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1,3-DIPOLAR CYCLOREVERSION OF A 1,3,4-OXADIAZOLIDINE AS A CONTROLLED AZOMETHINE IMINE SURROGATE FOR PYRAZOLIDINE SYNTHESIS

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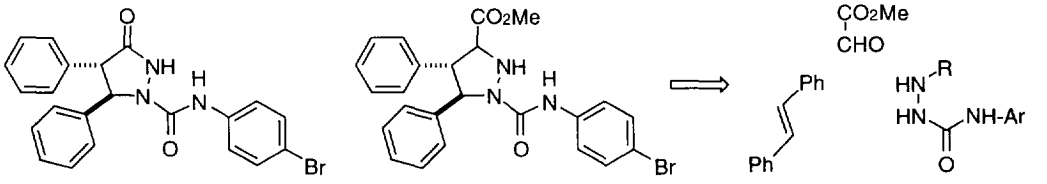
Summary: Azomethine imines were generated in a controlled manner through a thermally allowed 1,3-dipolar cycloreversion of 1,3,4-oxadiazolidines and subsequently trapped with dipolarophiles. This method results in the construction of the pyrazolidine heterocycles. A new method for the selective formation of the key semicarbazide substrate, from benzylidene hydrazone, is also disclosed. Copyright © 1996 Elsevier Science Ltd

The search for selective cholecystokinin (CCK) receptor ligands has lead to the development of potent CCK-A and CCK-B antagonists.[1] From an interesting pyrazolidinone series, LY288513 emerged as a very promising pre-clinical candidate.[2] Contemplating the pyrazolidine heterocycle as an attractive subunit, we considered general synthetic approaches for isosteres and analogues, such as pyrazolidine **1**, and sought access *via* 1,3-dipolar cycloaddition chemistry.[3] The synthesis of pyrazolidines *via* either intramolecular or intermolecular 1,3-dipolar cycloaddition has been extensively documented.[4] During the course of our work on the preparation of **1** and analogues, however, we found a novel approach for the formation and trapping of azomethine imines, which we discuss herein. Furthermore, synthesis of the key semicarbazide **2** was accomplished in a uniquely selective manner.

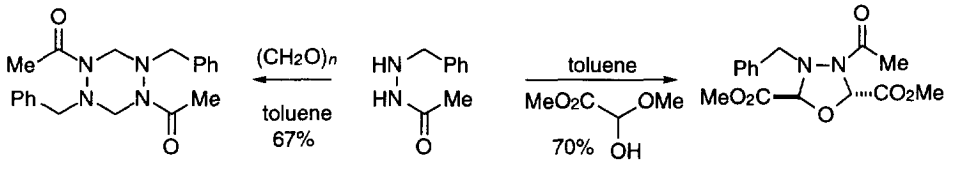


LY288513 **1** **2**

Condensation of hydrazide **3**[5] with paraformaldehyde in toluene, either in the presence or absence of the dipolarophile *trans*-stilbene, under azeotropic water removal resulted in the formation of the centrosymmetric hexahydrotetrazine **4** in 67% yield. Oppolzer had previously noted hexahydrotetrazine formation under similar conditions employing substoichiometric dipolarophile[3,6] and found that these heterocycles do not dissociate

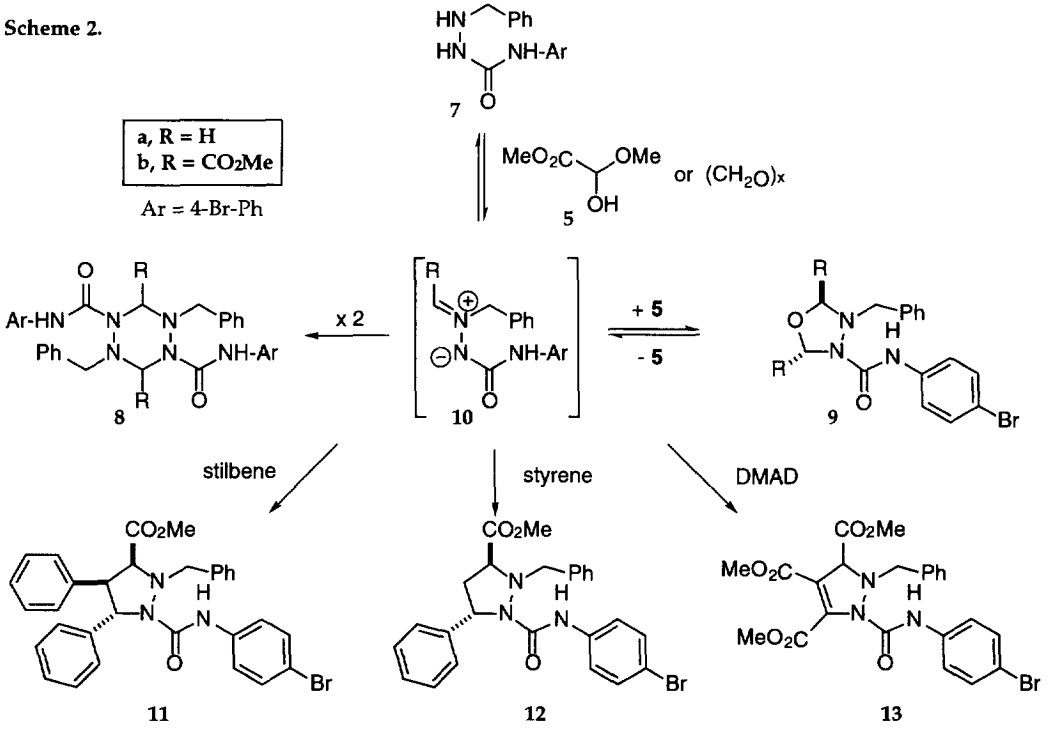
back to the dipole at temperatures up to 180 °C. Reaction of hydrazide **3** under the same conditions, but with excess methyl glyoxylate hemiacetal (**5**),[7] afforded oxadiazolidine **6** as the predominate product.[8] We were unable to isolate any dipolar cycloadduct with *trans*-stilbene, a very poor dipolarophile, under these conditions.

