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Practical synthesis of a functionalized 1-oxo-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid

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ABSTRACT

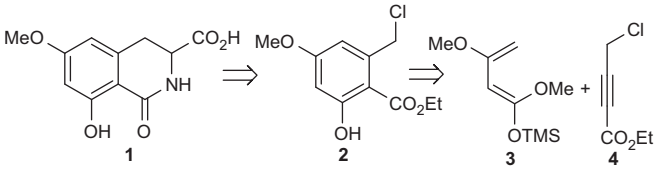
The synthesis of a functionalized 1-oxo-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid has been performed in 10 steps from the readily available dimedone. Only three purifications by flash chromatography are required through the whole sequence. The key step is the reaction between a dimedone derivative and a chlorotetrolic ester, that gives a tetrasubstituted benzene ring (through a Diels–Alder/retro- Diels–Alder process) bearing the substituents in the suitable positions for further functionalization.

The 1-oxo-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid structure, such as **1**, is related to inhibitors of WNV protease[1] and to molecules having selective central nervous system (CNS) action.[2] Additionally, 1-oxo-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acids can also be used in the synthesis of 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acids,[3] which are constrained analogues of phenylalanine with several pharmacologically relevant properties.[4] As part of our ongoing research program directed toward the synthesis of biologically active molecules,[5] 1-oxo-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid **1** was designed as an important target.

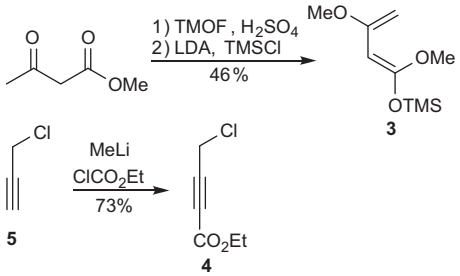
Our initial strategy to obtain the required functionalized 1-oxo-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid **1** was based on the manipulation of the tetrasubstituted benzene **2**, which could be obtained by a Diels–Alder reaction of Brassard's diene (**3**)[6] and chlorotetrolic ester (**4**) followed by aromatization (Scheme 1).

The chlorotetrolic ester **4** was prepared from propargyl chloride (**5**)[7] and the Brassard's diene (**3**) was obtained from methyl acetoacetate (Scheme 2).[8]

The cycloaddition of Brassard's diene (**3**) and **4** was investigated under several conditions, including the presence of Lewis acids, such as $ZnCl_2$ and $AlCl_3$. Table 1 summarizes the most important reactions. The best result was the isolation of **2** and **6**, in 25% and 20% yields, respectively, when the two components were heated to 80 °C without solvent (entry 3). Increasing the temperature, decomposition was observed (entry 4), whereas no reaction was observed at lower temperature (entries 1 and 2).



Scheme 1. Initial retrosynthesis for **1**.



Scheme 2. Preparation of Brassard's diene **3** and chloro-tetrolic ester **4**.

Considering the results using the Brassard's diene, we tuned our attention to the use of the more reactive diene **8**, whose fixed *s-cis* configuration could favor the Diels–Alder cycloaddition. The diene **8** was obtained from dimedone (**7**) by two different ways. The synthesis of **8** is feasible in one step from **7**. However, 2.2 equiv of TMSOTf should be used and the purification of crude **8** by distillation

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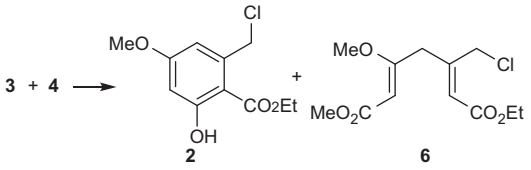
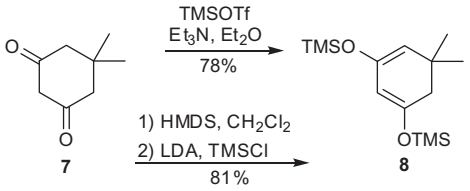
Table 1
Reaction of Brassard's diene (**3**) with **4**



Entry	Conditions	Product (isolated yield)
1	Neat, rt	No reaction
2	Neat, 50 °C	No reaction
3	Neat, 80 °C, 45 h	**2** (25%), **6** (20%)
4	Neat, 100 °C, 45 h	Decomposition
5	THF or toluene, 80 °C	No reaction
6	Neat, $ZnCl_2$ or $AlCl_3$ (10 mol %), rt	No reaction
7	Neat, 1 equiv $AlCl_3$, rt	Decomposition
8	Toluene or benzene, 0.5 equiv $AlCl_3$, 80 °C	**2** (13%)
9	Toluene, 1 equiv $AlCl_3$, 80 °C	**2** (15%)

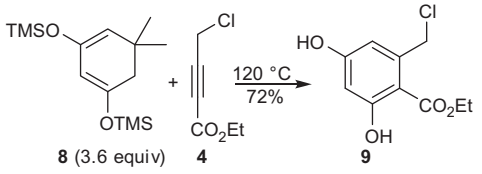


Scheme 3. Preparation of Diene **8**.

