

# SYNLETT Spotlight 105

## Dimethyl 1,2,4,5-Tetrazine-3,6-dicarboxylate

Compiled by Sébastien Naud



This feature focuses on a reagent chosen by a postgraduate, highlighting the uses and preparation of the reagent in current research

Sébastien Naud was born in 1979 in Les Sables d'Olonne, France. He studied chemistry at the University of Nantes where he obtained his Masters. Currently he is doing Ph.D. under the supervision of Prof. Didier Dubreuil in the same university. His area of research includes the synthesis of pyrrole-based cyclic as well as acyclic C-nucleosides from the corresponding pyridazine C-nucleosides by ring contraction.

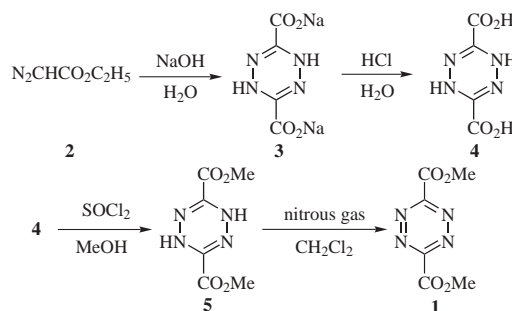
Laboratoire de Synthèse Organique (UMR-CNRS 6513; FR-CNRS 2465), Université de Nantes, UFR des Sciences et des Techniques, 2 rue de la Houssinière, B.P. 92208, 44322 Nantes cedex 3, France  
E-mail: sebastien.naud@chimie.univ-nantes.fr

### Introduction

Aza heterocyclic compounds, due to their presence in a number of biologically active compounds such as alkaloids, are very important in the field of medicinal and therapeutic chemistry. They can be synthesized through various ways, the hetero Diels–Alder reaction being one of them.<sup>1,2</sup> For example, dimethyl 1,2,4,5-tetrazine-3,6-dicarboxylate (**1**) has been extensively used for the synthesis of nitrogen-containing heterocyclic compounds through inverse electron demand hetero Diels–Alder reactions.<sup>3</sup> Herein, I would like to discuss this reagent.

Dimethyl 1,2,4,5-tetrazine-3,6-dicarboxylate (**1**) is a bright-red crystalline solid and can be synthesized on large scale through four steps from ethyl diazoacetate (**2**) (Scheme 1).<sup>4,5</sup>

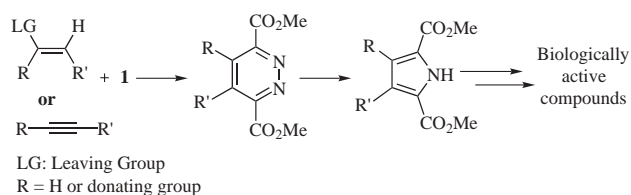
Its synthesis starts with a base-promoted dimerization of ethyl diazoacetate (**2**) followed by acidification of the sodium salt (**3**) with concentrated hydrochloric acid and esterification to afford the diester (**5**). Finally, oxidation with nitrous gas affords **1** in 34% overall yield.



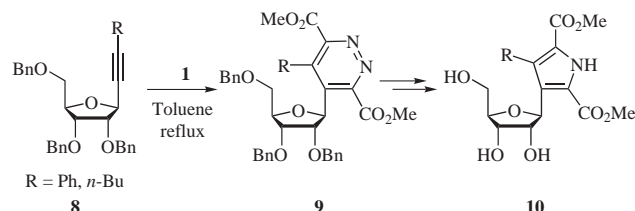
Scheme 1

### Abstracts

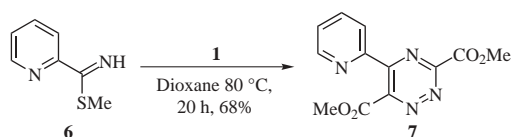
(A) As stated earlier, compound **1** undergoes hetero Diels–Alder reaction with alkenes, bearing a leaving group, or acetylenes and subsequent loss of nitrogen to afford pyridazines. Moreover, these diazines can be easily converted into the corresponding pyrrole derivatives by reductive ring contraction.<sup>6</sup> This method was first utilized by Kornfeld.<sup>7</sup> Boger successfully used this methodology for the synthesis of a number of natural products possessing anti-tumor or antibiotic activities.<sup>8–15</sup>



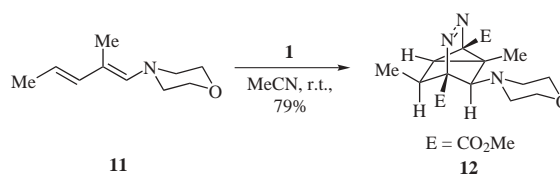
(B) Recently our group reported the application of 1,2,4,5-tetrazine-3,6-dicarboxylate (**1**) for the synthesis of pyridazine C-nucleosides **9** from alkynyl C-nucleosides **8**.<sup>16</sup> These pyridazines on chemical (Zn/AcOH) or electrochemical<sup>17,18</sup> extrusion of a nitrogen atom afforded novel pyrrole C-nucleosides **10** in good yields.



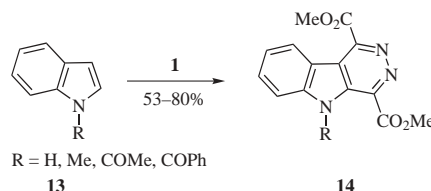
(C) It has been shown by Boger and co-workers that tetrazine **1** reacts with heterodienophiles such as **6** in Diels–Alder reactions to provide 1,2,4-triazines **7**.<sup>19</sup> The synthesis of streptonigrin, which has antitumor and antibiotic properties, is an excellent application of this protocol.



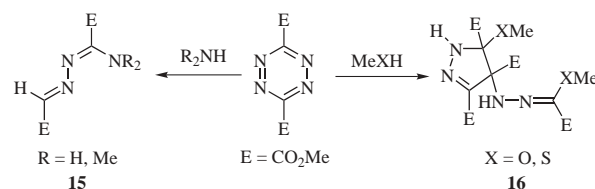
(D) Smith and co-workers have described a ‘tandem’ Diels–Alder reaction sequence in which both double bonds of dienamine **11** reacted with a single tetrazine unit to yield the strained azo-bridged compound **12** in good yield.<sup>20</sup> This is the first example of a bridged tricyclic ring system which otherwise would be very difficult to synthesize.



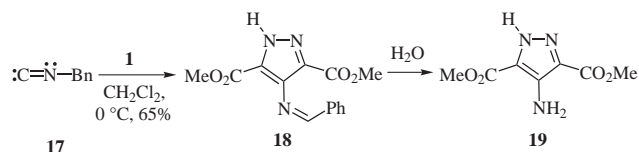
(E) Tetrazine **1** has also found application in the field of medicinal chemistry. Snyder has synthesized 5*H*-pyridazino[4,5-*b*]indoles **14** by [4+2] cycloaddition reaction of indoles **13** with **1**.<sup>21</sup> These pyridazinoindoles showed excellent antihypertensive activity.



(F) During the reaction of nucleophiles with tetrazine **1**, very different compounds such as azines (**15**) can be obtained by addition of ammonia or dimethylamine. On the other hand, pyrazoles **16** can be obtained by addition of methanol or methanethiol to **1**.<sup>22</sup>



(G) Tetrazine **1** can also afford [4+1] cycloadducts. Seitz showed that **1** reacts with benzylisocyanide **17** to give iminopyrazole **18** which, upon hydrolysis, afforded the corresponding aminopyrazole **19**.<sup>23</sup> This aminopyrazole showed interesting pharmacological activity.



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