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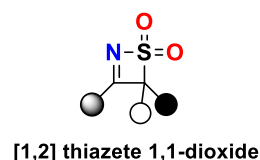
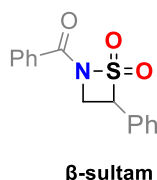
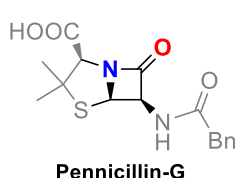
[1,2]-thiazete S,S-dioxide scaffold synthesis

Virgil PIERRON,¹ Alexandre TOURON,¹ Pierre THUÉRY,¹ Emmanuel NICOLAS,¹ Lucile ANTHORE-DALION¹

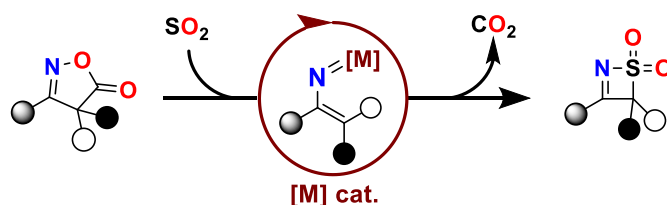
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The discovery of new scaffolds improves the quality of chemical libraries, which is a powerful tool in drug discovery. Focusing on 4-member N-heterocycles, β -lactams, such as penicillin-G, have shown bactericidal properties.¹ The analogous β -sultames, less described, have also shown interesting biological activities.² Judging by these previous examples, the thiazete 1,1-dioxide scaffold could be worth adding to chemical libraries. However, this cycle remained a synthetic challenge until 1963³ with the first synthesis. The 1st structural confirmation appeared only in 2002.⁴ And today, synthetic methodologies have still remained scarce.

4-member N-heterocycles in pharma:



This Work :



The primary way to obtain thiazete dioxide relied on azide reagents.⁴ Herein, we report a CO₂-SO₂ exchange methodology. As a starting material, isoxazolones are known to be stable precursors of nitrene-like species in the presence of organometallic complexes.⁵⁻⁶ The most significant challenge resides in the control of the intermediate, which can easily undergo a cyclization toward the corresponding azirine,⁵ or an [3+2] intramolecular cycloaddition if the substrate bears an alkene group.⁶ In the presence of SO₂, we witnessed first the [3+1] addition forming the desired thiazete dioxide, which structure has been confirmed through XRD.

¹ Eagle H., Musselman A. D.; *J. of Exp. Med.* **1947**, *85* (2), 175–186

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³ B. J. R. Nicolaus, E. Bellasio, E. Testa; *Helv. Chim. Acta*, **1963**

⁴ Clerici, F.; Gelmi, M. L.; Soave, R.; Lo Presti, L. *Tetrahedron* **2002**, *58* (25), 5173–5178 / Blackburn, J.; Molyneux, G.; Pitard, A.; Rice, C. R.; Page, M. I.; Afshinjavid, S.; Javid, F. A.; Coles, S. J.; Horton, P. N.; Hemming, K. *Org. Biomol. Chem.* **2016**, *14* (6), 2134–2144

⁵ Okamoto, K.; Shimbayashi, T.; Yoshida, M.; Nanya, A.; Ohe, K. *Angew. Chem. Int. Ed.* **2016**, *55* (25), 7199–7202

⁶ Shimbayashi, T.; Matsushita, G.; Nanya, A.; Eguchi, A.; Okamoto, K.; Ohe, K. *ACS Catal.* **2018**, *8* (9), 7773–7780