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Synthesis of pyridazines functionalized with amino acid side chains

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Abstract

A simple route for the preparation of 3,4,6-substituted pyridazines is described by using Tebbe olefination of esters then Diels–Alder reaction of the resulting enol ethers with tetrazine.

Keywords: Pyridazine; Tetrazine; Tebbe reagent; Inverse electron demand Diels–Alder reaction

The pyridazine ring is often encountered as a structural component of compounds possessing biological activity: analgesic,[1] antibacterial,[2] antiinflammatory,[3] antihypertensive[4] or antihistaminic[5] activities have all been reported. This heterocycle is also useful for the preparation of other heterocycles,[6] π-conjugated organic materials with desirable electronic properties[7] and self-assembled supramolecular architectures.[8] These pharmacological and technological properties of pyridazines encourage the development of methods for their synthesis and functionalization.[9] The inverse electron demand Diels–Alder reaction (IEDDAR) between 1,2,4,5-tetrazine diester **1** (Fig. 1) and electron-rich dienophiles has proven to be an effective synthetic route toward substituted pyridazines,[10] and we apply it here.

In connection with our studies on the synthesis of heterocyclic α-helix mimetics,[11] the preparation of 3,4,6-trisubstituted pyridazine **2a**, bearing an indole side chain was required (Fig. 1). This structure is inspired by Hamilton's terephthalamide scaffold **3** known to disrupt protein–protein interactions[12] when $R_{1–3}$ are typically side chains of hydrophobic amino acids. The pyridazine scaffold offers remote hydrophilic sites, regioselective functionalization[11]

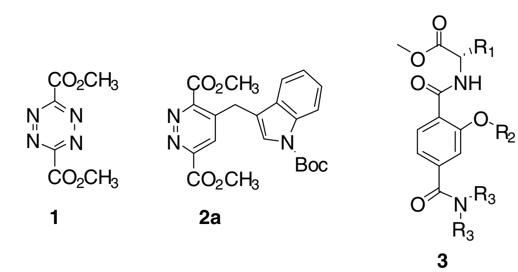

Fig. 1. Structures of tetrazine **1**, pyridazine **2a** and Hamilton's terephthalamide scaffold **3**.

and a variety of amino acid side chains for small library synthesis.

As a first approach to compound **2a**, the diester **1**[13] was reacted with the commercially available 2-methoxy-3,4-dihydro-2*H*-pyrane to give pyridazine **4** in good yield. Subsequent treatment under standard Fischer indole synthesis[14] conditions led predominantly to the decomposition of the starting material and the formation of the desired compound **5** in a disappointing 13% yield[11c] (Scheme 1).

A shorter, higher yielding route was found in the IEDDAR employing a dienophile with the indole ring already present in its structure. Different electron-rich dienophiles such as enamines,[15] ketene acetals,[16] or enol ethers[17,18] have been employed in this type of [4+2] cycloaddition reaction. Since the conversion of esters into enol ethers

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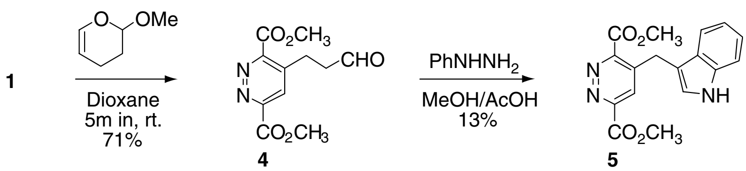
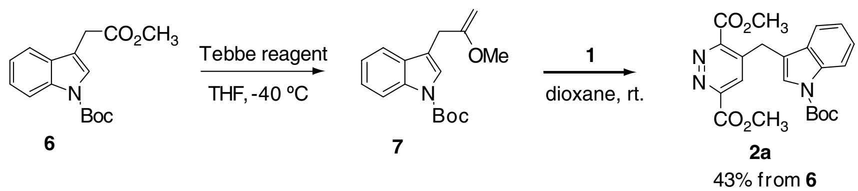
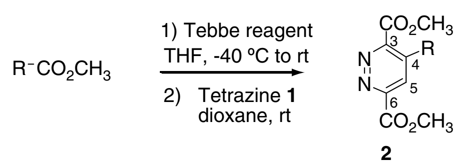


