

Synthesis of pyridazines functionalized with amino acid side chains

Enrique Mann, Lionel Moisan, Jun-Li Hou, Julius Rebek, Jr. *

The Skaggs Institute for Chemical Biology, The Scripps Research Institute, Mail MB-26, 10550 North Torrey Pines Road, La Jolla, CA 92037, USA

Received 25 October 2007; revised 20 November 2007; accepted 26 November 2007

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.

© 2007 Elsevier Ltd. All rights reserved.

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 antihypertensive⁴ or antihistaminic⁵ activities have all been reported. This heterocycle is also useful for the preparation of other heterocycles,⁶ π -conjugated organic materials with desirable electronic properties⁷ 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 interactions¹² when R_{1-3} are typically side chains of hydrophobic amino acids. The pyridazine scaffold offers remote hydrophilic sites, regioselective functionalization¹¹

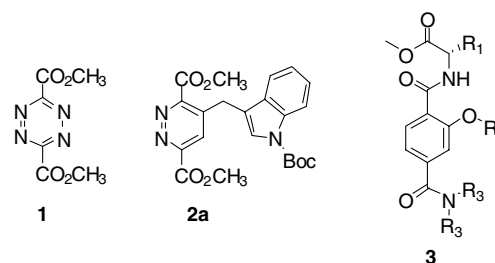


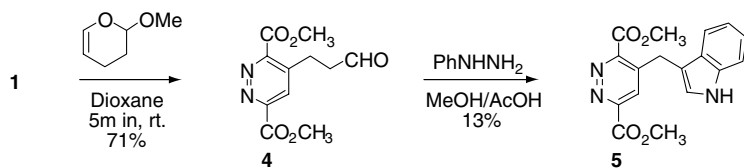
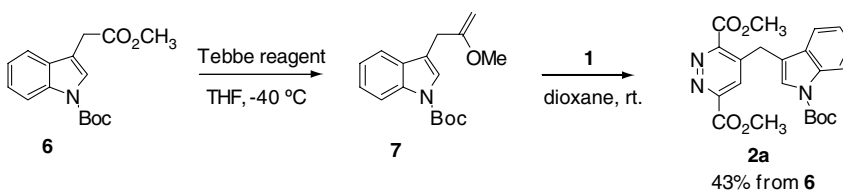
Fig. 1. Structures of tetrazine **1**, pyridazine **2a** and Hamilton's terephthalamide scaffold **3**.

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-2H-pyran to give pyridazine **4** in good yield. Subsequent treatment under standard Fischer indole synthesis¹⁴ 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

* Corresponding author. Tel.: +1 858 784 2250; fax: +1 858 784 2876.
E-mail address: jrebek@scripps.edu (J. Rebek, Jr.).

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

Table 1 (continued)

Entry	Ester	Product	Yield (%)
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.

Acknowledgments

We are grateful to the Skaggs Institute for Research and to Novartis for support. The Spanish Ministerio de Educacion y Ciencia (Secretaria de Estado de Universidades e Investigacion) provided a Postdoctoral Fellowship to E.M. We thank Professor D. L. Boger for advice and helpful discussions.

