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Convenient and Simple Esterification in Continuous-Flow Systems using *g*-DMAP

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The utility and applicability of polyethylene-*g*-polyacrylic acid-immobilized dimethylaminopyridine (*g*-DMAP) as a catalyst in a continuous-flow system were investigated for decarboxylative esterification. High catalytic activity toward acylation was provided by *g*-DMAP containing a flexible grafted-polymer structure. During decarboxylation, carboxylic acids and alcohols were converted cleanly using di-*tert*-butyl dicarbonate (Boc_2O) as a coupling reagent, which reduced by-products. In addition, the use of Boc_2O resulted in the formation of *tert*-butyl esters. These esterifications dramatically reduced the reaction time under continuous-flow conditions, with a residence time of approximately 2 min. This highly efficient esterification procedure will provide more practical industrial applications.

Polymer-immobilized reagents and catalysts have promoted environmentally friendly and sustainable chemistry.[1,2] A variety of catalysts for these syntheses were developed by introducing functional groups into polystyrene supports.[3] However, the ability of reagents to access the catalytic site can be difficult owing to the closed framework of the cross-linked polystyrene.[4] Therefore, attention focused on the use of graft polymers to accumulate highly reactive side chains on the surface of the trunk polymer. For example, polyethylene-*g*-polyacrylic acid (PE-*g*-PAA) has flexible grafted chains on the chemostable polyethylene trunk that can be functionalized.

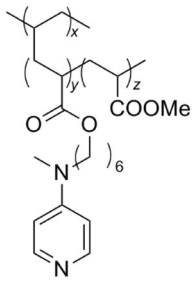
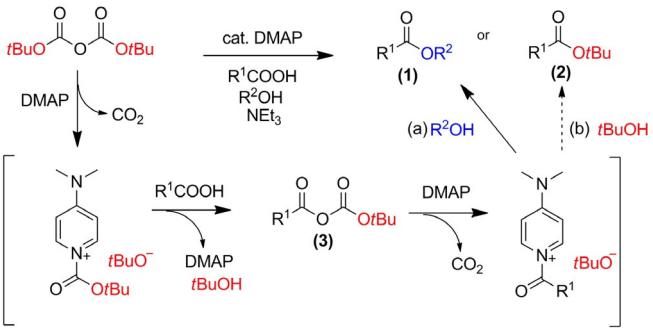


Figure 1. Structure of *g*-DMAP.

A previous study reported PE-*g*-PAA-supported dimethylaminopyridine (*g*-DMAP) as a heterogeneous organocatalyst for continuous-flow acylation systems (Figure 1).[5] The *g*-DMAP possessed highly accessible reactive sites and chemical stability, owing to the structure of PE-*g*-PAA. Acylation using *g*-DMAP with acid anhydride produced the desired products in good yields. The present study describes the application of *g*-DMAP in continuous esterification reactions using a wide variety of carboxylic acids and alcohols. As an extension of dimethylaminopyridine (DMAP)-mediated esterification,[6] the esterification was reported to proceed via an acylpyridinium salt after generation of the mixed anhydride.[7] However, by-products of the coupling reagents, such as dicyclohexylcarbodiimide/DMAP, hindered esterification in a continuous-flow system.[8] Decarboxylative esterification using the effective di-*tert*-butyl dicarbonate (Boc_2O)/DMAP system had the advantage of volatile by-products (Scheme 1).[9,10] Thus, herein a continuous-flow system using *g*-DMAP for decarboxylative esterification in the Boc_2O/DMAP system was developed.



Scheme 1. Decarboxylative esterification with Boc_2O/*g*-DMAP.

Initially, decarboxylative esterification as a batch method was investigated using 0.1 M 1-phenylethyl alcohol, 1.5 equivalents of 3-phenylpropanoic acid, 1.65 equivalents of Boc_2O and triethylamine (NEt_3), and 3.3 mol% *g*-DMAP in toluene at room temperature. Good activity was obtained (see the Supporting Information for optimized conditions).

After the initial experiments, a continuous-flow system with Boc_2O/*g*-DMAP was investigated using several different alcohols and carboxylic acids. Batch and flow conditions were compared using the same substrate ratio and solvent (Table 1). Continuous-flow reaction conditions were based on previously optimized values; sufficient time (ca. 60 min) was required to replace the reaction solution, as the reactor was filled with solvent before operation. The extent of conversion in the product was determined periodically by HPLC using an internal standard. Esterification within the Boc_2O/*g*-DMAP system under both conditions was effective, demonstrating that *g*-DMAP can be applied to continuous-flow systems and reused with different substrates and solvents. Although the rate of product for-

