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# " Reagent Explosion " : an Efficient Method to Increase Library Size and Diversity.

**H.Bienaymé**

Rhône-Poulenc Technologies, C.R.I.T. BP 62, 69192 St-Fons Cedex, France

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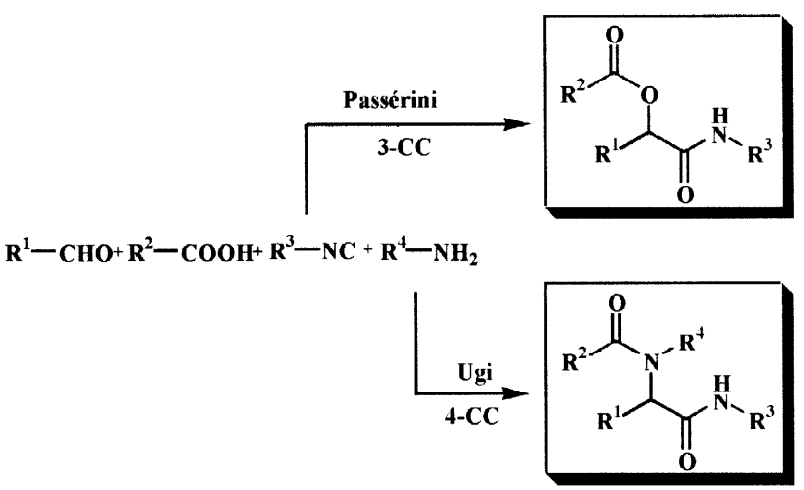
**Abstract :** Methyl-β-(N,N-dialkylamino)-α-isocyanoacrylates, readily prepared from the reaction between various secondary amines, N-formylimidazole diethylacetal and methyl isocyanoacetate, can be used to increase the diversity of the isonitrile input in multi-component condensation, such as the Passérini reaction. 

Multi-component condensations (M-CC), a former relatively confidential reaction class, have recently emerged as one of the most powerful tool for the generation of large collections of molecules (libraries) in combinatorial synthesis.[1] This renewed interest originates from the high convergence, and often relatively simple reaction protocol, of such chemical processes : starting from only 20 chemically distinct building blocks for each reactant, 8000 ($=20^3$) and 160000 ($=20^4$) adducts are theoretically accessible in one step using respectively a three and a four-component condensation. This is illustrated with the Ugi and Passérini M-CC which have recently found widespread use in high throughput synthesis (scheme 1).[2,3]




**Scheme 1**

However, to reach the kind of figure required for the generation of original « leads » ($10^3$ to $10^5$ molecules), each reactant class should be well represented (both in term of number and structural diversity). If this is true for amines, carboxylic acids and aldehydes, isonitriles however remain scarce, as only about 12-15 are commercially available, most of them being aliphatic.

Herein we report our investigation on the Passérini reaction, and our solution to provide structurally diverse isonitriles in a straightforward manner.

