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Facile and efficient addition of terminal alkynes to benzotriazole esters: synthesis of D-*erythro*-sphingosine using ynones as the key intermediate

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ABSTRACT

From the perspective of synthesis, ynones are compounds of considerable interest because of their occurrence in a wide variety of biologically active molecules and as key synthetic intermediates. In this context, a facile and highly efficient synthesis of ynones was developed based on the high reactivity of benzotriazole esters formed in situ. Lithium acetylides can alkylate various carboxylic acids in yields ranging from 60% to 92%. To determine whether our methodology is useful for synthesising complex and biologically relevant molecules, we synthesise D-*erythro*-sphingosine in four steps and with 33% overall yield from L-serine.

The synthesis of α,β-acetylenic carbonyl compounds, or ynones, has attracted considerable interest because they appear as key intermediates during the synthesis of natural compounds.[1] The attractive utility of ynones has led many organic chemists to focus on developing methods for their synthesis; the goals of exploring new synthetic strategies include the following: (a) palladium-catalysed coupling reactions between acyl chlorides and terminal alkynes,[2] (b) the acylation of alkynyl organometallic reagents based on silver,[3] copper,[4] zinc,[5] indium,[6] silicon,[7] aluminium[8] and tin[9] using acyl chlorides, (c) the palladium-catalysed reaction between acyl chlorides and lithium alkynyltriisopropoxyborates[10] and (d) the addition of alkynyllithium reagent tomorpholine[11] and Weinreb amides.[12]

Despite having made considerable progress, the synthesis of ynones in high yield with good functional group tolerance remains a notable challenge. An alternative approach involves transforming the carboxylic acid into a stable, yet highly reactive, intermediate that can be formed under mild reaction conditions. Consequently, we thought to use 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (EDC) and 1-hydroxybenzotriazole (HOBT), which is a classic coupling system in peptide chemistry,[13] to furnish the benzotriazole esters **I** and **II** (Equation in Table 1) as an attractive alternative to acyl chlorides during the synthesis of ynones. Carbodiimides dehydrate the carboxylic acid, facilitating the nucleophilic addition of an alkoxy group and generating the corresponding ester[14] or lactone.[15] HOBT circumvents problematic side reactions, such as *N*-acylurea formation or racemisation, during peptide bond formation. Numerous HOBT derivatives[16] have been synthesised for use in either solution or solid phase. However, in every case, species **I** and **II** were proposed as reaction intermediates (Equation in Table 1).[17] In our hands, benzotriazole esters **I** and **II** have become important intermediates during the synthesis of macrolactones,[18] *ter*-butyl esters[19] and alcohols from carboxylic acids.[20] Therefore, in this study, we report a facile and highly efficient synthesis of ynones based on the highly reactive benzotriazole esters **I** and **II** formed in situ at room temperature. Lithium acetylides can alkylate various carboxylic acids in yields ranging from 40% to 92%. Finally, we used the reaction as a key step during the total synthesis of D-*erythro*-sphingosine.

The formation of benzotriazol esters **I** and **II** is a rapid process that may occur at room temperature in different solvents, such as $CHCl_3$, CH_2Cl_2 or THF, without the need for rigorously dry conditions. Therefore, we initially studied the formation of benzotriazole esters of phenyl acetic acid **1a** using an EDC/HOBT system in CH_2Cl_2. Once those benzotriazole esters are formed, as established by thin layer chromatography (TLC), the solvent is eliminated; to remove the residual water, the intermediates can be co-distilled

