

# SYNLETT Spotlight 383

## 1,3-Dipoles: Nitrile Imines, Nitrile Oxides and Nitrile Sulfides

Compiled by Péter Ábrányi-Balogh

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

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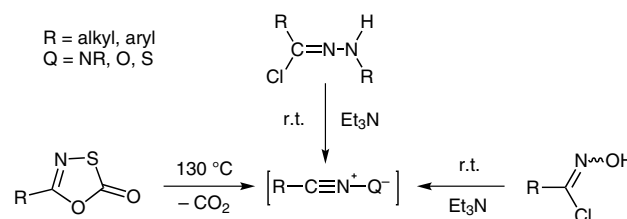
### Introduction

The 1,3-dipolar cycloaddition is a classic and widely used reaction in modern synthetic organic and pharmaceutical chemistry that consists of the reaction of a dipolarophile with a 1,3-dipole yielding various five-membered heterocycles (by our examined reagents: oxazoles, diazoles, thiazoles, oxadiazoles, thiadiazoles and their iso or saturated variants).<sup>1</sup> These heterocycles are versatile synthetic intermediates, playing a significant role in the synthesis of many biologically active natural products,<sup>2</sup> alkaloids,<sup>3</sup> chemically modified oligonucleotides,<sup>4</sup> peptides<sup>5</sup> and other pharmacologically active compounds<sup>6</sup> or prevailing drugs.<sup>7</sup>

### Preparation

All 1,3-dipoles are relatively unstable linear molecules that can be generated in situ (Scheme 1).<sup>1a</sup> A simple way to form nitrile imines is the dehydrohalogenation of hy-

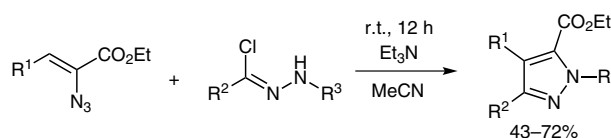
dracilic halides using a base, mostly triethylamine.<sup>1b,2a</sup> Nitrile oxides may be generated from nitro compounds or from the halogenation of aldoximes followed by a dehydrohalogenation caused by an adequate base. In the reactions of nitrile oxides high *syn*-selectivity can be observed.<sup>1a,7</sup> The formation of in situ nitrile sulfides is attained by the thermal or microwave-assisted thermolysis and also photolysis of various heterocyclic compounds containing a C=N–S bond.<sup>8</sup>



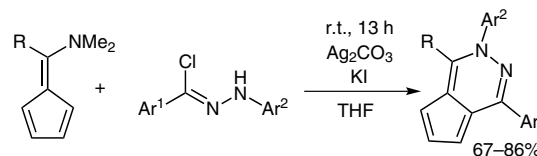
**Scheme 1** Simple ways to the in situ generation of dipoles

### Abstracts

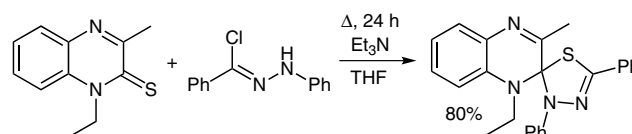
(A) Tetrasubstituted pyrazoles were formed from 2-azidoacrilates and hydrazonyl chlorides in moderate to good yields. The reactions were carried out under mild conditions in acetonitrile in the presence of triethylamine at room temperature.<sup>6b</sup>



(B) A simple route for one-pot synthesis of cyclopenta[*d*]pyridazine through 1,3-dipolar cycloaddition was described. Many conditions were tested and Ag<sub>2</sub>CO<sub>3</sub> proved to be the best base with catalytic amount of potassium iodide in tetrahydrofuran at room temperature.<sup>9</sup>



(C) New spiro[thiadiazoline-quinoxaline]s were synthesized by 1,3-dipolar cycloaddition at the C=S bond. The hydrazonyl chloride was reacted with quinoxaline-2-thiones with triethylamine in boiling tetrahydrofuran for one day.<sup>2d</sup>



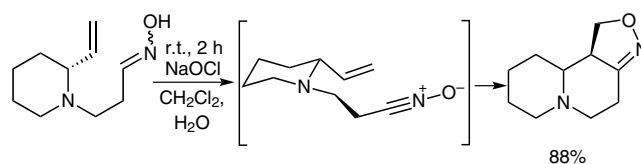
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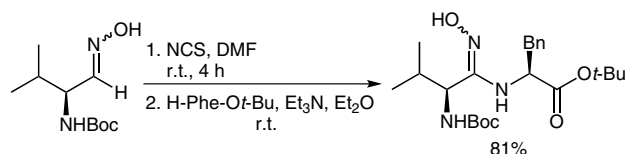
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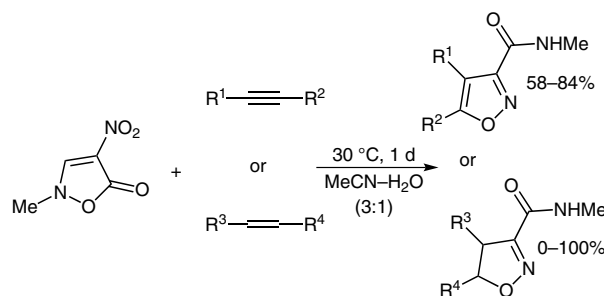
(D) In the key step of the total synthesis of enantiopure (+)-epilupine an intramolecular cycloaddition of a nitrile oxide was accomplished. The oxime was treated with 10% aqueous solution of NaOCl at room temperature and a single product was obtained in 88% yield.<sup>3b</sup>



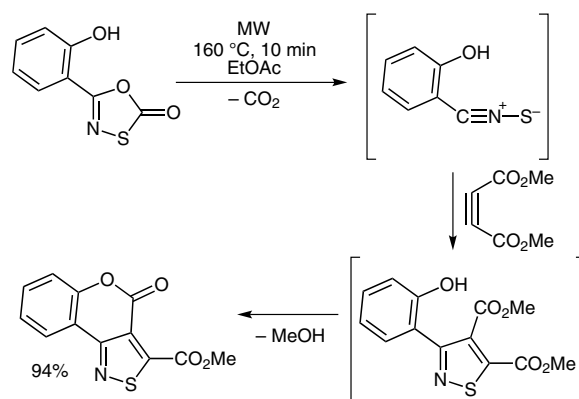
(E) A nitrile oxide as an active ester equivalent was used to prepare a key amidoxime precursor. The oxime was chlorinated with *N*-chlorosuccinimide and triethylamine was used as base to liberate the active agent that reacted with the phenylalanine derivative overnight at room temperature. This method was used for Fmoc-based solid-phase synthesis of acyclic and cyclic peptides and peptidomimetics.<sup>5</sup>



(F) Nishiwaki et al. observed that nitroisoxazolone served as precursor of nitrile oxide. In the present method only water was required for the generation of the active reagent. An aqueous solution of nitroisoxazolone and the dipolarophile was stirred in acetonitrile at 30 °C for one day. The cycloaddition afforded functionalized isoxazoles and isoxazolines in good yields.<sup>10</sup>



(G) The 1,3-dipolar cycloaddition of nitrile sulfides generated by microwave-assisted decarboxylation of 1,3,4-oxathiazol-2-ones has been investigated. The dipole precursors were reacted and trapped in a microwave reactor with dipolarophiles (e.g., ethyl cyanoformate, dimethyl acetylenedicarboxylate) at 140–200 °C for 10–30 minutes to achieve various cycloadducts in 56–96% yields.<sup>8c</sup>



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