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[B0005]

Polymer-Supported Reagents as Versatile Tools in Combinatorial Chemistry and Total Synthesis

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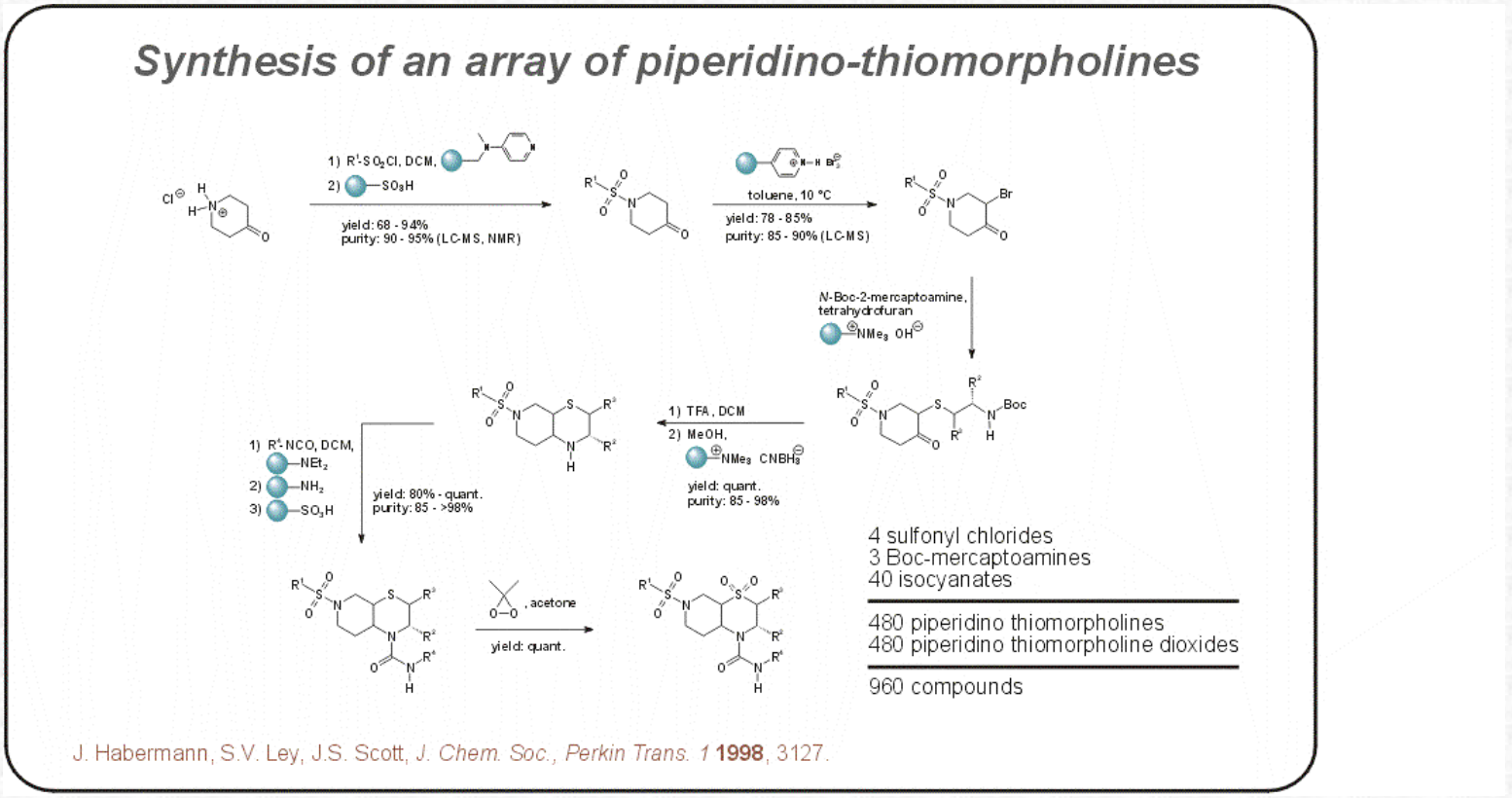
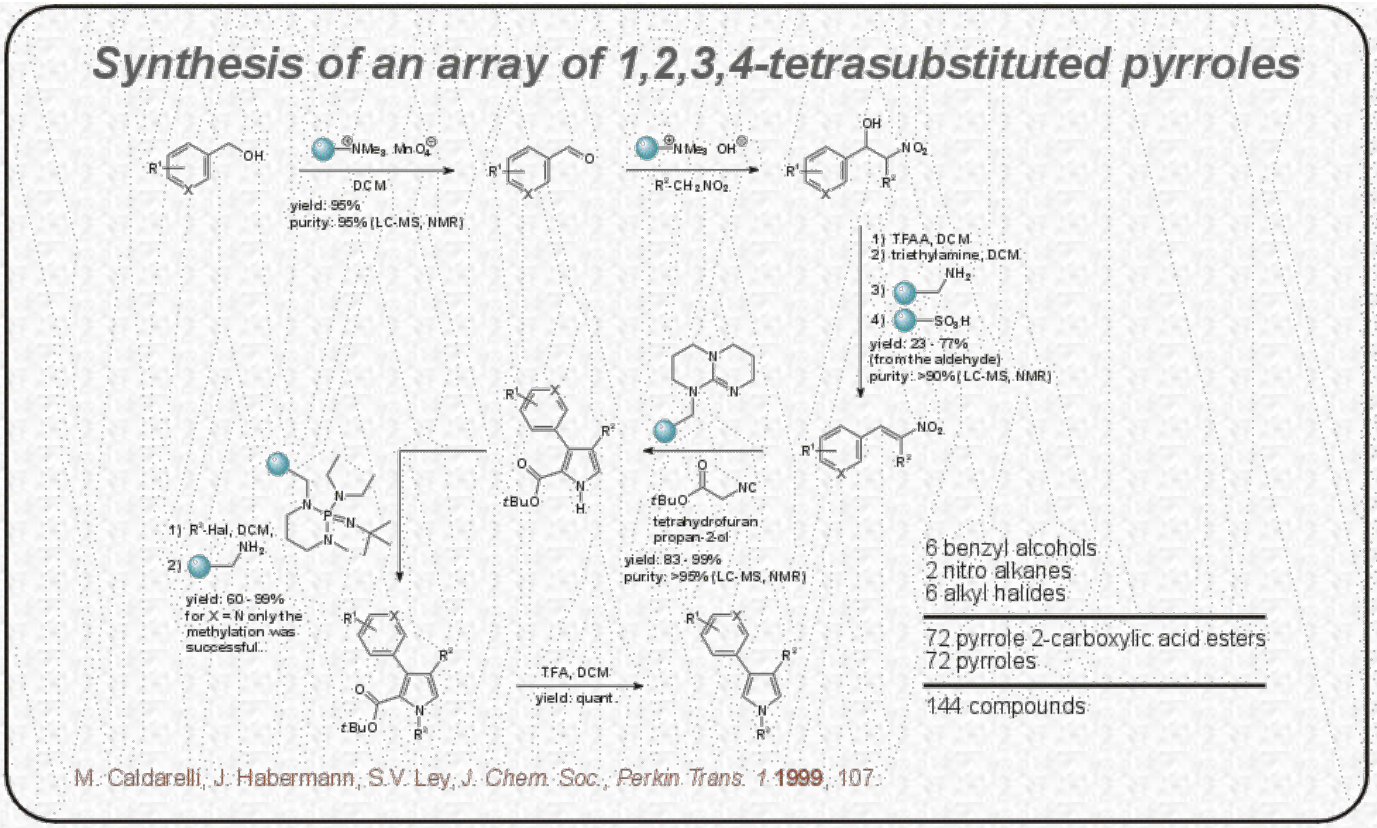
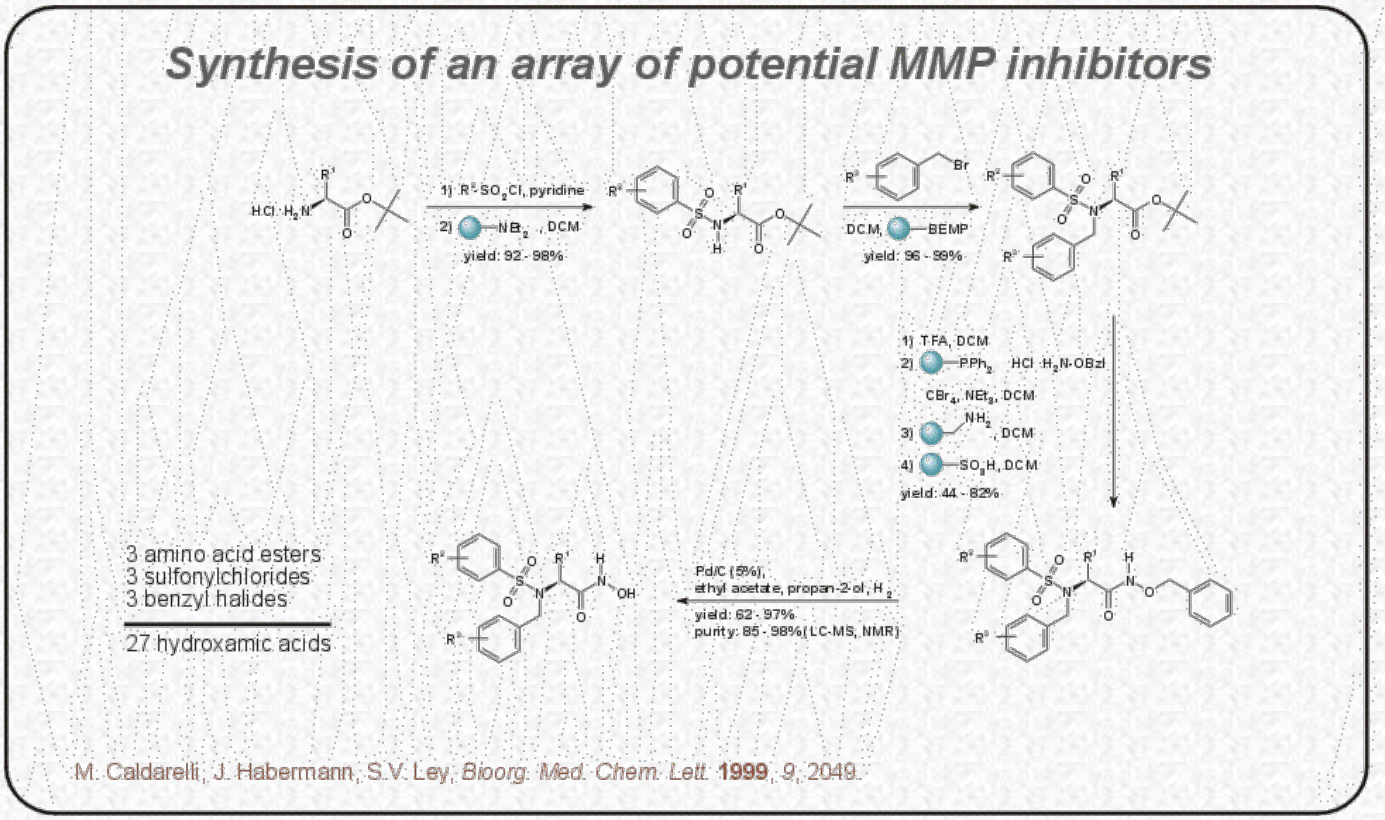
The growing speed of biological evaluation of potential drug substances during the past years has imposed the need to develop new methods for the fast and efficient generation of new chemical entities. In general, chemical libraries containing large numbers of compounds may be prepared either on polymer supports or in solution. The use of supported reagents combines the advantages of polymer-supported reactions (*e.g.* allowing the application of a large excess of the reagent without the need for additional purification steps) with the benefits of solution phase chemistry (*e.g.* the ease of monitoring the progress of the reaction by simply applying LC-MS or TLC techniques). While, many solid-supported reagents have been described, only a few have been used in combinatorial chemistry. Furthermore, multi-step sequences using polymer-supported reagents are rare, although there is a growing interest in sequestering agents on solid supports. Recent work in our group has focussed on the development of orchestrated multi-step methods using polymer-supported reagents for the preparation of chemical compound libraries.

