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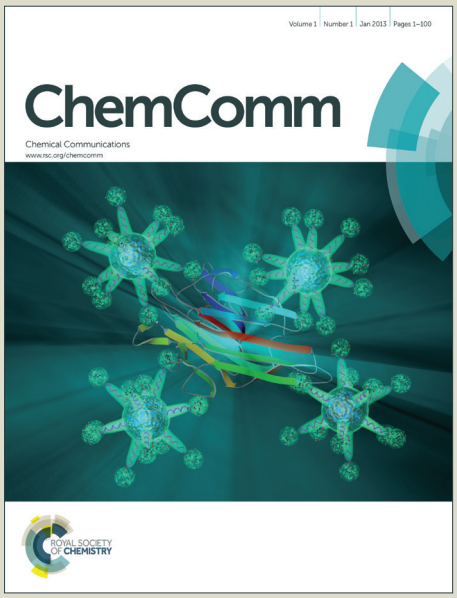

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A Novel Aromatic Carbocation-based Coupling Reagent for Esterification and Amidation Reactions

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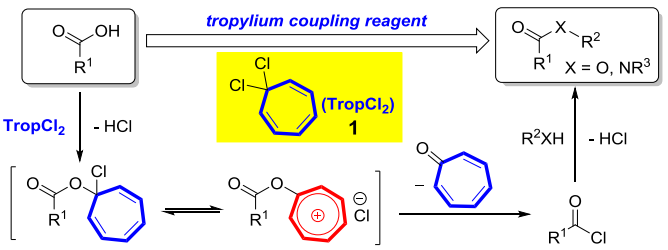
A novel tropylium-based coupling reagent has been developed to facilitate the synthesis of a series of esters, amides, lactones and peptides under mild reaction conditions. Remarkably, this reagent can be used in catalytic amount in conjunction with a sacrificial reagent, offering a new and efficient method for nucleophilic coupling reactions of carboxylic acids.

The coupling reactions of carboxylic acids with alcohols or amines to produce esters or amides are fundamental processes in organic synthesis.[1] Esterification reactions offer access to important products in chemical and pharmaceutical industries, such as fragrances, polymers, plasticizers and paints.[2,3] On the other hand, the amide moiety is a common feature in biologically important synthetic and natural products, especially proteins.[4] In principle, esters and amides can be produced from the condensation reaction between carboxylic acids and the corresponding nucleophilic precursors. However, these reactions are normally unfavourable due to the adverse thermodynamics of the condensation/hydrolysis equilibria.[2-5] In order to achieve efficient synthesis of the products, activation of the carboxylic acid groups and removal of the water by-product are often required. There have been numerous synthetic methods and coupling reagent systems developed for this purpose, most notably the dehydration reactions with carbodiimide, phosphonium, uronium, immonium, imidazolium and Mukaiyama-type pyridinium reagents with aid from the acyl transfer reagents such as DMAP and its analogues.[3-5] The use of chlorinating reagents, triazine-based reagents and other types of activating systems is also a common approach for carboxylic acid coupling reactions.[4] These methods are efficient for the synthesis of esters, amides and peptides; many of them are, however, disadvantaged from the generation of undesired by-products as well as the difficult preparation of the coupling reagents.[6] Therefore, the development of novel methods for esterification and amidation reactions remains a topical challenge in synthetic chemistry.

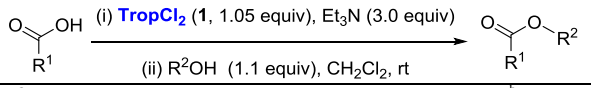
In search for a simple and readily available coupling reagent for the synthesis of esters and amides, we envisage that our recently developed tropylium aromatic cation system will be capable of activating carboxylic acids for nucleophilic derivatization.[7] Aromatic cation activation is an emerging area in organic chemistry[8,9] yet its potential applications in synthetic organic chemistry have not been fully explored and evaluated. Herein, we describe our development of the first tropylium-based reagent system for efficient synthesis of a range of esters, amides, lactones and especially oligopeptides. This coupling reagent can also be used on catalytic scale to smoothly facilitate the esterification and amidation coupling reactions of carboxylic acids under mild conditions.

