014**, *16*, 2976–2981.

19. Huang, R. F.; Zhang, X. H.; Pan, J.; Li, J. Q.; Shen, H.; Ling, X. G.; Xiong, Y. *Tetrahedron* **2015**, *71*, 1540–1546.

20. Sheng, H.; Li, J. Q.; Liu, Q.; Pan, J.; Huang, R. F.; Xiong, Y. *J. Org. Chem*. **2015**, *80*, 7212–7218.

21. Poon, K. W. C.; Dudley, G. B. *J. Org. Chem*. **2006**, *71*, 3923−3927.

22. General procedure for the preparation of DPM esters (**5a-5x**): To a solution of benzoic acid (0.12 g. 1.00 mmol) and 2-diphenylmethoxypyridine (0.39 g, 1.50 mmol) in DCE (4 mL) $BF_3{\cdot}OEt_2$ (0.028 g. 0.20 mmol) was added. The mixture was stirred at room temperature for 6h. The reaction mixture was extracted with ethyl acetate (2 x 10 mL), and then washed with water (10 mL), followed by brine (10 mL). The organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The resulting residue was then purified by flash column chromatography on silica gel with hexane-CH_2Cl_2 as eluent to afford the desired product **5a** as a white solid (0.175 g, 95%).

Highlights

- Direct DPM esterification from carboxylic acids.
- Catalytic boron trifluoride-diethyl etherate was used.
- DPM esterification at room temperature.
- Easy to perform in one step.