Old dog new tricks in the antibiotic toolbox: β-lactam synthesis through diodomethane addition onto amide dianions.

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Abstract: We propose a novel route for the quick and easy synthesis of a broad range of β-lactams. The synthesis involves a [3+1] cyclization of amide dianions with diiodomethane. In opposition to the seminal work of Hirai et al, the reaction proved to be a general and efficient approach towards azetidinones. The easiness of the process was confirmed by DFT calculations and its power demonstrated by a diversity oriented synthesis of β-lactams with 4 point of diversity brought by the choice of Ugi adducts as starting materials.

Since the discovery of penicillin and the demonstration of its efficiency as antibiotics agents,[1] the attention of the chemist community has been focused on the family of β-lactams.[2] This interest was further confirmed by the discovery of further classes of highly active monocyclic and bicyclic derivatives (Figure 1). At the turn of the 70s, growing resistance associated to β-lactamase triggered hydrolysis, seemed to limit the future developments of β-lactams, a situation further aggravated by the emergence of multidrug-resistant strains in the last 20 years .[3] However, against all expectations, we are assisting to a rebirth of β-lactams in pharma activities. Indeed, slower disclosure of new families of antibiotics together with general resistance for all classes of antibiotics led to reexamine the interest of β-lactams in association with β-lactamase inhibitors.[4] This renewal of β-lactam antibiotics is now urging chemists to propose innovative syntheses combining both efficiency and diversity.

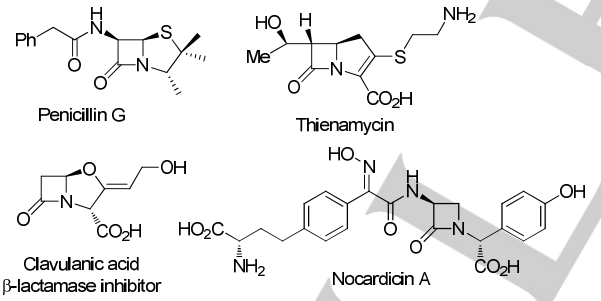
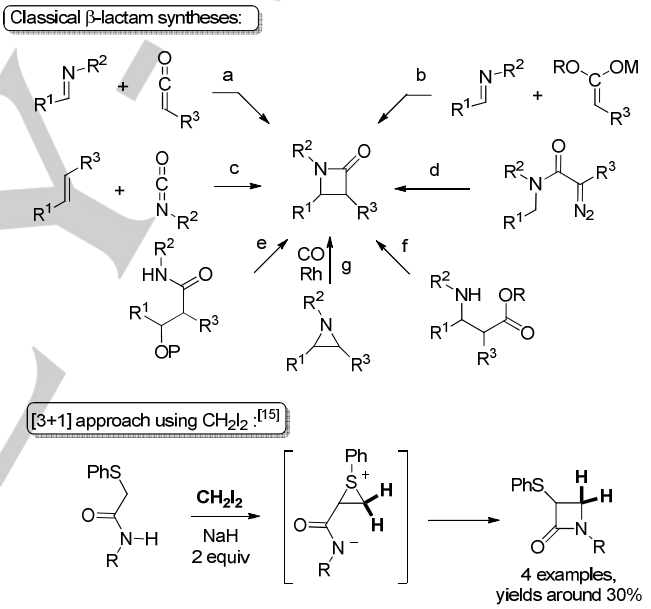


Figure 1. Examples of β-lactam antibiotics and β-lactamase inhibitors.

Since the first synthesis of Staundinger in 1907,[5] many different methods are available for the construction of the β-lactam core (scheme 1). [6] Among these, [3+1] strategies such as CO insertion certainly represent the least explored approaches.[7] We were particularly puzzled by a seminal report by Hirai et al in 1979 using diiodomethane acting as a double electrophile towards thiophenylamide dianions.[8] A three-steps mechanism involving an episulfenium ion was proposed (Scheme 1). Albeit an amazingly simple procedure, low reported yields and narrow scope have prevented chemists to use the method. Herein, we demonstrate that the reaction can be transformed into a general and efficient access to β-lactams without requiring any sulfur substituent.



Scheme 1. Strategies for β-lactam preparation.