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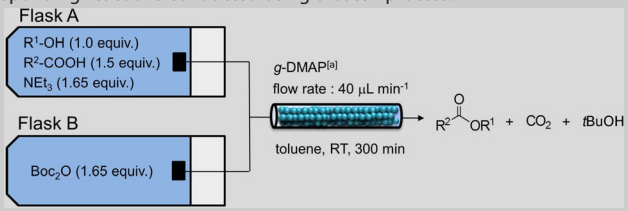
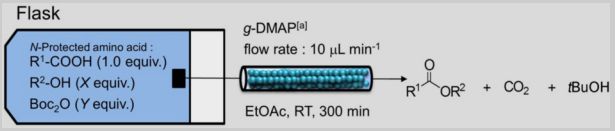
Table 1. Continuous esterification process using various alcohols and carboxylic acids in the Boc_2O/*g*-DMAP system, and comparison to corresponding reactions conducted using a batch process.[a]



Entry	R^1–OH	R^2–COOH	Batch yield[b] [%]	Flow conv.[c] [%]
1	1-phenylethyl	3-phenylpropanoic	99	92
2	1-phenylethyl	cinnamic	81	87
3	3-phenylpropyl	3-phenylpropanoic	89	92
4[d]	3-phenylpropyl	cinnamic	85	99[e]
5[d]	benzyl	3-phenylpropanoic	79	84[e]
6	benzyl	cinnamic	93	95
7	L-menthol	3-phenylpropanoic	64[f]	79[f,g,h]

[a] *g*-DMAP (Lot No. 01, $f = 2.54$ mmol g^{-1}) with 0.25 mmol functionality was loaded and used repeatedly. [b] Alcohol (0.1 M), molar ratios are same with flow conditions, fresh *g*-DMAP (Lot No. 02, $f = 2.51$ mmol g^{-1}, 3.3 mol%) was used, RT, 24 h, isolated yield. [c] Alcohol (0.6 M), determined by HPLC of crude product. [d] Different Lot number catalyst was used. [e] *g*-DMAP (Lot No. 02, $f = 2.51$ mmol g^{-1}) with 0.15 mmol functionality. [f] Solvent: ethyl acetate. [g] Flow rate: 20 μL min^{-1}. [h] *g*-DMAP (Lot No. 02, $f = 2.51$ mmol g^{-1}) with 0.11 mmol functionality.

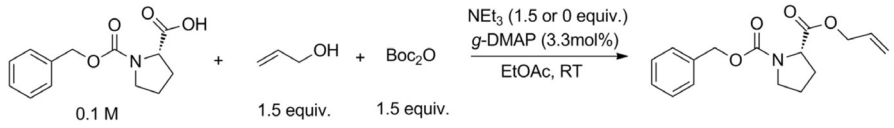
Table 2. Continuous esterification with *N*-protected amino acids and various alcohols using a Boc_2O/*g*-DMAP system under auxiliary base-free conditions, and comparison to corresponding reactions under batch conditions.[a]



Entry	R^1–COOH	R^2–OH	Batch yield[b] [%]	Flow conv.[c] [%]
1[d]	Z-Pro	L-menthol	62	79
2[d]	Z-Pro	allyl	41	90
3[e]	Z-Pro	cinnamyl	48	82
4[e]	Boc-Pro[f]	benzyl	89	95
5[g]	Z-Phe	allyl	95	95

[a] *g*-DMAP (Lot No. 02,$f = 2.51$ mmol g^{-1}) with 0.12 mmol functionality loaded in the reactor and used repeatedly. [b] R^1–COOH (0.1 M), molar ratios are same with flow conditions, *g*-DMAP (Lot No. 02, 3.3 mol%), RT, 24 h, isolated yield. [c] R^1–COOH (0.2 M), determined by HPLC of crude product. [d] $X = 1.3$, $Y = 1.3$. [e] $X = 1.5$, $Y = 1.5$. [f] *N*-(*tert*-butoxycarbonyl)-D-proline [g] $X = 1.7$, $Y = 1.7$.

mation was reduced under a lower flow rate (20 μL min^{-1}), the conversion efficiency improved (Table 1, entry 7). However, the batch reaction required 24 h, whereas the residence time in the catalyst tube using the continuous-flow system was only 2 min at a flow rate of 40 μL min^{-1}, demonstrating the advantages of continuous-flow systems.[5] This suggests that Boc_2O/*g*-DMAP can be a beneficial coupling reagent for various substrates if individual reaction conditions are optimized.



Scheme 2. The esterification of Z-Pro with allyl alcohol using the Boc_2O/*g*-DMAP system.