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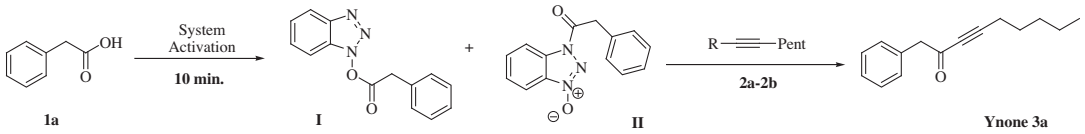
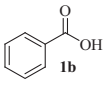
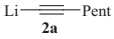
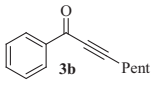
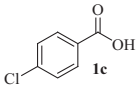
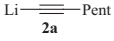
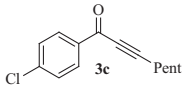
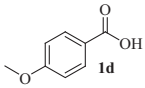
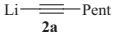
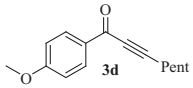
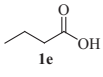
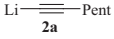
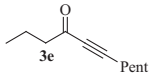
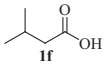
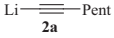
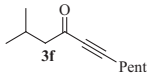
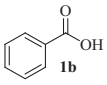
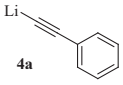
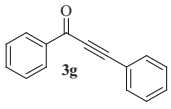
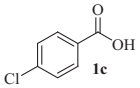
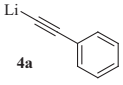
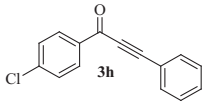
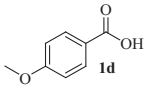
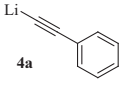
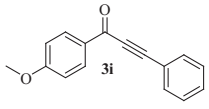
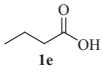
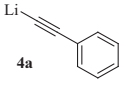
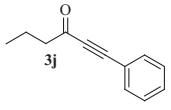
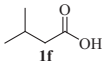
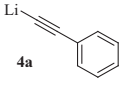
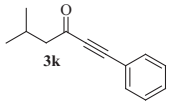
Table 1
Optimisation of reaction conditions for the synthesis of ynone **3a**



Entry	R	Activation system	Reaction conditions	Yield[c] %
1	**2a** Li[a]	EDC/HOBT[b]	THF, −70 °C, 15 min. and then rt 15 min.	92
2	**2b** H	EDC/HOBT[b]	P_2-Et, THF, −70 °C 15 min. and then rt 15 min.	–
3	**2b** H	EDC/HOBT[b]	P_2-Et, THF, rt 18 h.	–
4	**2b** H	EDC/HOBT[b]	Hydrotalcite, THF, reflux, 18 h.	–
5	**2b** H	EDC/HOBT[b]	$[PdCl_2(PPh_3)_2]$, CuI, TEA, THF or 1,4-dioxane, rt to reflux, 1 h to 18 h.	–

[a] Reagents and conditions to prepare lithium acetylides: alkyne (3 mmol), *n*-BuLi (3.1 mmol), THF, −70 °C, 15 min.
[b] Reagents and conditions: Carboxylic acid (1 mmol), EDC (1.1 mmol), HOBT (1.1 mmol), CH_2Cl_2, rt, 10 min. The organic layer was concentrated in vacuo and subsequently co-distilled with dry toluene.
[c] Yield of isolated product after chromatographic purification.