CH_2I_2 may react with two equivalents of nucleophiles as early reported by Wislicenus who treated ethyl benzoylacetate with sodium ethanolate and CH_2I_2 in ethanol.[9] Beside the work of Hirai, the sole reported addition onto amide NH derivatives was performed on derivatives **1** and led only to **2** [10] which probably explain the low yields observed in Hirai's study (Scheme 2). Indeed, double intermolecular additions became the main synthetic pathway when trying to perform the reaction in more concentrated medium.[8]

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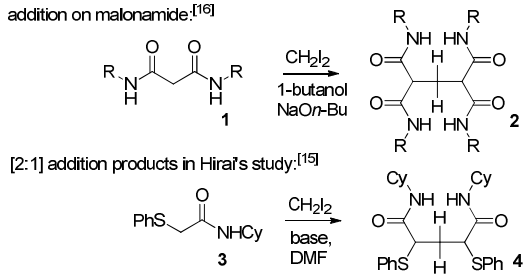
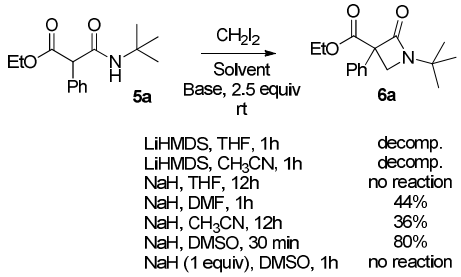


Scheme 2. CH_2I_2 addition to malonyl derivatives and ketoesters.

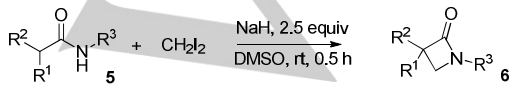
Considering these previous elements, we decided to prepare the *NH-tert*-butyl malonamide **5a** as a platform to test our envisioned β-lactam formation. While preventing elimination processes toward methylene intermediates, the phenyl substituent was expected to afford an easier access to dianionic intermediates and faster cyclizations. The amide was obtained in 65% yield heating the related malonyl diester with one equivalent of *t*-butyl amine under microwave conditions. Strong bases (2.5 equiv) were then added to **5a** in various solvents followed by the addition of 1.5 equivalent of diiodomethane.

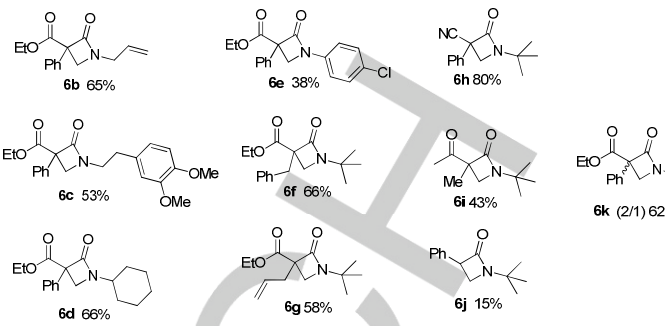


Scheme 3. β-lactam formation from amide **5a**.

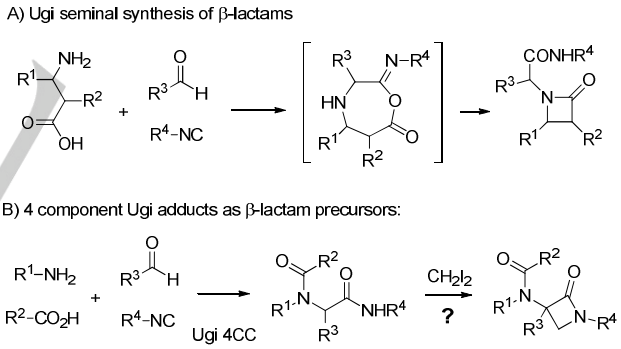
Whereas LiHMDS and KHMDS failed to give the expected β-lactam at room temperature in both acetonitrile and THF, we were delighted to observe the formation of the expected **6a** when the reaction was performed with sodium hydride at room temperature. The highest 80% yield was obtained choosing DMSO as solvent (Scheme 3). When the same reaction was attempted with only one equivalent of base the starting material was recovered unchanged after one hour. The lack of any coupling under these conditions praises for the formation of more nucleophilic dianionic species when two equivalents of base are used. The former optimized conditions were selected for the preparation of β-lactams **6** from a set of different NH-amides **5** (Table 1).

