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Green Esterification of Carboxylic Acids Promoted by *tert*-Butyl Nitrite

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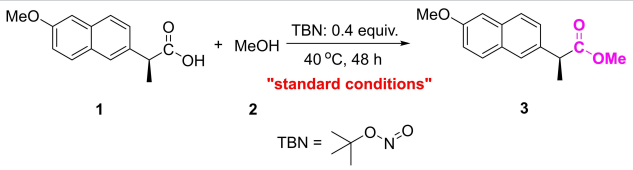
In this work, the green esterification of carboxylic acids promoted by *tert*-butyl nitrite has been well developed. This transformation is compatible with a broad range of substrates and exhibits excellent functional group tolerance. Various drugs and substituted amino acids are applicable to this reaction under near neutral conditions, with good to excellent yields.

Esters are ubiquitous structural motifs in pharmaceuticals, agrochemicals, polymers, functional organic materials, natural products and solvents, and also serve as important building blocks for synthetic chemistry.[1] Consequently, extensive efforts have been made to identify highly efficient esterification methods, and numerous approaches have been developed to accomplish this transformation.[2,3] Among these methods, the Brønsted[4] or Lewis acid[5]-catalysed condensations of carboxylic acids and alcohols with the release of water remain the most popular. However, these techniques are of limited use in complex synthetic procedures because they do not allow the transformation of substrates with certain more reactive functional groups. Other possible reagents for esterification reactions include PPh_3-based catalysts,[6] solid-supported catalysts,[7] ionic liquids[8] and zeolites.[9]

As noted, many drugs and biologically active molecules contain ester moieties.[10] Consequently, carboxylic acids represent important starting materials for the synthesis of pharmaceuticals and agrochemicals. The most fruitful basis for the discovery of a new drug is to start with an old drug.[11] In fact, it is evident that the late-stage modification of drugs and bioactive molecules by esterification can provide a reliable and facile path to the discovery of new drugs. Although numerous esterification techniques exist, these approaches are not generally applicable to the late-stage esterification of complex bioactive compounds, which often carry multiple functional groups that can undergo undesired side reactions. Current esterification methods also usually require acidic or otherwise harsh conditions and exhibit low efficiency or selectivity in such cases.

Table 1. Optimization of reaction condition for **3**.[a]



Entry	Variation from the "standard conditions"	Yield [%][b]
1	none	95
2	0.05 mmol TBN was used	75
3	0.10 mmol TBN was used	83
4	0.15 mmol TBN was used	93
5	Add 0.5 mmol H_2O	91
6	Add 1 mmol H_2O	87
7	Add 50 mg $MgSO_4$	trace
8	Add 50 mg 4A MS	trace
9	Add 0.5 mmol Na_2CO_3	Not Detected
10	Add 0.5 mmol Et_3N	Not Detected
11	Add 0.5 mmol 2,6-di-tert-butylpyridine	Not Detected
12	25 °C instead of 40 °C	63
13	no TBN	Not Detected

[a] All data represent the average of two experiments. [b] Isolated yield.

The reagent *tert*-butyl nitrite (TBN) is a versatile synthetic intermediate in organic chemistry and has attracted a great deal of attention from the synthetic community in recent years.[12,13] TBN is inexpensive and commercially available, and is also easy to handle. Moreover, it typically provides the environmentally-friendly compound *tert*-butanol (*t*BuOH) as the sole by-product. This multi-task reagent can also trigger a variety of important transformations, such as nitrosation, nitration, oximation, oxidation and the construction of *N*-containing heterocycles. Because TBN generates nitrous acid in the presence of water,[13p–r,x–z] we anticipated that it might act as a Brønsted acid-type catalyst to promote the esterification reactions of carboxylic acids and alcohols. In sharp contrast to the traditional catalyst sulfuric acid, nitrous acid is readily decomposed so that the reaction system remains close to neutral. As a result, various functional groups are less likely to undergo side reactions during the esterification of complex molecules.