Thiomorpholine and ***pyrrole*** analogues have found applications in medicine and agriculture. Therefore development of a simple, fast and flexible method to generate libraries of such compounds was desirable. We have designed a route to piperidino-thiomorpholines as potentially interesting scaffolds using a series of polymer-supported reagents. The first reaction steps have been carried out on a gramme-scale.

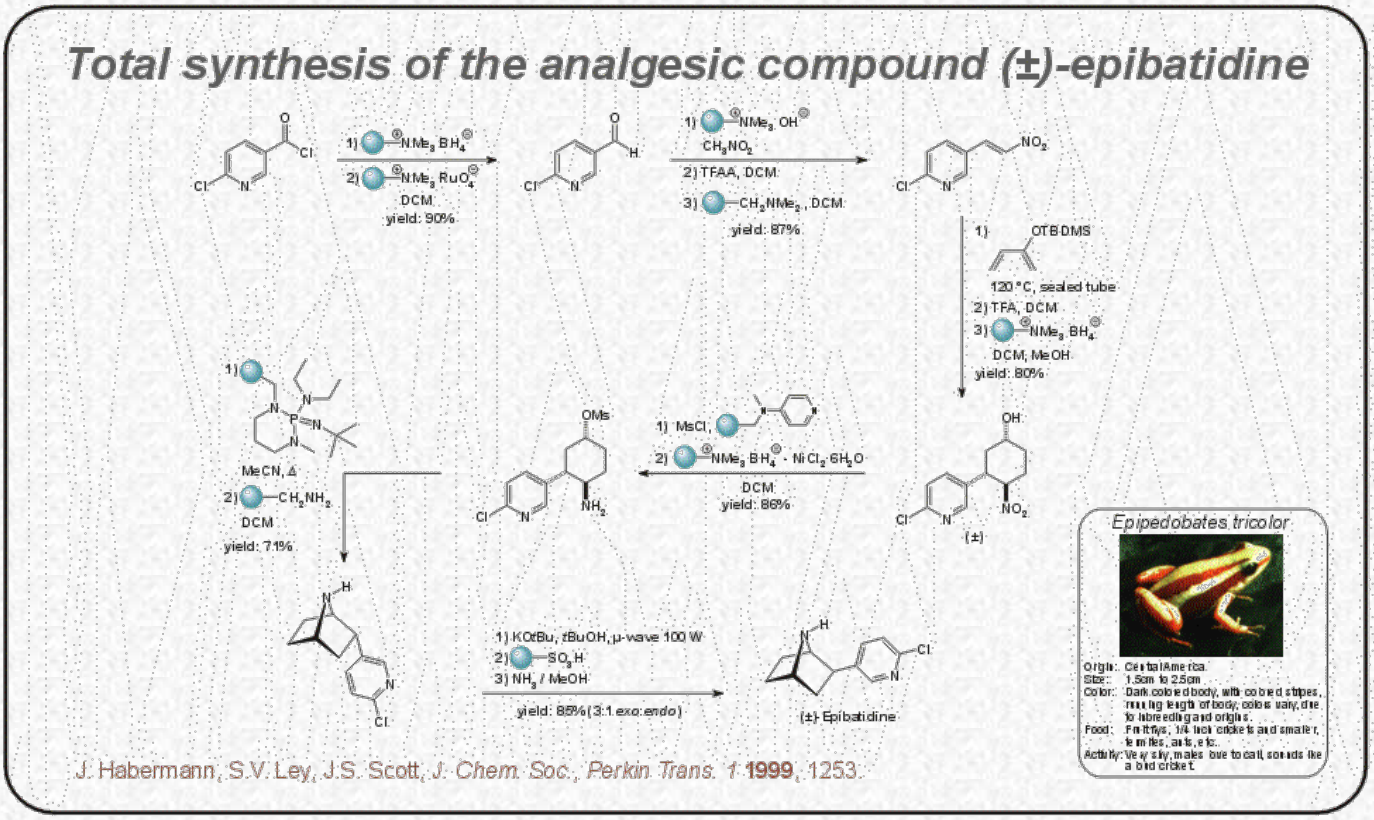




Hydroxamic acid derivatives exhibit a variety of pharmaceutical properties, of which their inhibitory effect on the matrix metalloproteinase (MMP) class of enzymes is probably the most important. These enzymes are mediators for the breakdown of structural proteins of the extracellular matrix. During the past years extensive synthesis programmes have focussed on the development of synthetic MMP inhibitors. Screening libraries revealed non-peptidic inhibitors leading to the development compound CGS-27023 A. Based on this structural knowledge we synthesised a set of analogues using polymer-supported reagents.