Scheme 1.



We had a similar experience with semicarbazide **7** and defined conditions under which hexahydrotetrazine **8** or oxadiazolidine **9** could be formed in excellent yields. Likewise, under some conditions up to 10% of dipolar cycloadducts **11-13** could be isolated, but the major product was oxadiazolidine **9**. Although Oppolzer had demonstrated the thermal stability of the hexahydrotetrazine series, the oxadiazolidine stability remained unknown and allowed us to consider its potential for 1,3-dipolar cycloreversion.[9] The mass spectrometric behavior of oxadiazolidines, using electron impact induced fragmentation, has been demonstrated to mimic a retro-1,3-dipolar cycloaddition.[10] Moreover, we reasoned that generating high concentrations of dipole **10** in

Scheme 2.



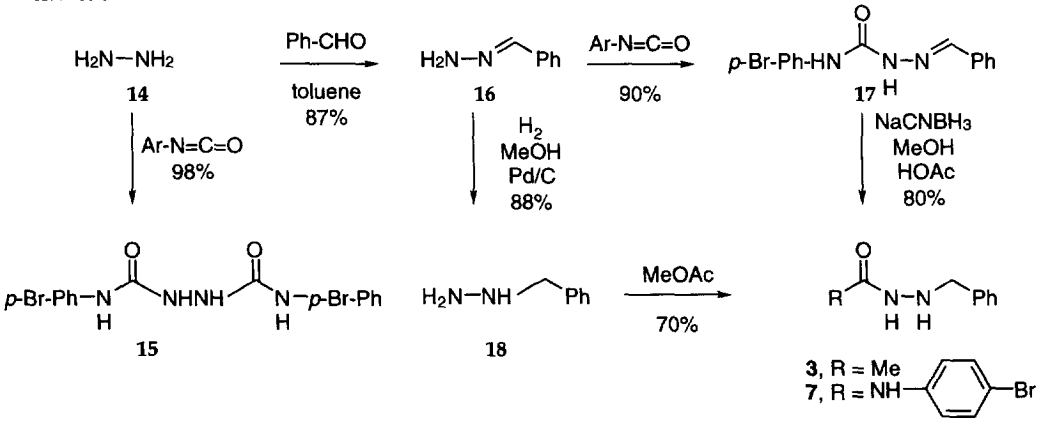
the absence of a suitable dipolarophile (or with an ineffective dipolarophile) would result in dimerization, and a controlled formation *via* cycloreversion of **9** might be preferred.

1,3,4-Oxadiazolidine **9b** was efficiently prepared in 70% yield by heating semicarbazide **7** with excess hemiacetal **5** at reflux in toluene (3 h). NMR analysis of the oxadiazolidine structure proved to be consistent with reported[8e] spectroscopic data (84.2 ppm-C^2; 6.13 ppm, s, C^2H; 91.4 ppm-C^5; 5.35 ppm, s, C^5H), along with other characteristic spectral data (*m/z* 477, 479 and λ_{max} = 247).[11] The oxadiazolidine **9b** undergoes a *retro*-1,3-dipolar cycloaddition, followed by cycloaddition, during slow addition (3 h) to a solution of *trans*-stilbene in toluene containing catalytic *p*-TsOH at reflux. After continued stirring at this temperature for 22 h, the cycloadduct **11** (mp 192 °C) was isolated in 92% yield. The same cycloreversion-cycloaddition reaction to produce **11** was also possible under purely thermal conditions using xylenes as the solvent.