Naproxen,[14] a very common medication, was selected as the model substrate to test our hypothesis. We started our investigation by assessing the reaction of naproxen (**1**) and methanol (MeOH) in the presence of TBN as a catalyst (Table 1). After heating at 40 °C for 48 h, the desired product (**3**) was obtained in an acceptable 75% yield (entry 1). Increasing the amount of catalyst was found to increase the yield significantly (entries 2 and 3). These trials indicated that 40 mol% TBN in

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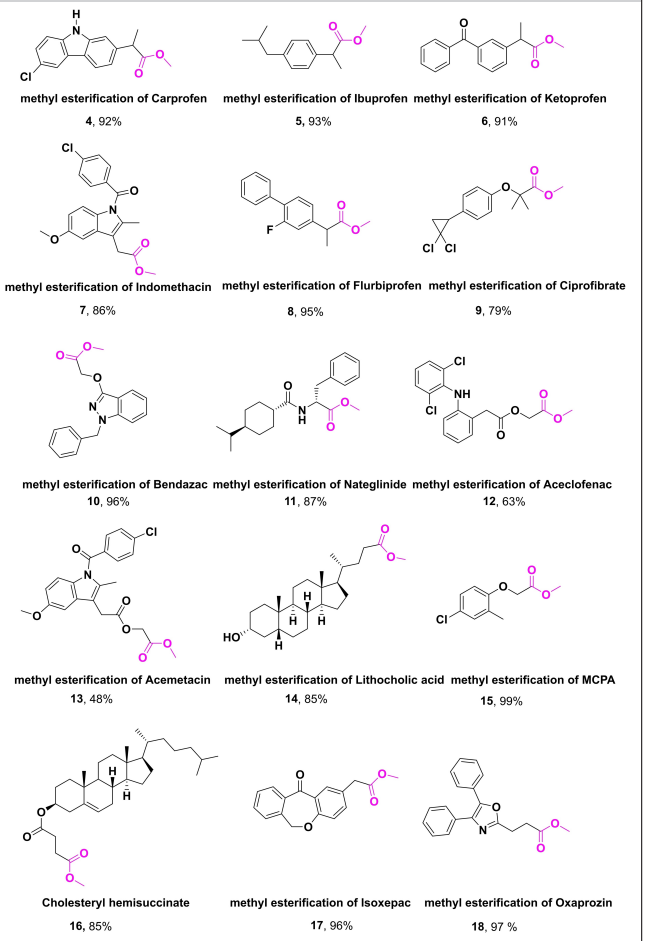
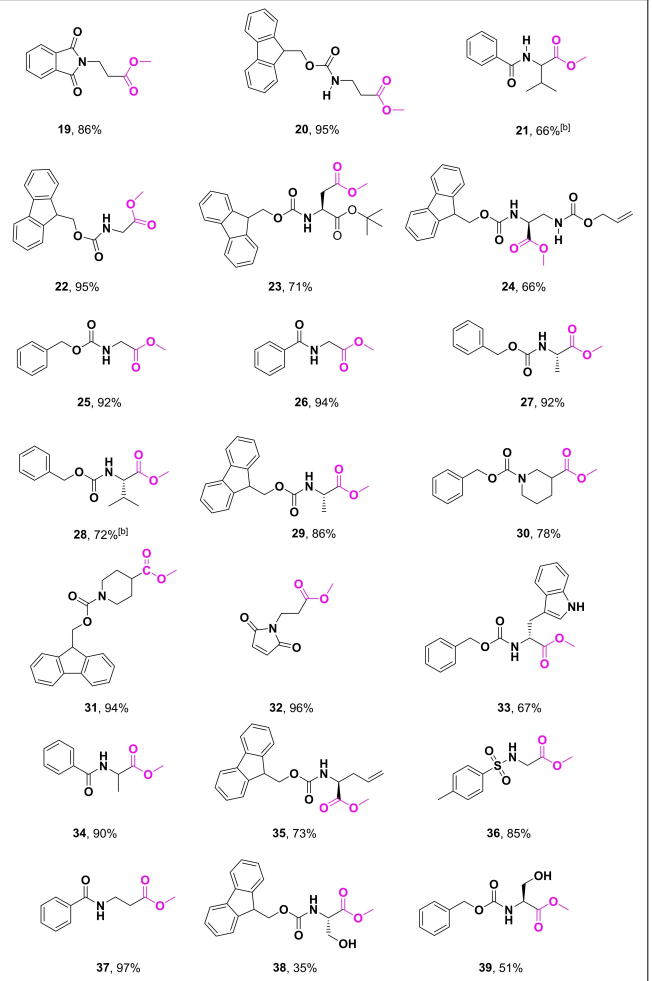
Table 2. The direct methyl esterification of approved drugs and biologically active compounds.[a]



[a] Reaction conditions: carboxylic acid (0.5 mmol), MeOH (2.0 mL), TBN (0.2 mmol), at 40 °C under air atmosphere for 48 h.