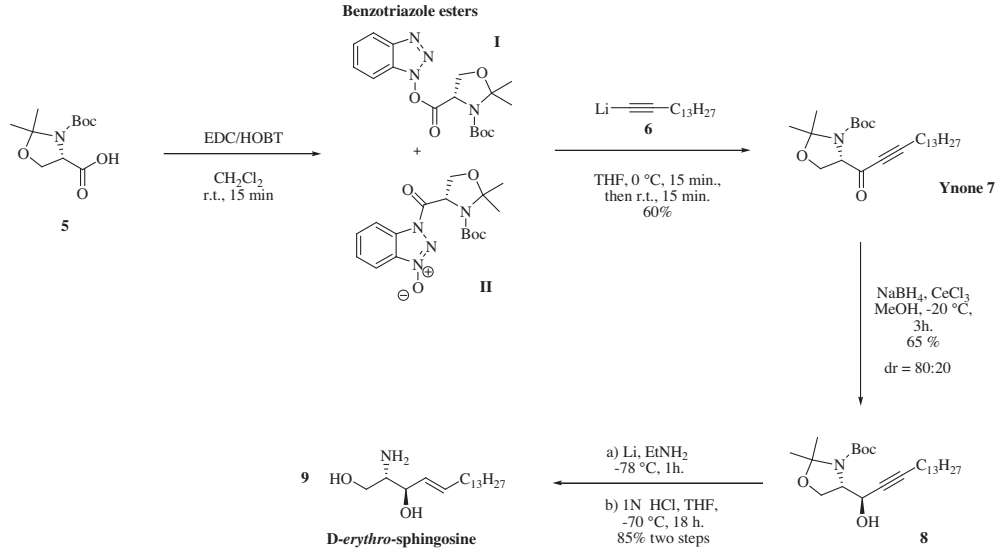
Table 2
The reaction scope for the synthesis of ynones from benzotriazole esters and lithium acetylides

Entry	Carboxylic acids	Terminal Alkynes	Ynone	Yield[a] %
1				75
2				60
3				70
4				60
5				65
6				78
7				75
8				77
9				65
10				68

[a] Yield of isolated product after chromatographic purification.

with toluene or dried under vacuum.[21] Subsequently, lithium pentylacetylide **2a** was added in THF, furnishing the desired ynone **3a** in 92% yield (Table 1, entries 1 and 2). [22] Unfortunately, attempts to generate the acetylide using other bases, such as hydrotalcite or phosphazene bases (EtP_2), do not generate **3a** (Table 1, entries 2–4). Similarly, when the reaction was carried out under Sonogashira conditions (Pd^0/Cu^I),[2] ynone **3a** was not observed, even after long reaction times; in this case a complex reaction mixture was obtained (Table 1, entry 5).

With the optimised conditions in hand, the scope of these reactions was investigated using different carboxylic acids. Aromatic and aliphatic carboxylic acids smoothly underwent transformation



Scheme 1. Synthesis of D-*erythro*-sphingosine.

to generate the desired products (**3b**–**3k**), in moderate to excellent yields (60–78%, Table 2). Moreover, the reactions worked well with aromatic carboxylic acids (**1b**–**1d**) to give ynones **3b**–**3d** and **3g**–**3i** (Table 2, entries 1–3 and 6–8). Aliphatic carboxylic acids (**1e** and **1f**) were also compatible, furnishing moderate yields (Table 2, entries 4,5,9,10). Notably, the activation time varied between the aromatic and aliphatic carboxylic acids. The latter required short activation times (10–30 min), while aromatic carboxylic acids needed one hour or more. However, the activation reaction may be easily monitored by TLC to ensure the activation is complete.

Finally, to determine whether our methodology is useful for the synthesis of complex and biologically relevant molecules, we examined its applicability during the synthesis of D-*erythro*-sphingosine **9** from acid L-serine derived **5** (Scheme 1).