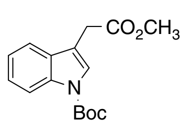
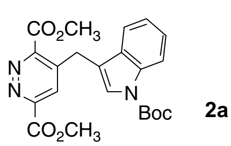
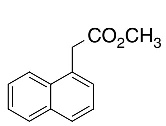
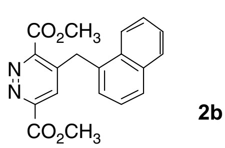
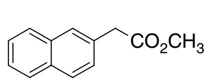
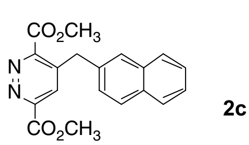
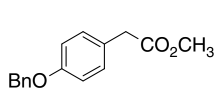
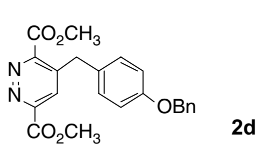
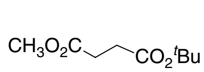
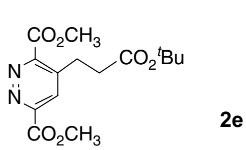
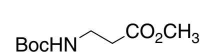
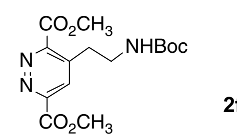
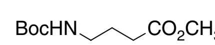
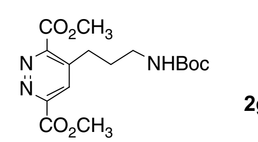
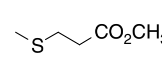
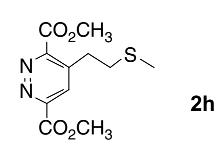
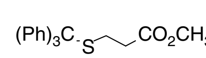
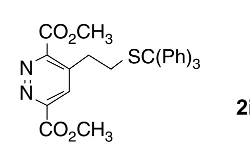
Scheme 1. Fischer indole synthesis approach to pyridazine **2a**.



Scheme 2. Synthesis of pyridazine **2a**.

Table 1
Synthesis of 4-substituted pyridazines **2a**–**i**



Entry	Ester	Product	Yield (%)
1			43
2			65
3			54
4			58
5			41
6			39
7			31[a]
8			41
9			35[a]

[a] Yields determined from tetrazine **1**.

by reaction with the Tebbe reagent is a well established procedure,[19] the *N*-Boc protected derivative **6** of the commercially available methyl-2-(1*H*-indol-3-yl) acetate was selected as the precursor of the electron-rich dienophile **7** (Scheme 2). Treatment of compound **6** with the Tebbe reagent in tetrahydrofuran at low temperature afforded the desired enol ether **7**, and reaction with tetrazine **1** at room temperature to afford pyridazine **2a** in 43% overall yield from compound **6**.[20]

The scope of this method was expanded with several commercially available esters which were subjected to the sequence (Table 1). The Tebbe reaction is compatible with the presence of a variety of functional groups such as carbamates (**2f–g**), ethers (**2d**), thioethers (**2h–i**) or sterically challenged esters (**2e**), allowing the preparation of pyridazines containing substituents that are conveniently protected side chains of functional amino acids. Various compounds containing either aromatic or aliphatic substituents in position 4 of the pyridazine core were prepared. The best yields were obtained with esters with aromatic rings in their structures (entries 1–4). For example, the synthesis of compound **2e**, which features a *tert*-butyl ester of a glutamic acid residue, began with the commercially available *tert*-butyl methyl glutarate (entry 5). The Tebbe reagent showed exclusive regioselectivity, giving the enol ether of the less hindered methyl ester.

In summary, we have developed a method for the preparation of functionalized 4-substituted pyridazines from esters via Tebbe olefination, and IEDDAR reaction of the resulting enol ethers. This procedure yielded, among other examples, several pyridazines with protected side chains of common amino acids. In addition, aldehyde **4** provides a function that can be elaborated into uncommon side chains.

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