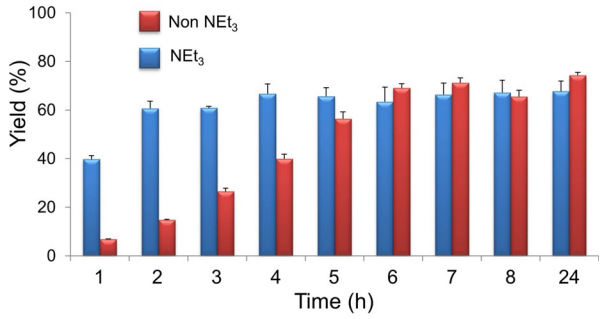


Figure 2. Effect of NEt_3 on esterification of Z-Pro with allyl alcohol using the Boc_2O/*g*-DMAP system in a batch process.

The reaction was then performed under auxiliary-base-free conditions. The auxiliary-base effect of NEt_3 was determined for esterification of *N*-(carbobenzyloxy)-D-proline (Z-Pro) with allyl alcohol in a batch process (Scheme 2; Figure 2). In this esterification with DMAP, NEt_3 was important owing to the deprotonation step in enhancing the nucleophilicity of carboxylic acids for catalytic activity of DMAP.[11] As a result, in the absence of NEt_3, the reaction proceeded more gradually than the reaction under auxiliary-base conditions. However, this drawback was improved by employing the continuous-flow system, which decreased the reaction time significantly. Several esterification reactions between *N*-protected amino acids and alcohols without auxiliary base were investigated and compared under batch and flow conditions at room temperature (Table 2). In the continuous-flow system using an HPLC pump, all reagents were placed together in a flask. Catalytic activity for the esterification of Z-Pro with unsaturated and secondary alcohols in the batch process was improved dramatically through the use of this continuous-flow system (Table 2, entries 1–3). These results suggest that *g*-DMAP plays an important role in esterification, not only as a highly nucleophilic base catalyst, but also through enhancement of the nucleophilicity of the carboxylic acids as an auxiliary base.

Finally, the efficacy of the Boc_2O/*g*-DMAP system for *tert*-butyl esterification of various carboxylic acids was investigated (Table 3).[9,12] As indicated in Scheme 1 (b), Boc_2O reacted with carboxylic acids to afford mixed carbonic–carboxylic anhydrides (3) with one equivalent of *tert*-butyl alcohol (*t*BuOH). The mixed carbonic–carboxylic anhydrides (3) then underwent nucleophilic attack by *g*-DMAP, resulting in formation of the acylpyridinium salt and its corresponding *tert*-butyl ester, ac-

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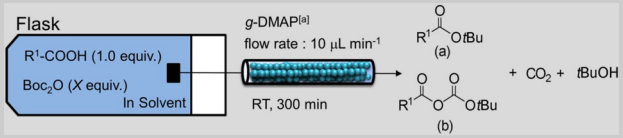
Table 3. Continuous *tert*-butyl esterification of various carboxylic acids in the Boc_2O/*g*-DMAP system.[a]



Entry	R^1-COOH	Boc_2O [equiv.]	Solvent	Flow Conv.[b] [%]
1	Z-Pro	1.5	Toluene	(a) 88[c]
2	Z-Phe	2.0	*t*BuOH	(a) 79
3[d]	2-Phenylbutyric acid	2.0	THF	(a) 81[d]
4[d]	Abietic acid	2.0	THF	(a) nd[d,e]
				(b) > 99[d]

[a] *g*-DMAP (Lot No. 02, $f = 2.51\ mmol\,g^{-1}$) with 0.25 mmol functionality loaded in the reactor and used repeatedly. [b] R^1–COOH (0.2 M), determined by HPLC of crude product. [c] 76 h. [d] *g*-DMAP (Lot No. 02, $f = 2.51\ mmol\,g^{-1}$) with 0.22 mmol functionality loaded in the reactor and used repeatedly. [e] Not determined.

companied by CO_2 evolution. High conversion of *N*-(carbobenzyloxy)-D-phenylalanine (Z-Phe) occurred using *t*BuOH (Table 3, entry 2) indicating that *t*BuOH functions as solvent and nucleophilic reagent. In abietic acid, which is a sterically hindered carboxylic acid, a *tert*-butyl carbonic abietic anhydride intermediate was formed without formation of the *tert*-butyl ester.

In conclusion, a useful continuous-flow system was developed using coupling reactions involving Boc_2O/*g*-DMAP for decarboxylative esterification with carboxylic acids and alcohols. This continuous-flow system not only reduced the production of by-products, but also dramatically decreased the reaction time because of the graft-polymer-supported catalyst. However, further optimization is needed for the reactions. These results suggest a broad scope for graft-polymer-supported catalysts in flow systems.

Acknowledgements

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