Sphingolipids were named by Johann Ludwig Wilhelm Thudichum[23] in 1884 after the Greek Sphinx due to their enigmatic function, emerging in recent decades as a family of key signalling molecules, including sphingosine **9**.[24] Sphingolipids, together with glycerophospholipids and cholesterol, are essential building blocks that play essential roles as structural cell membrane components and participate in higher order physiological processes, including inflammation and vasculogenesis.[25] Recent studies implicate sphingolipids in numerous common human diseases, including microbial infections, diabetes, various cancers, Alzheimer's disease, and many others.[26] The basic sphingolipid structure consists of a sphingosine linked to a fatty acid through an amide bond with the 2-amino group and a polar head group at C-1 through an ester bond. There are four sphingosine stereoisomers with a wide range of biological activities.[27] The D-*erythro* isomer is the most common metabolite and has been meticulously studied. Because sphingosine and its derivatives are available in limited amounts from natural sources, there is a continuing interest in developing efficient methods for their synthesis. Numerous methods for synthesising sphingosine are reported in the literature,[27] and they can be classified into four categories: (i) those using carbohydrates as the source of chirality, (ii) those that use the Sharpless asymmetric epoxidation to generate the asymmetric centres, (iii) those using an aldol reaction with a chiral auxiliary, and (iv) those using serine as the source of chirality. However, most methods require multistep reactions and result in low total yields. Consequently, our choice of starting material was dictated by the type of reaction necessary for developing a cost-effective and efficient synthesis. Therefore, the synthesis began with the addition of lithium acetylide **6** to benzotriazole esters **I** and **II**, generating ynone **7** in 60% yield. Subsequently, the ketone was reduced with $NaBH_4$ (65% yield), while Benkeser's reduction conditions were used to reduce the alkyne and eliminate the protective groups (85% yield, two steps) to obtain D-*erythro*-sphingosine **9** (Scheme 1). The total synthesis from acid L-serine-derived **5** was performed with 33% overall yield in only four steps: (i) ynone preparation, (ii) carbonyl reduction, (iii) alkyne reduction and (iv) deprotection. Synthetic D-*erythro*-sphingosine **9** exhibited a 72–74 °C melting point (lit.[28] mp 72–75 °C), $[\alpha]_D = -1.6$ (*c* 0.9 in $CHCl_3$) (lit.[28] $[\alpha]_D = -1.6$) (*c*1 in $CHCl_3$)), and the 300 MHz ^1H and 75 MHz ^{13}C NMR spectroscopic data matched those reported for the synthetic product.[28]

In summary, we developed new protocol to synthesise ynones in yields ranging from 60% to 92% from benzotriazol esters and lithium acetylides. This approach facilitated efficient synthesis of D-*erythro*-sphingosine in four steps from L-serine with a 33% overall yield. We believe that our protocol demonstrates an attractive use of benzotriazole esters as acyl synthons, transcending their simple use as peptide-coupling intermediates

Acknowledgment

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Supplementary data

Supplementary data associated with this article can be found, in the online version, athttp://dx.doi.org/10.1016/j.tetlet.2013.10.082.

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21. *General procedure for the preparation of benzotriazole esters:* A solution of carboxylic acid (1 mmol), EDC (1.1 mmol) and HOBT (1.1 mmol) in CH_2Cl_2 (20 mL) was stirred at room temperature until the starting material disappeared. The reaction was monitored by TLC. The solvent was eliminated under reduced pressure, and the residue was co-distilled three times with dry toluene to obtain benzotriazole esters **I** and **II**. These compounds were dissolved in anhydrous THF (5 mL) and stored under argon before the next reaction. Completely anhydrous conditions were crucial for attaining good yields.
22. *General procedure for the synthesis of ynones:* To a flame-dried, single-necked 50 mL round-bottomed flask equipped with a magnetic stir bar was added a solution of acetylene (3 mmol) in anhydrous THF (10 mL). The solution was cooled to −78 °C before *n*-BuLi (3.1 mmol) was added via syringe through the septum. The reaction was stirred for 15 min at −78 °C. Subsequently, a solution of the benzotriazole esters (1 mmol) in anhydrous THF was added slowly through the septum using a syringe. The mixture was stirred for 15 min at −78 °C. The cooling bath was removed and the reaction solution was allowed to warm to room temperature before being quenched with saturated aqueous ammonium chloride solution. The aqueous layer was separated and extracted with ethyl acetate (3 × 15 mL). The combined organic layers were washed successively with 10% citric acid solution (2 × 20 mL), 10% $NaHCO_3$ solution (2 × 20 mL), 10% K_2CO_3 solution (2 × 20 mL) and brine (3 × 20 mL), dried over magnesium sulfate, filtered and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography on silica gel using Hexane-EtOAc.
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