Table 3. The direct methyl esterification of amino acids.[a]



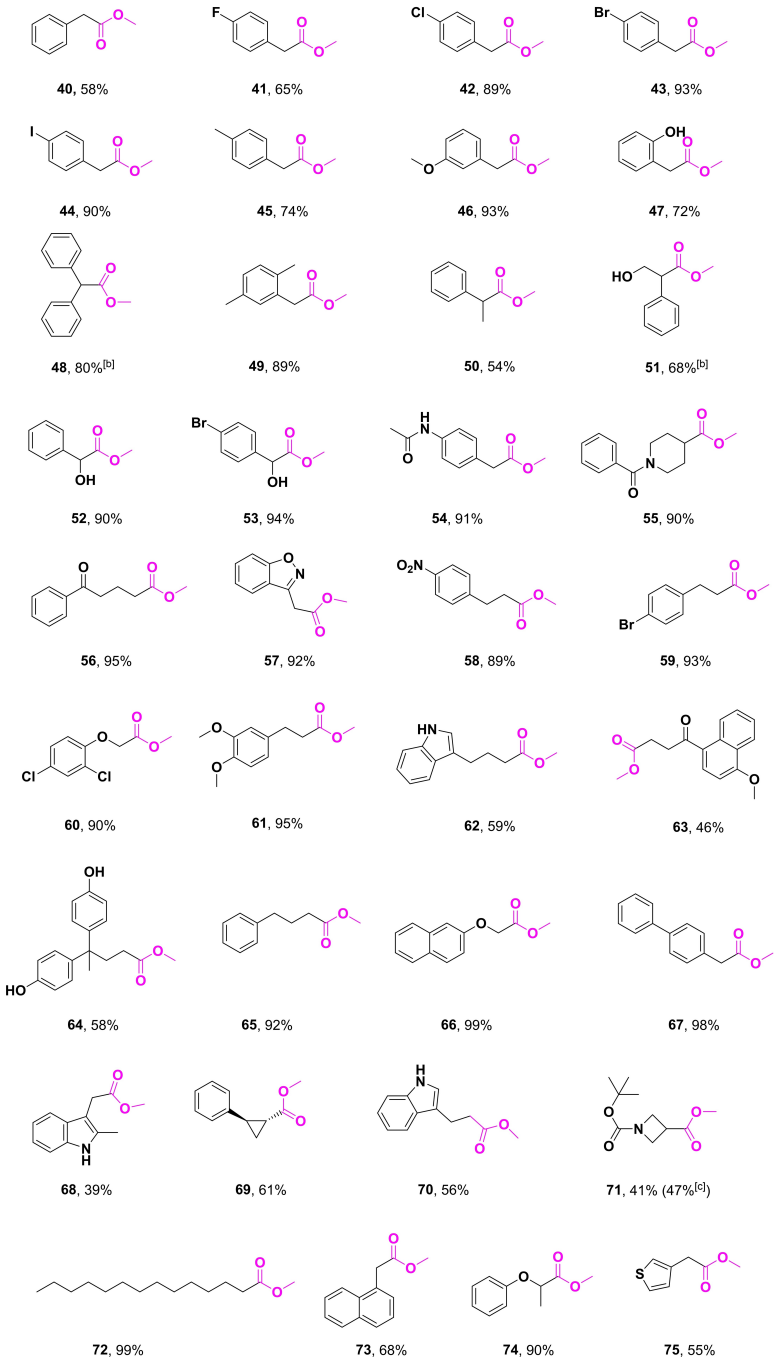
[a] Reaction conditions: carboxylic acid (0.5 mmol), MeOH (2.0 mL), TBN (0.2 mmol), at 40 °C under air atmosphere for 48 h. [b] at 60 °C.