Preliminary studies in our group revealed that 1,1-dichlorocycloheptatriene/chlorotropylium chloride **1**,[10] efficiently converted phenylacetic acid to its corresponding acid chloride (Scheme 1, R^1 = Bn),[7] facilitating one-pot coupling reactions with alcohols to produce several ester derivatives (entries 1-3, Table 1). The reactions proceeded smoothly at ambient temperature in several commonly used organic solvents. The optimal reaction conditions utilized dichloromethane solvent with 1.05 molar equivalents of 1,1-dichlorocycloheptatriene in the presence of an organic base such as triethylamine or DIPEA to quench the resulting hydrogen chloride and increase the reaction rate.[11] Reagent **1** is normally formed *in situ* by treating tropone with a sacrificial chlorinating reagent such as oxalyl chloride.[11] It can also be quantitatively prepared from tropone and stored in solution or solid form in the refrigerator for months. As tropone is one of the by-products in the coupling reactions, **1** can actually be regenerated from the reaction mixture.



Scheme 1. 1,1-dichlorocycloheptatriene mediates esterification and amidation coupling reactions of carboxylic acids

Table 1 Esterification reactions of carboxylic acids



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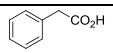
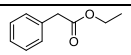
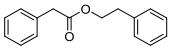
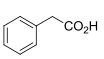
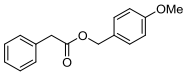
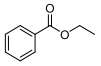
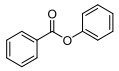
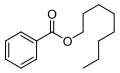
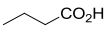
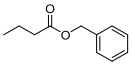
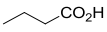
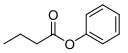
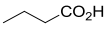
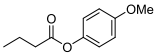
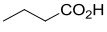
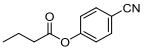
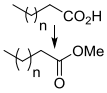
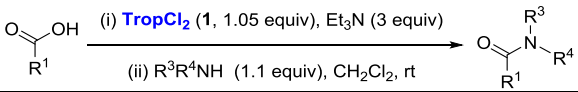
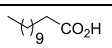
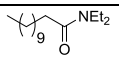
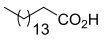
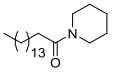
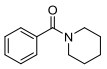
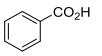
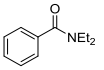
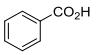
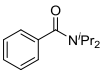
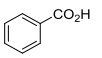
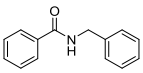
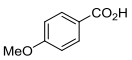
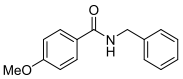
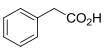
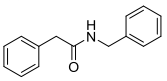
1			25	89
2			25	90
3			25	93
4			60	60
5			60	69
6			60	66
7			25	82
8			25	88
9			25	92
10			25	80
11-16		n = 5 (87%); n = 7 (85%) n = 9 (81%); n = 11 (80%) n = 13 (86%); n = 15 (82%)	25	varied

[a]See the Supporting Information for experimental details; [b]Reaction time (minutes) after the addition of carboxylic acids and before the addition of alcohol; [c]Yield of isolated product.

Table 2 Amidation reactions of carboxylic acids



Entry[a]	Substrate	Product	Time[b]	Yield[c]
1			25	74
2			25	72
3			60	68
4			60	71
5			60	61
6			60	63
7			60	65
8			25	85
9			25	86
10			25	79
11[d]			25	67
12[d]			60	62
13	Boc-*L*-Ala-OH	Boc-*L*-Ala-*L*-Phe-OMe	25	72 *dr* > 16:1
14	Boc-*L*-Phe-OH	Boc-*L*-Phe-*L*-Ala-OMe	25	75 *dr* > 14:1
15	Boc-*L*-Val-OH	Boc-*L*-Val-*L*-Phe-OMe	25	77 *dr* > 16:1

[a]See the Supporting Information for experimental details; [b]Reaction time (minutes) after the addition of carboxylic acids and before the addition of amine; [c]Yield of isolated product; [d]Aqueous ammonia (30% w/w, 10 equiv) was added instead of normal amine substrate.