References and notes

- Rohet, F.; Rubat, C.; Coudert, P.; Couquelet, J. *Bioorg. Med. Chem.* **1997**, *5*, 655–659.
- Tucker, J. A.; Allwine, D. A.; Grega, K. C.; Barbachyn, M. R.; Klock, J. L.; Adamski, J. L.; Brickner, S. J.; Hutchinson, D. K.; Ford, C. W.; Zurenko, G. E.; Conradi, R. A.; Burton, P. S.; Jensen, R. M. *J. Med. Chem.* **1998**, *41*, 3727–3735.
- Tamayo, N.; Liao, L.; Goldberg, M.; Powers, D.; Tudor, Y. Y.; Yu, V.; Wong, L. M.; Henkle, B.; Middleton, S.; Syed, R.; Harvey, T.; Jang, G.; Hungate, R.; Dominguez, C. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 2409–2413.
- Benson, S. C.; Palabrica, C. A.; Snyder, J. K. *J. Org. Chem.* **1987**, *52*, 4610–4614.
- Gyoten, M.; Nagaya, H.; Fukuda, S.; Ashida, Y.; Kawano, Y. *Chem. Pharm. Bull.* **2003**, *51*, 122–133.
- Naud, S.; Pipelier, M.; Viault, G.; Adjou, A.; Huet, F.; Legoupy, S.; Aubertin, A. M.; Evain, M.; Dubreuil, D. *Eur. J. Org. Chem.* **2007**, 3296–3310.
- Yasuda, T.; Sakai, Y.; Aramaki, S.; Yamamoto, T. *Chem. Mater.* **2005**, *17*, 6060–6068.
- Cuccia, L. A.; Lehn, J.-M.; Homo, J.-C.; Schmutz, M. *Angew. Chem., Int. Ed.* **2000**, *39*, 233–237.
- Nara, S.; Martinez, J.; Wermuth, C.-G.; Parrot, I. *Synlett* **2006**, 3185–3204.
- (a) Hamasaki, A.; Ducray, R.; Boger, D. L. *J. Org. Chem.* **2006**, *71*, 185–193; (b) Helm, M. D.; Moore, J. E.; Plant, A.; Harrierty, J. P. A. *Angew. Chem., Int. Ed.* **2005**, *44*, 3889–3892.
- (a) Biro, S. M.; Moisan, L.; Mann, E.; Carella, A.; Zhai, D.; Reed, J. C.; Rebek, J., Jr. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 4641–4645; (b) Volonterio, A.; Moisan, L.; Rebek, J., Jr. *Org. Lett.* **2007**, *9*, 3733–3736; (c) Moisan, L.; Dale, T. J.; Gombosuren, N.; Biro, S. M.; Mann, E.; Hou, J. L.; Rebek, J. Jr. *Heterocycles* **2007**, available from: [COM-07-S\(U\)45](#).
- (a) Yin, H.; Hamilton, A. D. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 1375–1379; (b) Yin, H.; Lee, G.-I.; Sedey, K. A.; Rodriguez, J. M.; Wang, H.-G.; Sebt, S. M.; Hamilton, A. D. *J. Am. Chem. Soc.* **2005**, *127*, 5463–5468.
- (a) Boger, D. L.; Panek, J. S.; Patel, M. *Org. Synth.* **1992**, *70*, 79; (b) Naud, S. *Synlett* **2004**, 2836–2837.
- Hutchins, S. M.; Chapman, K. T. *Tetrahedron Lett.* **1996**, *37*, 4869–4872.
- Geyelin, P. H.; Raw, S. A.; Taylor, R. J. K. *ARKIVOC* **2007**, Part 11, 37–45.
- Hartmann, K. P.; Heuschmann, M. *Tetrahedron* **2000**, *56*, 4213–4218.
- For previous use of cyclic or acyclic enol ethers as dienophiles for the IEDDAR with tetrazines see: (a) Gnichtel, H.; Gumprecht, C. *Liebigs Ann. Chem.* **1985**, *3*, 628–632; (b) Boger, D. L.; Sakya, S. M. *J. Org. Chem.* **1988**, *53*, 1415–1423; (c) Soenen, D. R.; Zimpleman, J. M.; Boger, D. L. *J. Org. Chem.* **2003**, *68*, 3593–3598.
- Akiyama, T.; Morita, H.; Fuchibe, K. *J. Am. Chem. Soc.* **2006**, *128*, 13070–13071.
- Hartley, R. C.; McKiernan, G. J. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2763–2793.
- Tebbe reagent: μ -Chlorobis(cyclopentadienyl)-(dimethylaluminum)- μ -methylene-titanium, Tebbe, F. N.; Parshall, G. W.; Reddy, G. S. *J. Am. Chem. Soc.* **1978**, *100*, 3611–3613. Representative general procedure: To a solution of the corresponding ester (1.04 mmol) in THF (12 ml) cooled at $-40\text{ }^{\circ}\text{C}$ is added Tebbe reagent (2.7 ml, 1.3 equiv, 0.5 M in toluene). After 30 min the temperature is raised to ambient over a period of 2 h. The mixture is then cooled to $-10\text{ }^{\circ}\text{C}$ and the reaction is quenched by the dropwise addition of NaOH (700 μ l, 2 M solution). Reaction mixture is then allowed to warm to room temperature. The solution is then diluted with excess of ether and filtered through a pad of Celite. Solvent is removed under reduced pressure and the crude residue is directly diluted in dioxane (10 ml) and added to a solution of tetrazine **1** (203 mg, 1.0 mmol) in dioxane (10 ml). After 18 h at room temperature, volatiles are removed and the crude residue is purified on silica gel (hexane/AcOEt mixtures) to afford the desired products.