*e-mail : hugues.bienayme@rhone-poulenc.com

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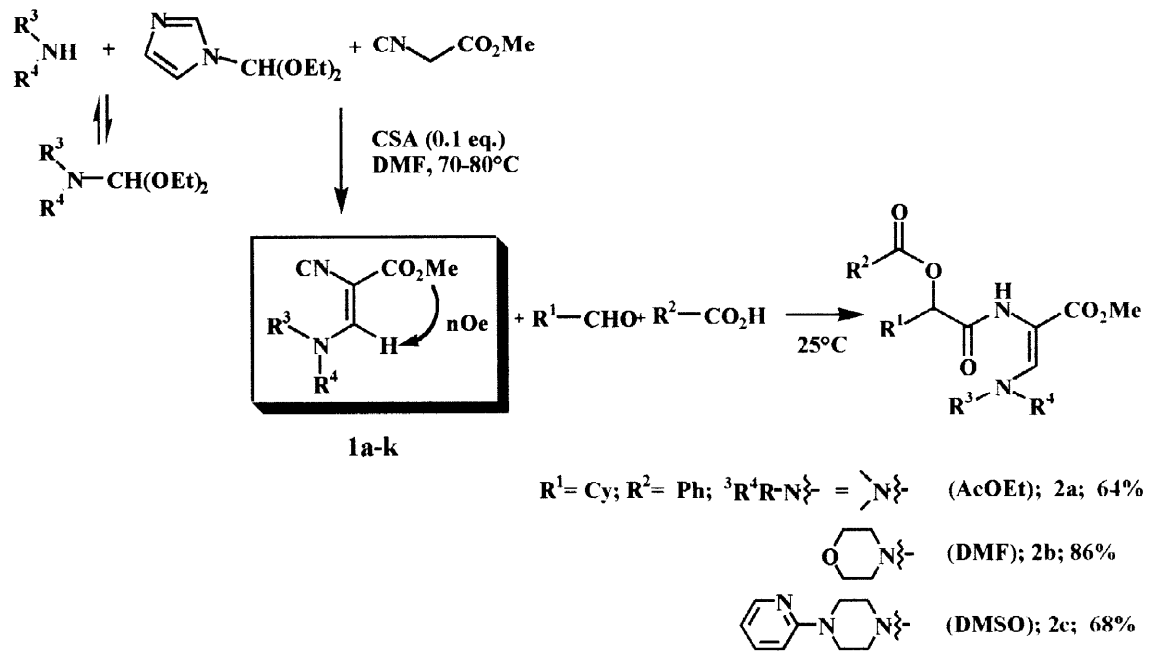
To circumvent the isonitrile paucity problem, while using the Passérini reaction, we employed a " reagent explosion » strategy: diversity and output of the M-CC is increased by prior functionalization of one of the reagent input.[4] Ideally, reagent diversification should be made as efficient as possible by introducing structurally diverse fragments in one step and should preferably not introduce an additional uncontrolled stereochemical element.

The commercially available methylisocyanoacetate, which not only possesses the required isonitrile function, but also an acidic nucleophilic carbon is an ideal substrate for further chemical diversification. The Bredereck-type condensation between active methylene compounds and N,N-dialkylformamide acetals was chosen for this purpose: reagent diversity would be introduced in the form of the well represented secondary amines and possibly in a single stereochemical form.

Although preparation of these new isonitriles is possible using N,N-dialkylformamide dimethylacetal, tedious and time-consuming preparation of these reagents would be required.[5]

For our high-throughput synthesis program we decided to explore a new and more efficient synthesis of the methyl-β-(N,N-dialkylamino)-α-isocyanoacrylate building blocks **1a-k**. This was accomplished by heating an equimolar mixture of a secondary amine, N-formylimidazole diethylacetal[6] and methylisocyanoacetate in DMF, in the presence of 10% camphosulphonic acid (CSA) as catalyst (scheme 2). Isonitriles **1a-k** were produced in variable yields but could be easily purified by aqueous extraction, filtration over silica and/or crystallisation (from methylene chloride / diethyl ether mixtures).

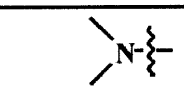
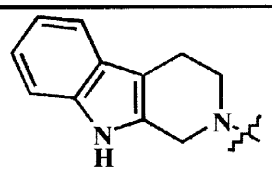
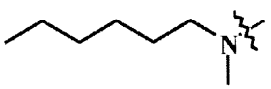
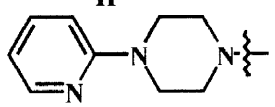
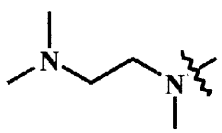
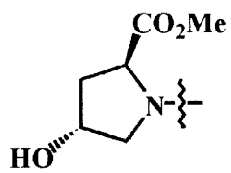
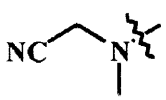
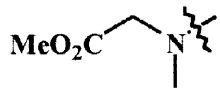
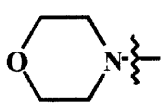
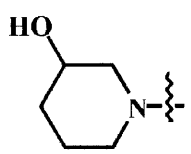
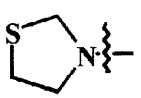
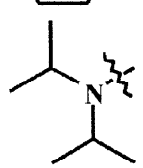
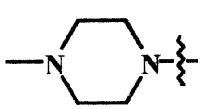
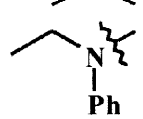
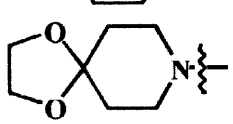
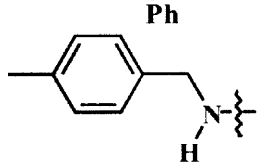
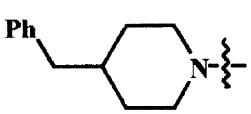