The coupling efficiency of **1** was subsequently investigated for the esterification reactions of a series of other carboxylic acids (Table 1). Under the developed conditions, a stoichiometric amount of **1** was used to facilitate the coupling reactions between several carboxylic acids and alcohol or phenol substrates to afford ester products in good to excellent yields (entries 4-14, Table 1). Aliphatic carboxylic acids (entries 1-3 and 7-14, Table 1) reacted smoothly within a short reaction time while benzoic acid underwent slightly more sluggish reactions. The difference in reactivity is presumably due to the decreased nucleophilicity of the conjugated carboxylic groups, making them less reactive towards tropylium chloride (**1**). Conjugated system can also stabilize the tropylium ester intermediates, rendering them less vulnerable to nucleophilic attack of the chloride anion (Scheme 1). Variation of the coupling substrates from alcohol (entry 7, Table 1) to phenols with different aromatic substituents (entries 8-10, Table 1) slightly affected the product yields. This can be attributed the fact that phenols can be deprotonated under the basic reaction conditions and the phenolates formed were more nucleophilic than alcohols. Obviously, the electron withdrawing substituent on the phenol substrate at entry 10 rendered it the least nucleophilic of the three phenol substrates, hence the lowest product yield. Methyl esters of several fatty acids were also produced smoothly in high yields (entries 11-16, Table 1). The achieved product yields of these equimolar coupling reactions demonstrate the comparable efficiency of this new coupling reagent to well- established systems in the literature.[3,5] Moreover, this is, to our knowledge, the first systematic study on the ability to mediate carboxylic acid coupling reactions of such a *simple chlorinated hydrocarbon reagent* like **1**, which conceptually opens up new possibilities for esterification and peptide coupling reactions.

Having success with the esterification, we subsequently investigated the scope of amidation reactions mediated by **1**. Under the similar reaction conditions developed for the esterification, several amines were coupled successfully with carboxylic acids in one-pot reactions to produce the corresponding amides in good to high yields (Table 2). Again, benzoic acids gave lower yields of amide products than aliphatic carboxylic acids due to the sluggish conversion of the conjugated acids to acid chlorides. Primary and secondary amines, including the bulky diisopropylamine, coupled with these carboxylic acids smoothly to give amide products in comparable yields (entries 1-10, Table 2). Interestingly, the *in situ* formed acid chlorides can also be quenched with aqueous ammonia solution to afford primary amides (entries 11 and 12, Table 2). The

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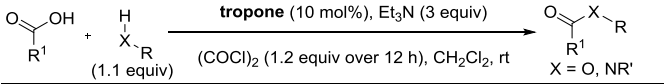
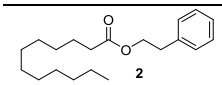
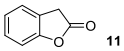
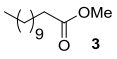
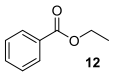
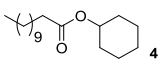
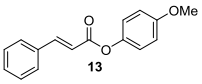
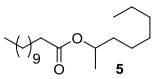
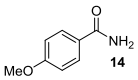
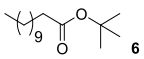
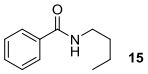
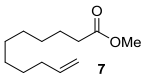
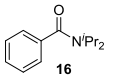
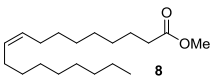
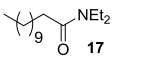
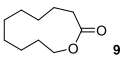
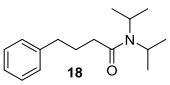
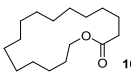
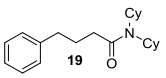
Table 3 Tropone-catalyzed coupling reactions of carboxylic acids[a]



Product	Yield	Product	Yield
 **2**	90	 **11**	92
 **3**	89	 **12**	14[b] 66[c]
 **4**	79	 **13**	11[b] 71[c]
 **5**	78	 **14**	trace[b] trace[c]
 **6**	trace	 **15**	9[b] 39[c]
 **7**	77	 **16**	18[b] 55[c]
 **8**	81	 **17**	58
 **9**	71[c]	 **18**	83
 **10**	73[c]	 **19**	77

[a]See the Supporting Information for experimental details; [b]No DMAP added; [c]DMAP (10 mol%) was added before the addition of oxalyl chloride.

peptide coupling reactions between several protected amino acids were carried out in good yields with promising level of racemization suppression,[11] proving that this tropylium-based coupling reagent can be used in peptide production (entries 13-15, Table 2).

