

SYNLETT Spotlight 456

Squaramides, Discovering a New Crucial Scaffold

Compiled by Juan V. Alegre-Requena



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

Interest in squaramides has grown drastically over the last few years. One of the reasons is that squaramides can be used in many different ways in important fields such as organic chemistry, medicine, and chemical biology.

First of all, the rigidity of their cyclobutadienedione rings, the restricted rotation around the C–N bonds,¹ and the possibility of having both acidic hydrogens² and basic functionalities in a single molecule make them effective bifunctional organocatalysts for asymmetric reactions.³

Furthermore, they act as ion detectors, forming hydrogen bonds with the corresponding anion or cation.^{2b,4} The interaction with anions through hydrogen bonding also brought them to the attention of studies regarding transmembrane anion transport.⁵

In addition, squaramides have shown antimalarial,⁶ antibacterial,⁷ and anticancer⁸ activity.

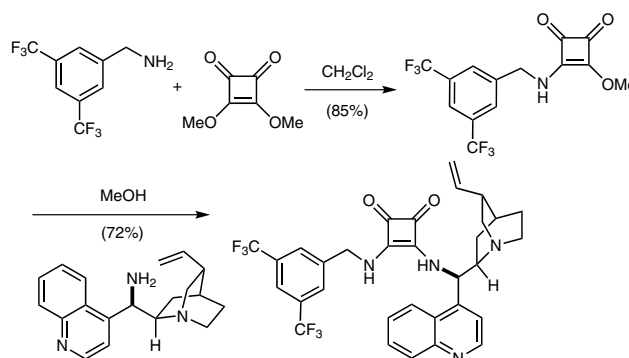
Abstracts

(A) Organocatalysts

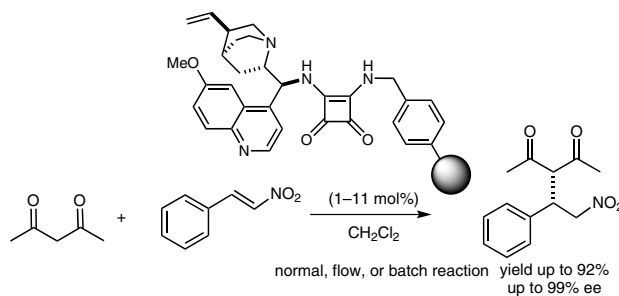
Soós and co-workers recently reported the asymmetric conjugate addition of different acetylacetoates to nitrostyrenes with high yields and enantioselectivities using immobilized squaramides.¹¹ The most appealing aspect of this work is that the reactions were carried out successfully in batch and flow reactors, bringing this catalyst closer to industrial applications.

Preparation

Squaramides are usually synthesized under mild conditions in high yields, and both symmetric and asymmetric squaramides are accessible (Scheme 1).⁹

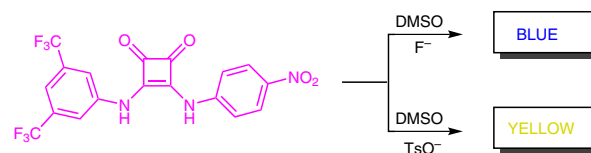


Scheme 1 Synthesis of an asymmetric squaramide by Rawal¹⁰



(B) Anion Sensors

Taylor and co-workers reported the use of a *N,N'*-diarylsquaramide as a colorimetric sensor for anions such as fluoride and tosylate.^{2a} The squaramide showed different colors depending on the anion present in a DMSO solution. This behavior seems to be in agreement with an enhanced acidity in comparison with ureas.



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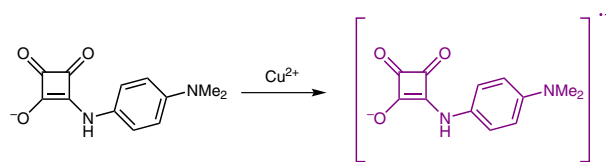
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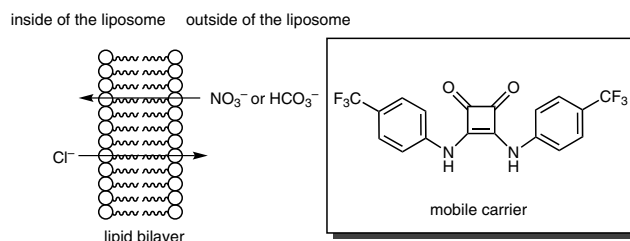
(C) Cation Sensors

Costa and co-workers developed a squaramide-based sensor for selective detection of Cu^{2+} .¹² When this compound chelates with Cu^{2+} , a zwitterionic colored radical species is formed rapidly, allowing the visual detection of Cu^{2+} . Interestingly, this compound can be used in water for the detection of Cu^{2+} , displaying good selectivity for this cation over other metallic cations.



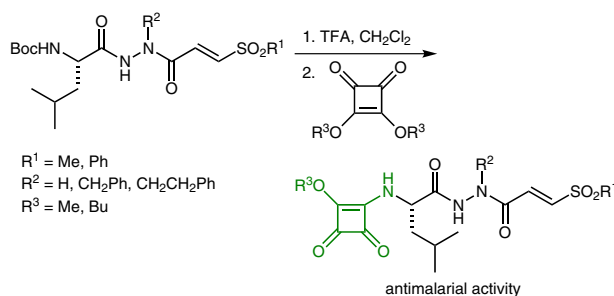
(D) Transmembrane Anion Transporters

Gale and co-workers reported the use of squaramides as anion transporters across lipid bilayers, obtaining better results than their urea and thiourea analogues.⁵ This research opens a door for the use of squaramide-based drugs in the treatment of diseases caused by malfunctioning ion channels.



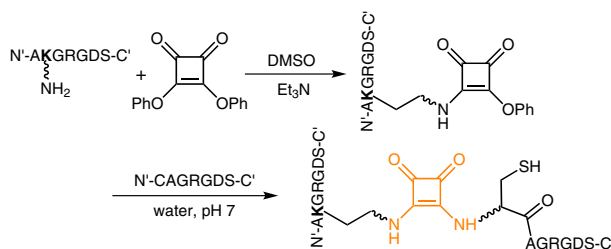
(E) Antimalarial Agents

Santos and co-workers synthesized squaramide aza vinyl sulfones that were shown to have antiplasmodial activities.⁶ These compounds could be used as medicines in the complex fight against malaria, an illness that infects millions of people every year and develops resistance to the drugs used in its treatment.¹³



(F) Linkers for Biomolecules

Luk and co-workers reported the coupling of peptides using squaramides as linkers.¹⁴ These reactions make squaramides suitable for modifying existing biomolecules, adding parts containing peptides to their structures. This peptide coupling is carried out using water as the solvent, which might make the use of this type of compound suitable for in vivo studies.



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