MeOH at 40 °C furnished an excellent yield (95%) of the esterification product (Table 1, entry 4). This reaction was also insensitive to moisture and could be carried out under ambient air. It should be noted that the addition of water only minimally affected the efficiency of the reaction (entries 5 and 6). In sharp contrast, the addition of various dehydrating agents, such as magnesium sulfate and molecular sieves, terminated the reaction (entries 7 and 8), indicating that water was essential to the *in situ* generation of nitrous acid. As anticipated, the addition of inorganic or organic bases also inhibited the formation of ester **3** (entries 9 and 10). The bulky base 2,6-di-*tert*-butylpyridine also inhibited the formation of ester **3** (entries 11). Additionally, **3** could be obtained in moderate yield when performing the reaction at room temperature (entry 12) but no product was obtained in the absence of TBN (entry 13). In addition, no obvious racemization was observed during this green esterification procedure (For details, see Scheme S1 in supporting information).

With the optimised conditions in hand, we next investigated the late-stage methyl esterification of a variety of approved drugs and biologically active compounds (Table 2). These trials confirmed that a wide range of highly functionalised esters (**4**–**18**) could be constructed in 48%–99% yields. Carprofen (**4**), nateglinide (**11**) and aceclofenac (**12**), all bearing a N–H group, underwent methyl esterification in high yields with high selectivity. Using lithocholic acid as the substrate afforded the ester **14** in 85% yield, indicating a tolerance for hydroxyl groups. Indole derivatives [indomethacin (**7**) and acemetacin (**13**)] also gave the corresponding esters in satisfactory yields. Ibuprofen, ketoprofen and flurbiprofen were all found to be suitable substrates for this esterification reaction (giving products **5**, **6** and **8**). Bendazac and oxaprozin, which incorporate nitrogen-containing heterocyclic moieties, also underwent esterification with excellent yields (products **10** and **18**). A carboxylic acid derived from cholesterol (product **16**) reacted with similar success. Furthermore, the esters **9**, **15** and **17** could be obtained in high yields from the corresponding biologically active carboxylic acids.

Amino acid esters are prevalent in synthetic chemistry, medicinal chemistry and chemical biology.[15] For these reasons, the development of methods for their synthesis has received

Table 4. The direct methyl esterification of carboxylic acids.[a]

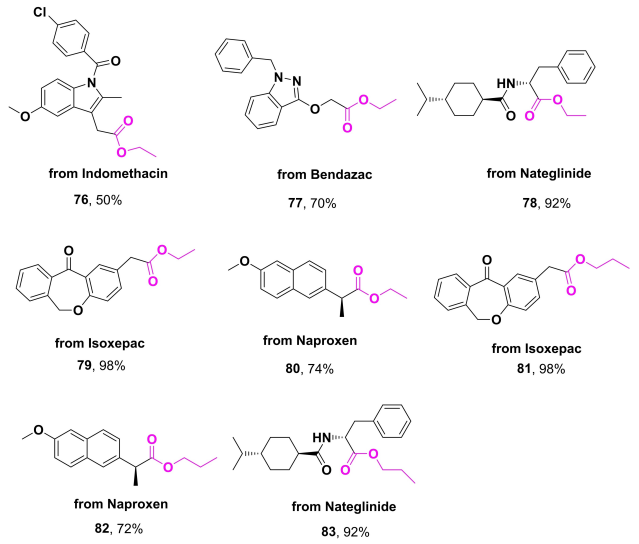


[a] Reaction conditions: carboxylic acid (0.5 mmol), MeOH (2.0 mL), TBN (0.2 mmol), at 40 °C under air atmosphere for 48 h. [b] at 60 °C. [c] 47% starting material was recovered.

much attention.[16] Although there has been important progress, the requirement to use hazardous reagents and harsh conditions as well as narrow substrates scopes remain challenging. Inspired by the above TBN-catalysed esterification reactions, we examined the application of this method to the esterification of amino acids, with the results presented in Table 3. This transformation was determined to be compatible with a diverse range of amino acids, including glycine, valine, alanine, tryptophan, serine and aspartic acid. Both Fmoc- and Cbz-protected amino acids furnished the desired products in high to excellent yields. Phthalimido (product **19**), benzamide (products **21** and **26**), maleimide (product **32**) and sulfonamide compounds (product **36**) also underwent esterification.

