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Synthesis of Rigid Hydrophobic Tetrazoles Using an Ugi Multi-Component Heterocyclic Condensation

Hugues Bienaymé* and K. Bouzid

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

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Abstract: A highly convergent four-component, two-step, one-pot reaction between an aldehyde, a primary amine, an alkyl-β-(N,N-dimethylamino)-α-isocyanoacrylate and hydrazoic acid to form a substituted bicyclic tetrazole is disclosed. Vast arrays of small organic « drug-like » molecules can be combinatorially prepared with such transformation.

To reach the high throughput required for combinatorial library synthesis[1], the most popular strategy relies on solid-phase chemistry. This is not, however, devoid of drawbacks such as time and efforts needed for chemistry development, additional steps required for linkage and cleavage from the support, resins compatibility, just to mention a few. Two other strategies are possible, though both largely underestimated by today's standards : solution-phase chemistry using supported reagents, and multi-component reactions[2].

Multi-component reactions, which are best carried out in solution, join in one synthetic step three (or more) chemically distinct functions through covalent bonds. Because they combine two major principles in organic synthesis, convergence and atom economy, they were prone to be recognized and used in combinatorial chemistry. Well known Passérini and Ugi reactions are the most representative examples of such multicomponent transformations, and to date both have been used for the purpose of "new lead generation " (from either academic and industrial groups)[3].

Despite its enormous synthetic potential, the Ugi reaction is restricted in terms of structural diversity : peptidic molecules are obtained (Scheme 1). Bioavailability may also be a problem for such hydrophilic structures, and thus for many applications, (rigid) hydrophobic molecules libraries would be of greater value. The present account deals with our first efforts toward the discovery of efficient heterocyclic multi-component reactions.

Given its occurrence in various bio-active substances, the tetrazole ring was chosen as a starting point for further elaboration. From earlier work, it was known that tetrazoles could be obtained from hydrazoic acid, isonitriles, aldehydes and amines[4]. In this variation of the classical Ugi reaction, the tetrazole ring is formed upon sigmatropic rearrangement of the transient α-addition intermediate (scheme 1). This chemical platform was thought efficient enough to generate libraries in the 10,000 compounds range (4 components, 3 diversity points), consistent with our new lead generation program.

We were not however fully satisfied with the relatively flexible and basic nature of the final α-alkylaminotetrazole scaffold, and decided to manipulate its physico-chemical and geometrical characteristics by incorporating the secondary amino residue into an additional ring.

* Fax: +(33) 4 72 93 67 21; E-mail: hugues.bienayme@rhone-poulenc.com

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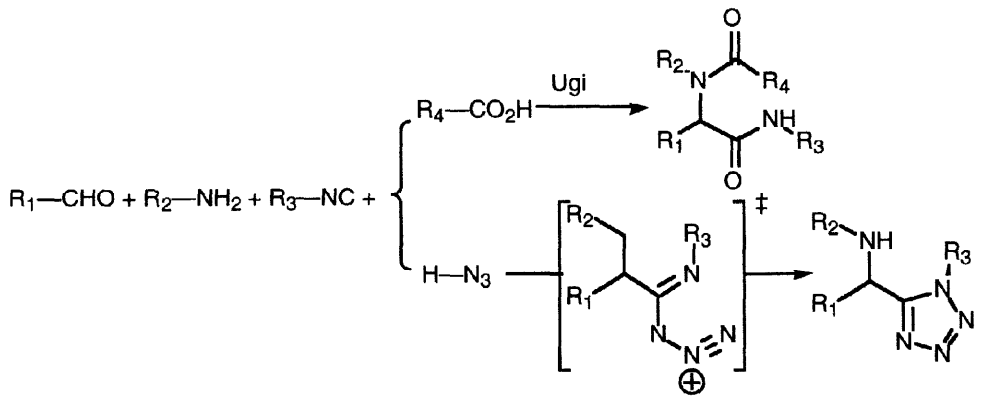
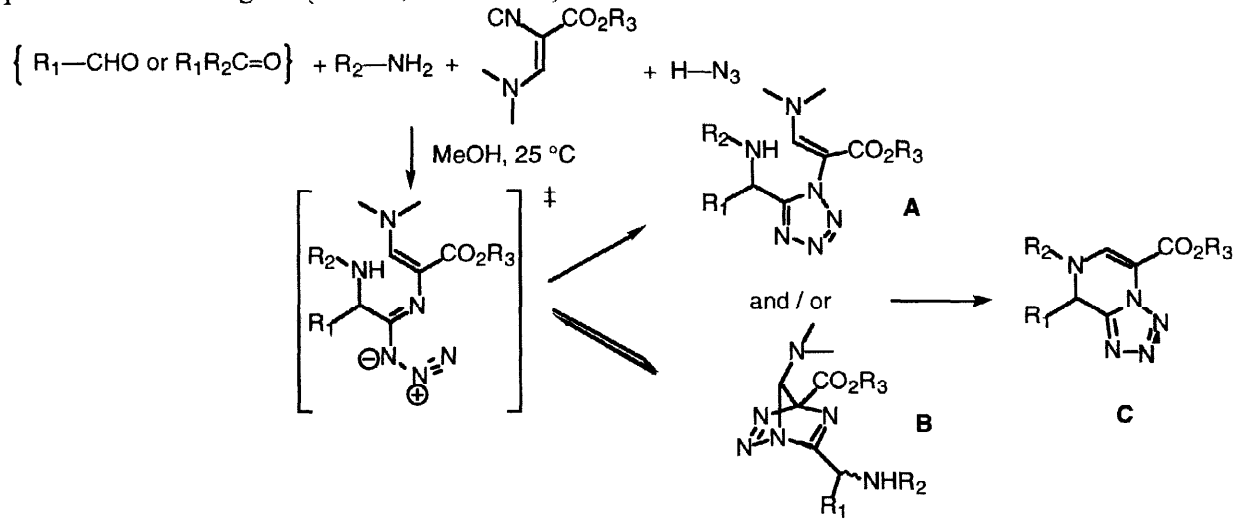