One of the interesting features of the reactions mediated by **1** is that the by-product, tropone (Scheme 1), can be isolated from the reaction mixtures in up to 96% yields. Tropone can be used to conveniently regenerate the dichloroheptatriene coupling reagent (**1**) by quick treatment with chlorinating reagents such as oxalyl chloride at room temperature, offering an apparent advantage over the established methods. Furthermore, side studies in our group showed that oxalyl chloride reacts much faster with tropone than carboxylic acids, alcohols or amines. These fascinating features encouraged us to investigate the possibility to mediate the coupling reactions using a catalytic amount of tropone with the slow addition of oxalyl chloride as the sacrificial chlorinating reagent. To our delight, the coupling reaction between phenyl ethanol and dodecanoic acid, employing the slow addition of oxalyl chloride (1.5 equiv over 24 h) into the reaction mixture containing the two above substrates, triethylamine and tropone (20 mol%), met with immediate success. The reaction was optimized using only 10 mol% of tropone with 1.2 equiv of oxalyl chloride added over 12 h at room temperature, affording the product in excellent yield (entry **2**, Table 3).[11] Control experiments were also performed where each of the three components: oxalyl chloride, the base and tropone catalyst was absent. These experiments afforded very low yields or no esterified products, confirming the necessity for each of them for a successful coupling reaction.[11]

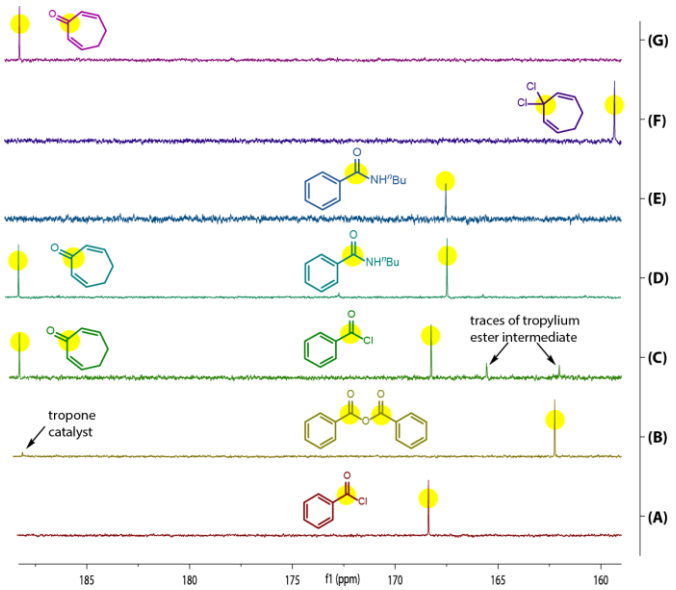
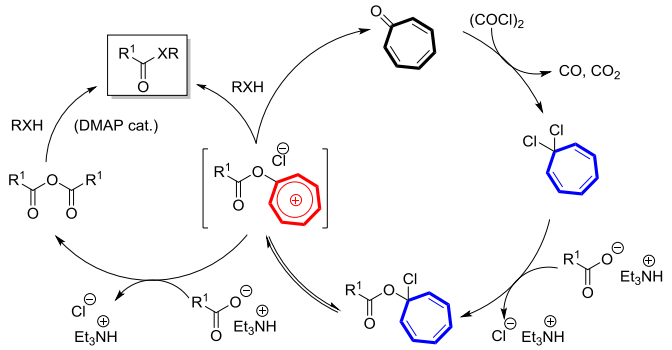


Figure 1. 13C NMR studies of reaction profiles (pertinent sections, 100 MHz, 25 °C, $CDCl_3$)

Under the optimal reaction conditions, a range of aliphatic carboxylic acid esters was produced smoothly in good to excellent yields (entries **2**-**8**, Table 3). Secondary alcohol substrates seemed to couple with carboxylic acids in lower yields than primary alcohol (entries **4** and **5** to **3**, Table 3) while tertiary alcohol was much less reactive, giving only trace amount of product **6** after prolonged reaction time. Intramolecular esterification coupling reaction went well to give a lactone in high yield (**11**, Table 3). Macrolactonization of ω-hydroxyl acids also worked efficiently to give the products in good yields (entries **9** and **10**, Table 3). Benzoic and cinnamic acids, however, did not work that well and generally gave mixtures of esters and acid anhydrides. With the addition of a catalytic amount of DMAP as acyl transfer reagent, benzoic and cinnamic acids were duly converted to their corresponding esters (entries **12** and **13**, Table 3).