It should be noted that this methodology is not only suitable for the late esterification of complex molecules, but is also applicable to small molecules (Table 4). Various substituted

Table 5. The late-stage esterification with other alcohols.[a]

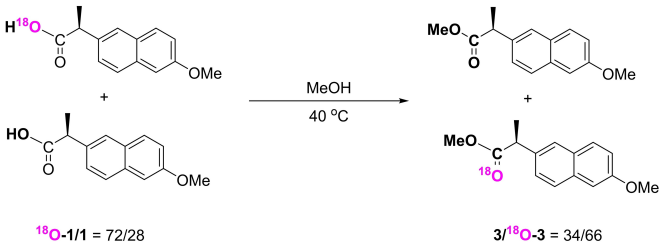


[a] Reaction conditions: carboxylic acid (0.5 mmol), alcohol (2.0 mL), TBN (0.5 mmol), at 80 °C under air atmosphere for 48 h.

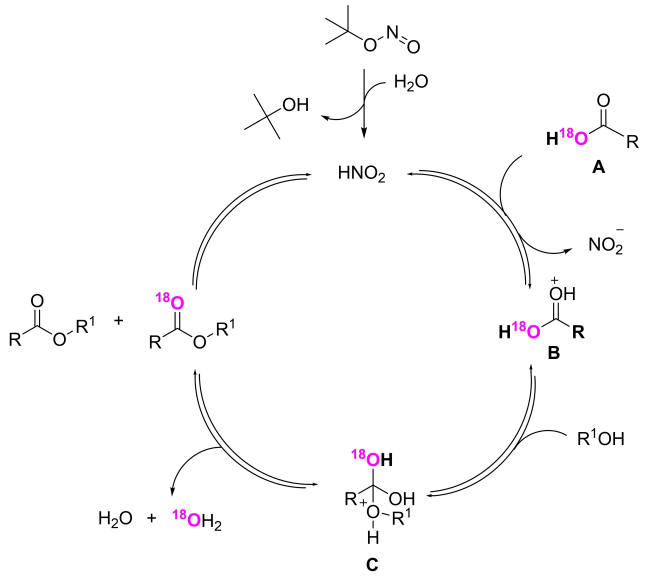
phenylacetic acids were found to generate the desired products in high yields. Heterocycles such as indoles (**62**, **68** and **70**), azetidine (**71**), piperidine (**55**), 1,2-benzoisoxazole (**57**) and thiophene (**75**) underwent smooth esterification with high selectivities and efficiencies. Mandelic acid was also employed and the desired product **52** was obtained with good selectivity in high yield. Diphenolic acid, which contains a reactive phenol moiety, produced the desired ester **64** in good yield. Carboxylic acids bearing halogens (**41**–**44**, **59**, **60**) and free hydroxyl (**47**, **51**–**53**, **64**), amide (**54**, **55**), ether (**60**, **61**, **63**, **66**, **74**), ketone (**56**, **63**), nitro (**58**), *N*-Boc (**71**) and cyclopropyl groups (**69**) were all found to be suitable substrates.

We subsequently examined the esterification of various approved drug molecules and biologically active compounds with other alcohols. As shown in Table 5, both ethanol and propanol could be used as reaction partners under modified conditions, delivering the corresponding esters in good to excellent yields. Unfortunately, secondary alcohols, tertiary alcohols and phenols are not suitable substrates for this transformation.

An isotope labelling experiment was carried out to elucidate the mechanism of the present TBN system. As shown in Scheme 1, both **3** and ^{18}O-**3** were obtained when ^{18}O-labelled naproxen was used as the substrate (For details, see Scheme S2 in supporting information), supporting evidence for the *in situ* generation of nitrous acid in this transformation. On the basis of the above experimental observations (Scheme 1 and entries 5–11 in Table 1) as well as previous reports, a plausible reaction mechanism was devised, as shown in Scheme 2. Initially, the hydrolysis of TBN results in the *in situ* generation of nitrous acid[13p–r,x–z] which is captured by carboxylic acid **A** to form intermediate **B**. Subsequent nucleophilic attack by the alcohol on **B** delivers the intermediate **C**. Finally, the decomposition of **C** leads to the desired ester with high selectivity.



Scheme 1. Isotope labelling experiment.



Scheme 2. The proposed mechanism.

In summary, a method for the green esterification of drugs, amino acids and complex natural products was developed. This technique is characterised by near neutral conditions and high functional group tolerance. Mechanistic studies confirmed the in situ generation of nitrous acid as the actual catalyst in this system.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: Carboxylic acids · Esterification · Green chemistry · *tert*-Butyl nitrite

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