Table 1. β-lactam formation from amides **5**



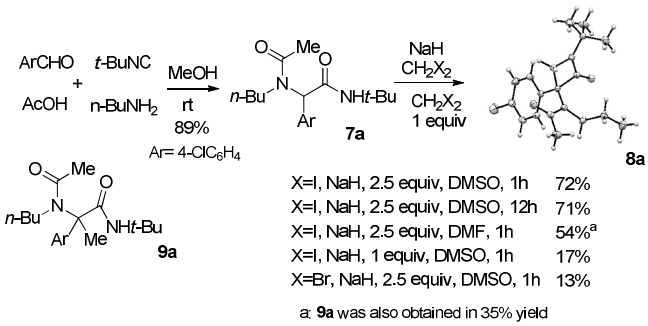


In order to attract the attention of medicinal chemists, this synthetic method still needs to increase its scope as many biological relevant β-lactams display an amino functionality at the 3 position (Figure 1, nocardicin A for instance). Moreover, regardless of the substitution patterns, modern drug design now focuses on syntheses allowing important structural diversity. In line with these requirements, diversity oriented synthesis of β-lactams have been the object of intense research efforts and multicomponent accesses to these scaffolds are highly desirable.[11] One of the seminal works in this direction was disclosed by Ugi forming β-lactams from β-aminoacids (Scheme 4A)).[12] Attracted by the straightforward four component preparation of potential precursors, we envisioned that Ugi adducts could be alkylated at their peptidyl position under basic treatment with diiodomethane and converted into β-lactams (Scheme 4B).



Scheme 4. En route to β–lactams with Ugi.

Thus, Ugi adducts **7a** was prepared in 89% yield under standard Ugi reaction conditions (MeOH, rt) and submitted to conditions close to ones optimised for our previous β-lactam formation. To our delight, we could observe the formation of the expected β-lactam **8a** in a 72% isolated yield under treatment with 2.5 equiv of sodium hydride in DMSO (Scheme 5). A single crystal X-ray analysis further confirmed its structure.[13]

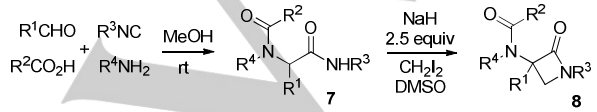


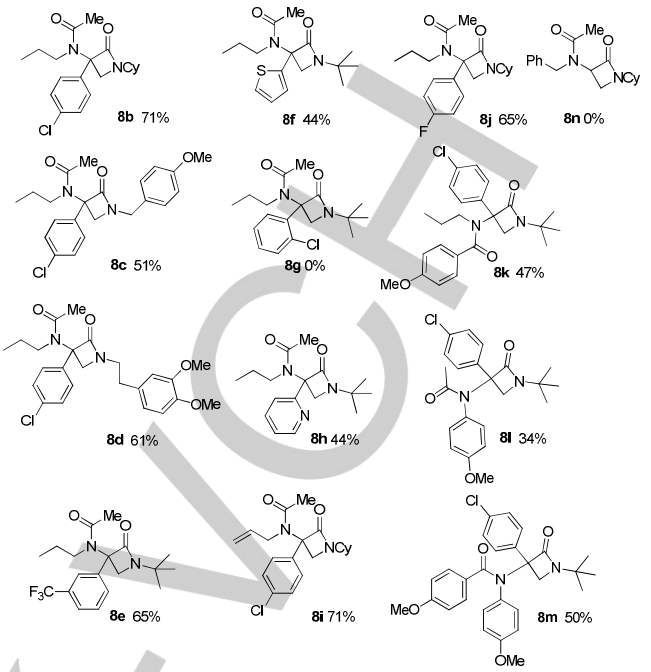
Scheme 6. β-lactam **8a** from Ugi adduct **7a**.

The results obtained with **7a** are particularly remarkable. Even though the ability to deprotonate the peptidyl position of Ugi adducts has been explored in various intramolecular trappings, the potential of intermolecular reactions with electrophiles at the peptidyl position suffers from the high steric hindrance of the site.[14] In our case, the formation of highly nuclephilic dianionic species certainly allows to overcome these difficulties. In agreement with this and similarly to what was observed for malonamide derivatives, a sluggish reaction occurs when **7a** was only treated with 1 equiv of NaH affording **8a** in only 17% yield. Diiodomethane seems to be much superior to dibromomethane in forming the β-lactams as shown by the low 13% yield of **8a** obtained when the reaction was conducted with the latter. The isolation of **9a** when performing the reaction in DMF demonstrates the existence of a competing reductive process which further explains the failure of Hirai's work to impose itself as a useful method in β-lactam synthesis as both starting materials and solvent proposed were leading to reduced yields. Such reduction may probably be explained by electron transfer processes associated to the use of strong bases in DMF.[15]

Various Ugi adducts **7** were then prepared and submitted to the NaH/DMSO optimised conditions to afford the β-lactams **8** displayed in Table 2. All Ugi adducts obtained from aromatic aldehydes gave lactams in good to moderate yields except for aryl moieties possessing substituents at the *ortho* position such as (**7g**) which failed to give any reaction with CH_2I_2. Regarding the isocyanide moiety, best yields of β-lactams were obtained when *tert*-butyl isocyanide was selected in the Ugi step, a trend that comforts the observations made with malonamide derivatives (Table 1). Less acidic Ugi adducts obtained using non aromatic aldehydes are not expected to be partners in the sequence as shown by the lack of reaction of the formaldehyde adduct (**7n**).