Scheme 1

To this end, readily available alkyl-β-(N,N-dimethylamino)-α-isocyanoacrylates[5] were prepared and evaluated in the four-component tetrazole synthesis. Simply mixing at room temperature (25 °C) molar methanolic solutions of an aldehyde, a primary amine, methyl-β-(N,N-methylamino)-α-isocyanoacrylate and trimethylsilyl azide (as a convenient source for hydrazoic acid in methanol[6]) in a ration 1/1/1/1.4 gave an intermediate adduct which could be either isolated or *in-situ* cyclized under diluted acidic conditions to the final stable bicyclic tetrazole **C**. Overall yields for this highly efficient process were fair to good (Table 1, entries 6-12).



Scheme 2

Interestingly, some discrepancies were observed when trying to analyze the first step intermediate : according to substituents, aza-norbornadiene structures **B** (resulting from an internal olefin/azide [3+2] cycloaddition) were sometimes isolated (alone or in equilibrium with tetrazole **A**). These diastereomeric mixtures, survived chromatography and were relatively stable at room temperature. However, upon treatment with diluted aqueous acids, they apparently reverted to the open-chain tetrazole **A** which finally cyclized to **C**. Bicyclic (racemic) adducts **C** were characterized by all usual criteria (^{1}H and ^{13}C-NMR, HRMS, IR).

As shown in Table 1, rearrangement and/or ring closure **A** or **B** → **C** is a high yielding (but slow) process (entries 2,3,5). Not surprisingly, the overall synthetic efficiency of this transformation is the reflect of the first multi-component lower yielding step (entries 1-5). In some cases, unwanted crystallization of intermediate **B** resulted in some material loss and apparent lower yields (entries 3,5).

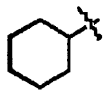
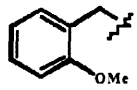
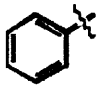
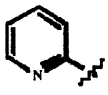
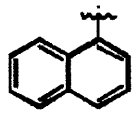
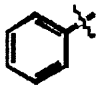
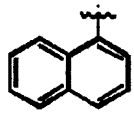
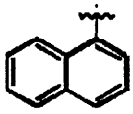
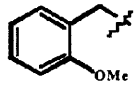
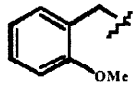
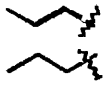
Entry	R1	R2	R3	Yield (A + B) Step 1 - %	Yield (C) Step 2 - %	Yield (C) Step 1+2 - %
1			Me	42	---	---
2			Me	68	100	---
3			Me	27 (cryst.)	100	---
4			Me	65	---	---
5			Me	46 (cryst.)	99	---
6			Me	---	---	81
7			Me	---	---	59
8			Me	---	---	46
9			Me	---	---	48
10			Me	---	---	46
11			Me	---	---	29
12			Me	---	---	72

Table 1

The combinatorial value of such reactions is of course directly linked to its scope and generality. It can be seen that diverse and chemically distinct reactants are tolerated : aliphatic, aromatic and heteroaromatic aldehydes. Even ketones do react, though the more sterically encumbered ones can be borderline (entry 11). Both aliphatic and aromatic amines are also good partners.

Yields reported in the Table refer to isolated, purified compounds. This may be of concern for combinatorial purposes as this reaction was intended to be carried out in solution and the products screened without resorting to tedious chromatographic purification. However, we have found that bicyclic tetrazoles **C** are neutral species in the crude reaction mixtures (pH < 1) and that a simple extractive high throughput protocol was successful for eliminating other nitrogen-containing by-products : purities obtained upon partitioning between methylene chloride and dilute hydrochloric acid

or water (when additional basic sites are present on the side chains) were judged sufficient for our screening purposes (usually > 80%).

In conclusion, we have exemplified that multicomponent reactions are precious tools for the rapid construction of chemical libraries. Our main objective was to find a new synthetic protocol to prepare hydrophobic heterocyclic molecules around a rigid template. Of special significance for solution phase combinatorial chemistry, simple reaction and purification protocols were designed. Using this chemistry, we have been successful in synthesizing diverse libraries. Further work is being carried out to find new highly efficient heterocyclic multi-component reactions.

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6. An alcoholic solvent is not only necessary for the *in situ* desylilation of trimethylsilylazide, but is also advantageous for the four-component reaction.