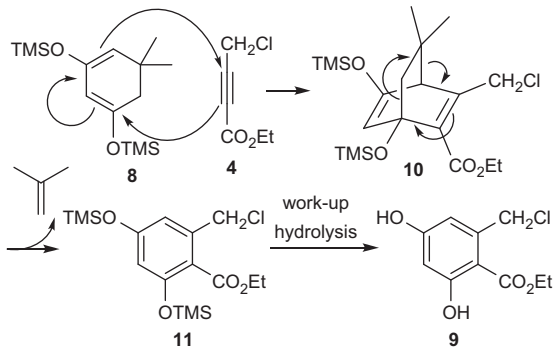
is mandatory to remove the excess of TMSOTf. To avoid these drawbacks, the two-step preparation was chosen for large scale reactions because the crude product was obtained pure enough to be used in the next step without any purification (Scheme 3).[9]

The reaction between the diene **8** and the alkyne **4** gave the desired aromatic compound **9** in 72% yield. Decreasing the excess of **8** to 2 equiv, compound **9** was obtained in 26% yield (Scheme 4).

The substituted benzene **9** is formed through a sequence of reactions.[10] First, a Diels–Alder reaction produces the bicyclic compound **10**, that undergoes a retro- Diels–Alder reaction furnishing isobutylene and **11**. After hydrolysis of the TMS groups during work-up, **9** is isolated (Scheme 5).

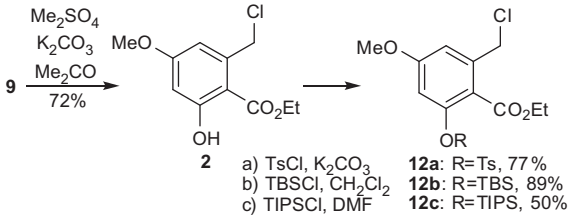


Scheme 4. Synthesis of **9** through Diels–Alder/retro-Diels–Alder.



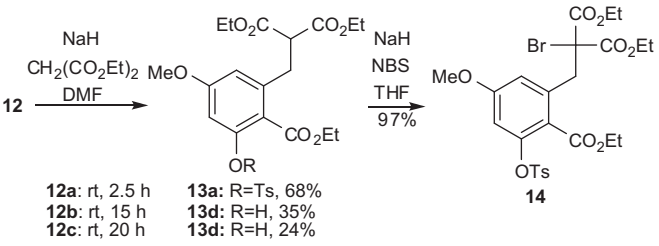
Scheme 5. Mechanism for the Formation of **9** through Diels–Alder/retro-Diels–Alder.

The two phenolic groups of **9** can be chemically distinguished because the phenol *ortho* to the ester is involved in an intramolecular hydrogen bonding, resulting in a higher pK_a value.[11] Thus, the next step was the selective methylation of the more acidic phenol group using dimethylsulfate, yielding **2**, after recrystallization. The remaining phenol group was then tosylated using TsCl, affording **12a**. The protection of the phenol **2** was also performed with TBS and TIPS, leading to **12b/c**, respectively (Scheme 6).



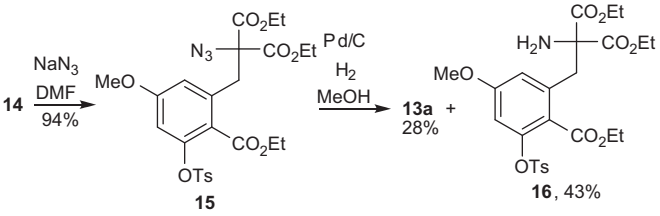
Scheme 6. Manipulating the two phenolic groups of **9**.

The alkyl chain was introduced via the substitution of the chlorine of **12a** by the anion of diethyl malonate, forming the triester **13a**, in 68% yield. When this transformation was performed with **12b,c**, the unprotected coupling product **13d** was obtained in only 35% and 24% yields, respectively. Using NaH as a base to remove the α-carbonyl hydrogen of the malonate moiety of **13a**, and NBS as a bromine source, compound **14** was prepared in 97% yield (Scheme 7).

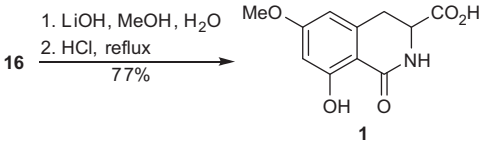


Scheme 7. Synthesis of the bromo ester **14**.

The azide **15** was formed after nucleophilic substitution of the bromine of **14** by an azide, using NaN_3 in DMF. Reduction of the



Scheme 8. Synthesis of **16**: introducing the nitrogen atom.



Scheme 9. Final step toward the target acid **1**.

azide group of **15** using 10% wt Pd/C in MeOH, under 2 atm of H_2 produced the amine **16** in 43%, together with **13a**, in 28% yield, which is formed from a hydrogenolysis (Scheme 8). The triester **13a** was recycled in the synthetic route. Using $Pd/CaCO_3$ as catalyst, only hydrogenolysis was observed.

When **16** was subjected to a basic hydrolysis using LiOH followed by a reflux in diluted acid to promote decarboxylation, the tetrahydroisoquinoline **1** was produced in 77% yield (Scheme 9).

In conclusion, a new and practical route to obtain a functionalized 1-oxo-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid was developed from the readily available dimedone. The synthesis is ten step long and only three purifications by flash chromatography are required through the whole sequence (see Supplementary data for details). The key step is the reaction between the dimedone derivative **8** and the chlorotetrolic ester **4**, that gives a tetrasubstituted benzene through a Diels–Alder /retro- Diels–Alder process. The sequence can be easily adapted to the synthesis of other 1-oxo-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acids.

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Supplementary data

Supplementary data (spectroscopic data and detailed experimental procedures) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.05.060.

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