**Scheme 2**

Using this " rapid " version of the Bredereck reaction, 11 different isonitriles (10 of which are new, table 1) were readily prepared. Structurally diverse secondary amines were successfully introduced : aliphatic, heteroatom-containing, carbo- and heterocycle-containing (entries 1-11). However, anilines, ester- and alcohol-containing, as well as bulky secondary and primary amines were found either unreactive or decomposed under these conditions, setting some limitations to this diversification protocol (entries 12-17). . Mention should be made that these isonitriles were all single Z stereoisomers (stereochemistry assigned from $^1$H-NMR nOe's effect, see scheme 2), a behaviour which is likely due to steric reasons. This observation is of crucial importance as it will have a strong impact on the future library size and complexity.

Interestingly, this variation of the Bredereck reaction allowed us to transform a traditional two component reaction into a three component one, with possible control over three substitution points in one

step: the isonitrile ester function, the secondary amine and the acylimidazole acetal (the « reagent explosion » principle).

| Entry | $R^3R^4N$- | | Yield[a] (%) | Entry | $R^3R^4N$- | | Yield[a] (%) |
|---|---|---|---|---|---|---|---|
| 1 |  | 1a | 82 | 10 |  | 1j | 63 |
| 2 |  | 1b | 35 | 11 |  | 1k | 74 |
| 3 |  | 1c | 30 | 12 |  | | - |
| 4 |  | 1d | 33 | 13 |  | | - |
| 5 |  | 1e | 55 | 14 |  | | - |
| 6 |  | 1f | 33 | 15 |  | | - |
| 7 |  | 1g | 41 | 16 |  | | - |
| 8 |  | 1h | 58 | 17 |  | | - |
| 9 |  | 1i | 58 | | | | |

a) Isolated yields, products were characterised by all usual means.

**Table 1**

These new reagents were evaluated in the Passérini reaction. They all gave the corresponding adducts in high yields as exemplified in scheme 2. Interestingly, dipolar aprotic solvents such as DMF and DMSO were found superior in this reaction, whereas the commonly employed methanol was not suitable. Importantly, isocyanide stereochemistry was retained throughout this MCC, yielding again pure Z-isomeric adducts (racemic).

As both the Bredereck and the Passérini reaction were conducted in the same solvent, we envisioned the possibility to carry out these two steps in « one-pot », according to the principle of M-CC union.[7] This was accomplished by heating (80°C) for 30 min. a mixture of N-formyl diethylacetal (1.5 eq.), methyl isocyanoacetate (1.0 eq.), morpholine (1.0 eq.) and benzoic acid (1.5 eq.) in DMF, followed by cooling at 25°C and adding cyclohexane carboxaldehyde (2.0 eq.). Adduct **2b** was thus obtained in a fair crystallised yield of 30%. This solution, though very efficient, was not retained for our library production.

Finally, a 4620-members library was prepared in solution (DMF) from 20 different carboxylic acids, 21 aldehydes (mainly aliphatic and electron-deficient aromatic) and the former 11 isonitriles, and screened with some success in various biological assays.

In conclusion, we have shown that the " reagent explosion " strategy offers definitive advantage for the rapid construction of combinatorial libraries using M-CC, when one of the reagent input is not readily available or not diverse enough.

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7. See for instance : Dömling, A. ; Ugi, I. *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 563.