Table 2. Ugi based 4-component library of β-lactams





The results obtained in these two sets of starting materials are indicative of the mechanism and intermediates involved. The recovery of unchanged **3a** and the low yield of **8a** under treatment with one equivalent of NaH at room temperature are consistent with the formation of a reactive dianionic intermediate upon addition of 2.5 equivalents of base. To give a better insight into the mechanism of the reaction, a DFT study of a Ugi adduct /diiodomethane/dimsyl anion was performed in DMSO (modelled as a polarizable continuum).[16] Ugi adduct **10** (resulting from an hypothetic Ugi reaction of methylisocyanide with methylamine, acetic acid and benzaldehyde) was selected as a model compounds. Our calculation show that the formation of the dianion in DMSO followed by the complexation with CH_2I_2 in a solvent cage (Fig 2-b) is overall a facile process. Interestingly, the requirement of a relatively planar structure for the dianionic intermediate is certainly associated with the lack of reactivity observed for Ugi adducts possessing substitutents which does not allow to reach easily this geometry (eg **7g**, Table 2). Due to the low energy barriers for the following steps, the model just indicates a slight preference for an initial alkylation at the carbon position. This selectivity is further comforted by the known reactivity of amide dianions with C-based electrophiles.[17] Thus the most probable mechanistic pathway is presented in figure 2. The dianion reacts with CH_2I_2 to yield an intermediate iodomethyl Ugi adduct (Fig. 2-d) which in turn undergoes an internal cyclization reaction to form the final β-lactam ring (Fig.2-f). Both addition and cyclization steps are characterized by very low barriers ($\{\Delta E^{\ddagger}_{b\to c}, \Delta E^{\ddagger}_{d\to e}\}$ <10 kcal/mol) and a high exothermicity. Due to the electron rich nature of the proposed dianionic species and the choice of a solvent prone to trigger $S_{RN}1$ processes, radical intermediates involving electron transfer in a chain reaction process should also be considered.[18]

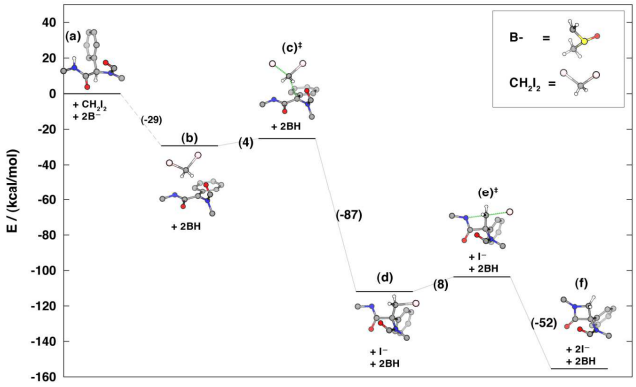


Figure 2: Simplified potential energy surface for β-lactam formation from **10**

As a conclusion, we have showcased the power of amide dianions by a [3+1] addition process with CH_2I_2 leading to β-lactams. Though this strategy was first described by Hirai et al in 1979, this seminal work was not followed by any other study on the topic probably due the low reported yields together with the highly focused structures of the starting materials (need of a thiophenyl substituant). Reasoning on the potential pitfalls of the reaction allowed us to raise both scope an efficiency transforming the process into a promising β-lactam synthesis. The simplicity of the protocol together with the multicomponent versions of the reaction will certainly stimulate medicinal chemists to explore more thoroughly this forgotten strategy. We are further extending this work to more diverse families of amide dianions as well as diastereoselective and enantioselective versions of the [3+1] addition.

Acknowledgements and dedication

We dedicate this work to our Colleague Mohammed Ali Hassan who passed away few months before the end of this study. We thank the Egyptian gouvernment for the fellowship of Alaa Zidan.

Keywords: keyword 1 • keyword 2 • keyword 3 • keyword 4 • keyword 5

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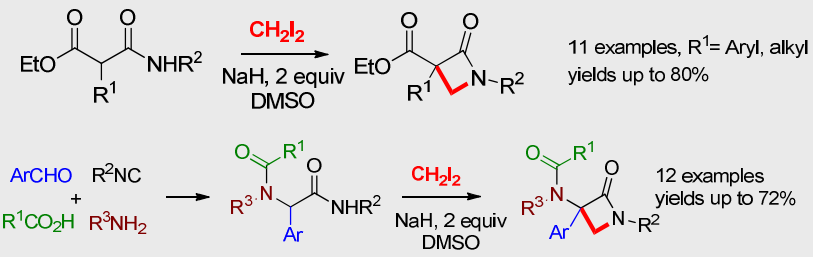

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