Direct reaction of semicarbazide **7** with hemiacetal **5** and *trans*-stilbene in toluene (catalytic *p*-TsOH, H_2O removal) leads primarily to formation of **9b** as a complex mixture with <10% yield of the desired product **11**. It was possible, however, to pre-form oxadiazolidine **9b** *in situ* followed by slow addition to the dipolarophile to afford cycloadduct **11** in 31% yield. However, the most efficient method for producing **11** was the thermal cycloreversion-cycloaddition of **9b** in the presence of a dipolarophile as described above. Therefore, this method[12] was extended in a similar manner and 1,3-dipole **10** could be generated and trapped with either styrene or DMAD, furnishing the corresponding adducts **12** (96%) or **13** (60%), respectively. The $J_{3,4}$ = 7.5 Hz and $J_{4,5}$ = 10.5 Hz coupling constants for pyrazolidine **11** are suggestive of a *cis* disposition between the neighboring ester and phenyl moieties and *trans* between the two phenyl moieties.[13] This stereochemical outcome is also consistent with the kinetically preferred endo transition state[4] and confirmed by the rapid equilibration (NaOMe, MeOH) to the thermodynamically more stable *trans*, *trans*-isomer.[4e]

1,3,4-Oxadiazolidine **9a** was similarly formed in good yield from the semicarbazide **7** and paraformaldehyde as above. However, under the cycloreversion-cycloaddition conditions it was less effective to produce the desired pyrazolidine adducts. Yields with the aforementioned dipolarophiles were typically < 50%.

Scheme 3.



Preparation of the requisite semicarbazide was first attempted by reaction of hydrazine (**14**) with Ar-N=C=O, but only the dimeric product **15** was obtained (98%, Scheme 3).[14] Since alkylhydrazines are known to be more

nucleophilic at the substituted nitrogen, we sought to minimize protection and reacted benzylidene hydrazine (**16**)[15] with the isocyanate.[16] Semicarbazone **17** (mp 210 °C) precipitated in 85% yield with analytical purity. Reaction of commercial *p*-bromophenyl semicarbazide with benzaldehyde proved to be a less efficient route to semicarbazone **17**. Reduction of the imine bond under nonhydrogenolytic conditions with $NaCNBH_3$ afforded the desired semicarbazide **7** (mp 170 °C) in 88% yield. The simple hydrazide **3** was prepared in 70% yield by heating benzyl hydrazine (**18**) in MeOAc.[5]

In summary, we have demonstrated a novel method for the generation of an azomethine imine from a 1,3,4-oxadiazolidine under controlled conditions and an efficient means for trapping it with dipolarophiles. The cycloreversion of oxadiazolidine **9** offers controlled formation of the dipole, preventing unwanted dimerization to the hexahydrotetrazine. The semicarbazide precursor was also selectively prepared in a mild and potentially very general manner.

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11. All compounds gave satisfactory spectroscopic analysis (300 MHz ^1H, 50 MHz ^{13}C NMR, HETCOR, FT-IR, mass spectra and HRMS).
12. Representative procedure for **13**: 1,3,4-Oxadiazolidine **9** (717 mg, 1.5 mmol) and dimethyl acetylene dicarboxylate (885 mg, 6.2 mmol) was stirred under gentle reflux in xylenes (5 mL) for 14 h. The reaction mixture was cooled to ambient temperature and concentrated in vacuo. The desired product was purified by chromatography over SiO_2 with heptane/EtOAc (3:1 → 1:1). The adduct was isolated in 60% yield as a slight yellow oil (470 mg): R_f = 0.6 (heptane/EtOAc, 1/1); hrms calcd 531.0642, obsvd 531.0621; λ_{max} = 301 (14800); ir ($CHCl_3$) 1745, 1710 cm^{-1}; nmr ($CDCl_3$) 68.6 ppm-C^3; 4.18 ppm, s, C^3H.
13. The ^1H NMR spectrum in d_6-DMSO displays clean signal resolution compared to $CDCl_3$ ($J_{3,4}$ = 7.8 Hz and $J_{4,5}$ = 9.9 Hz). Conformational minimization (Spartan, PM3) suggests the ring is highly puckered with calculated dihedral angles between H_3-H_4 = 28 ° and H_4-H_5 =158 °. The authors thank Tom Wilson for help obtaining this data and helpful discussions.
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16. The closest literature precedent is Tilles, H. (Stauffer Chemical Co.) US Patent 3712914, date 730123.

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