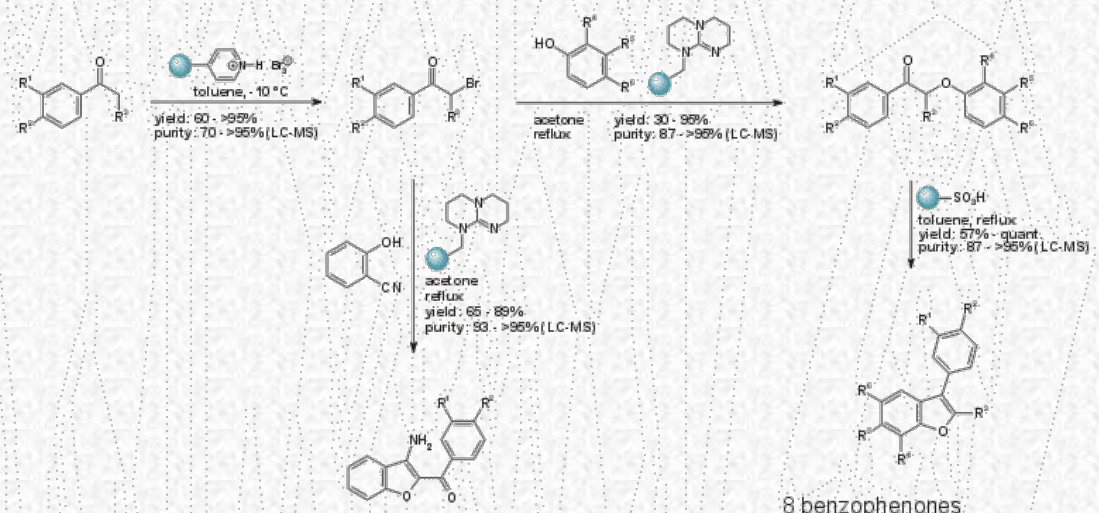


Polymer-supported reagents can be applied in the synthesis of ***natural products***. We were able to show this with the synthesis of (±)-epibatidine, a potent analgesic compound first isolated from the Ecuadorian poison frog *Epipedobates tricolor*. No chromatographic purifictaion steps are required to afford the product in >90% purity.



Halogenated or tosylated a ***-bromo ketones*** are valuable intermediates for the construction of different heterocycles which can be generated easily using a multi-step process employing polymer-supported reagents.

Synthesis of an array of benzofurans

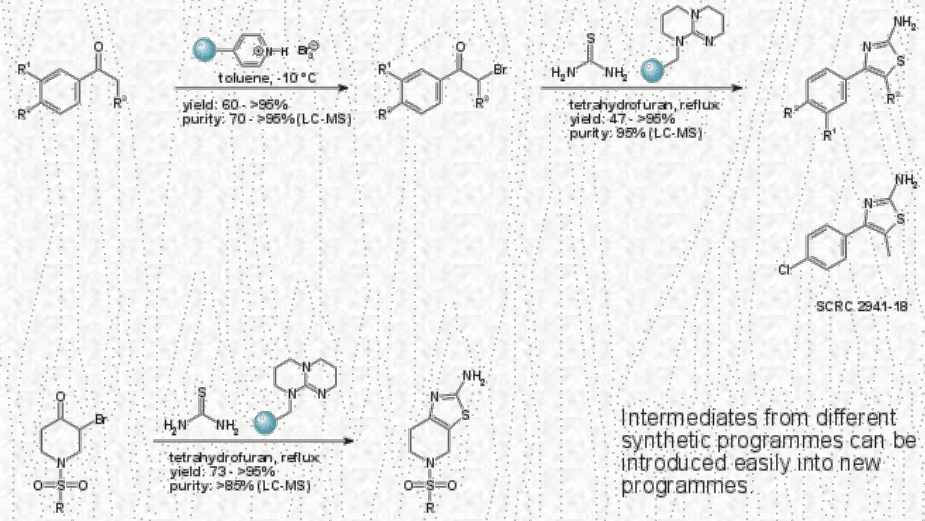


8 benzophenones
7 phenoles

25 benzofurans
(selected combinations)