The presence of acid anhydrides in the reaction mixtures was demystified by a study monitoring the transformation of benzoic acid by ^{13}C NMR spectroscopy (Figure 1) under different reaction conditions. We observed the reactions of: **(B)** benzoic acid with the slow addition of 1.2 equiv oxalyl chloride over 12 h in the presence of 0.1 equiv of tropone and 3.0 equiv of Et_3N; **(C)** benzoic acid with a stoichiometric amount (1.05 equiv) of pre-formed tropylium chloride (**1**) and 3.0 equiv of Et_3N after 45 minutes; **(D)** quenching of **(C)** after 60 minutes with *n*-butylamine (1.1 equiv). These were cross-referenced against ^{13}C NMR spectra of pure samples of **(A)** benzoyl chloride, **(E)** *n*-butylbenzamide, **(F)** tropylium chloride (**1**) and **(G)** tropone. Evidences from this study suggested that while a stoichiometric amount of tropylium chloride converted the acid to its acid chloride, a catalytic amount of tropylium chloride, formed *in situ* from tropone and oxalyl chloride, predominantly converted the acid to its anhydride instead.

For catalytic esterification reactions in Table 3, presumably the unreacted acids in the form of the carboxylate anions were



Scheme 2. Proposed mechanism for the tropone-catalyzed coupling reaction of carboxylic acids

more nucleophilic than the alcohol substrates and quickly reacted with the newly formed tropylium ester intermediates to form the anhydrides. The formation of acid chlorides from the tropylium ester intermediates, however, cannot be exclusively ruled out at the moment. Presumably, the alcohols reacted with these tropylium ester intermediates and as well as the newly formed anhydrides to afford the ester products. For aliphatic acids, the anhydrides were possibly reactive enough to directly react with the alcohol substrate to form the esters. On the other hand, the benzoic and cinnamic anhydrides were probably less reactive and reacted sluggishly with the alcohols if DMAP was not present. We propose a reaction mechanism to illustrate all these possible pathways (Scheme 2).

The catalytic amidation coupling reactions, employing 10 mol% tropone and the slow addition of oxalyl chloride, also proceeded smoothly, affording the products in good to high yields. The addition of a catalytic amount of DMAP was still essential for improved yields of benzamides (entries **15** and **16**, Table 3). Bulkier amines (entries **16**, **18**, **19**, Table 3) seemed to serve as better substrates for the coupling reactions than less hindered amines (entries **14**,[12] **15**, **17**, Table 3). Traces of cycloheptatrienimine by-products in these reaction mixtures suggested that the amines, being relatively more nucleophilic than the alcohols, competed with the carboxylate anions to react with tropylium chloride (**1**), leading to unwanted consumption of the reagents. Bulkier amines are less nucleophilic, hence less likely to proceed through this side-reaction.

Conclusions

In summary, we have developed a new coupling reagent system based on a very simple chlorinated hydrocarbon compound, namely 1,1-dichlorocycloheptatriene. Due to its unique property to equilibrate between its cycloheptratriene neutral form and the aromatic tropylium ion form, this reagent can provide the driving force for the esterification and amidation reactions of carboxylic acids. Using this newly developed reagent, several series of esters, lactones, amides and peptides have been produced in good to excellent yields under mild reaction conditions. This work has expanded the scope of aromatic cation mediated chemistry and offers a new alternative method for carboxylic acid coupling reaction. The application of this new method in combination with racemization suppressants such as HOBt to bioactive macropeptide and polypeptide coupling reactions is currently underway in our group and will be reported shortly.

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Notes and references

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† Electronic Supplementary Information (ESI) available: [Experimental procedures and characterization data]. See DOI: 10.1039/c000000x/

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