J. Habermann, S.V. Ley, R. Smits, *J. Chem. Soc., Perkin Trans. 1* **1999**, 2421.

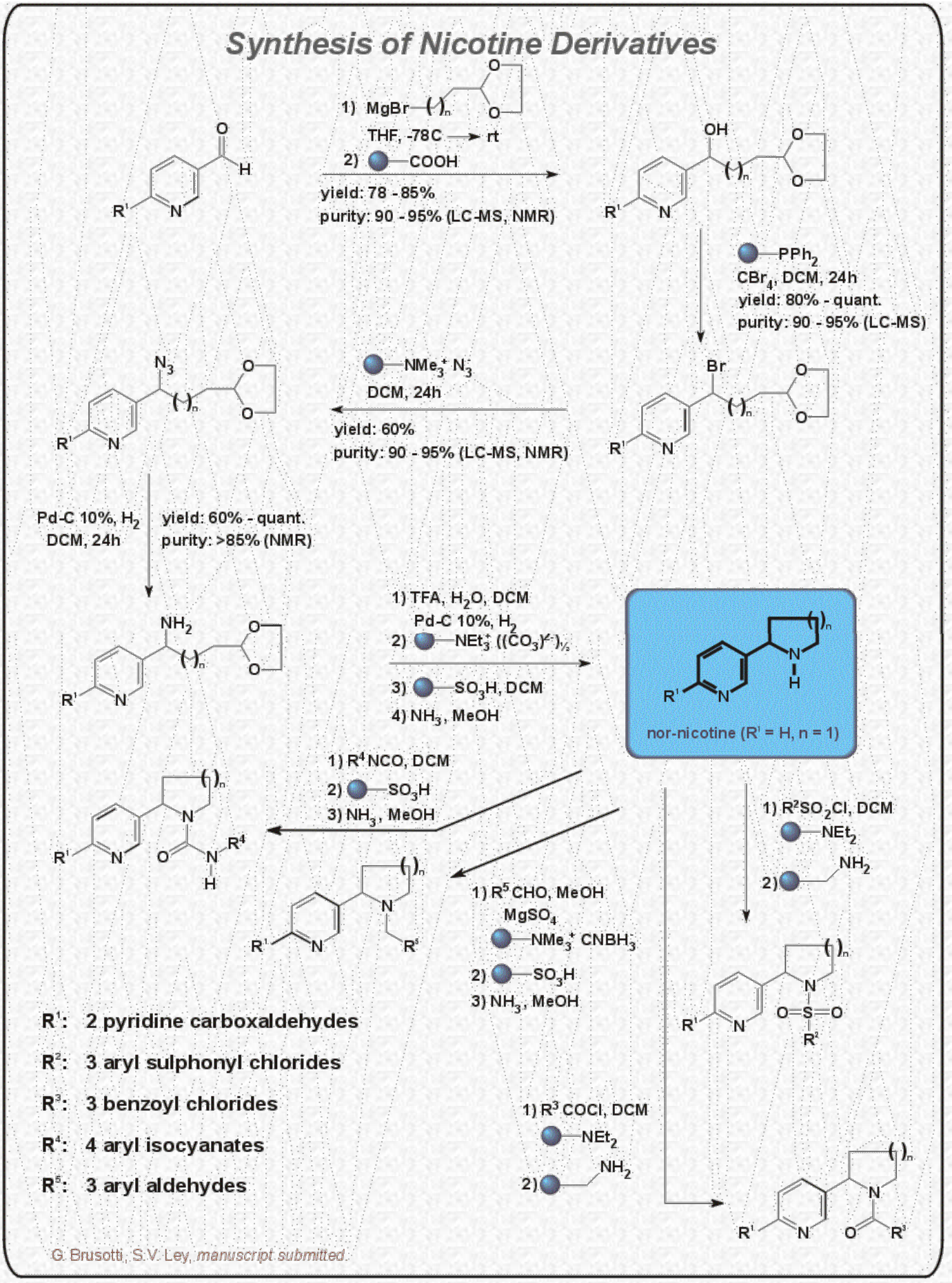
Synthesis of an array of amino-thiazoles



Intermediates from different synthetic programmes can be introduced easily into new programmes.

J. Habermann, S.V. Ley, J.J. Scicinski, J.S. Scott, R. Smits, A.W. Thomas, *J. Chem. Soc., Perkin Trans. 1* **1999**, 2425.

Polymer-supported reagents have found a further application in the synthesis of derivatives of ***nicotine***.



Conclusion: Polymer-supported reagents are ideally suited for combinatorial synthesis in solution. They allow the preparation of arrays and libraries in a mg- up to a

gramme-scale. No chromatographic purification was needed in the syntheses. The preparation of compounds using polymer-supported reagents benefits from a fast and easy reaction monitoring by NMR, TLC or LC-MS. In contrast to classical solid phase organic chemistry (SPOS), a minimum amount of time is required for the optimisation of reactions. Divergent coupling strategies are also possible. In principle, the number of reaction steps is unlimited when compared to SPOS. Reaction streams can readily be split and diverted to other combinatorial chemistry programmes. In addition, it is possible to include classical solution phase steps into a multi-step reaction sequence to enhance the versatility of the concept.

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