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Solution Phase Library of Perhydrooxazin-4-ones.

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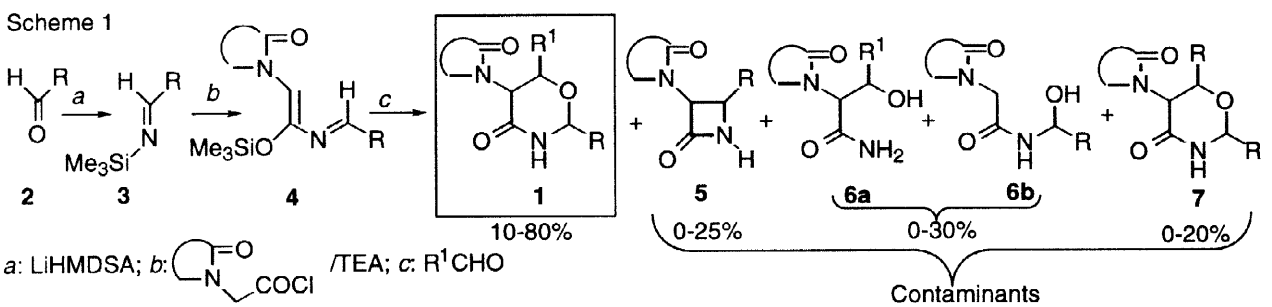
Abstract

A general approach to the solution phase parallel synthesis of perhydrooxazin-4-ones, which allows the preparation of milligram quantities of each individual member, is reported. An efficient purification method, using as "Sequestration Enabling Reagent" (SER) aminomethylpolystyrene resin in the presence of trimethylorthoformate is also described.

Keywords: Diels-Alder Reactions, Combinatorial Chemistry, Oxazines, Azadienes, Silylimines.

The use of combinatorial libraries for the identification of novel chemical leads or for the optimisation of promising lead candidates has emerged as a powerful method for the acceleration of the drug discovery process [1, 5]. Such libraries were usually prepared by solid-phase techniques, although solution-phase chemistry is a viable option for short synthetic sequences [6, 7]. Here we report one such example: the construction of a parallel perhydrooxazin-4-ones library based on a hetero Diels-Alder type of reaction producing six-membered cyclic compounds starting from aldehydes [8] (Scheme 1).

Scheme 1



The template **1**, which is representative of a set of oxazin-4-ones that have been examined, consists of a densely functionalized core. The added pendant groups provide the molecular diversity in the library's components. The elements of such a library can display biological activity *per se* or may be elaborated into different biological targets *e.g.* α-amino-β-hydroxy-acids (see below). Classical conditions for this reaction (low temperature, inert gas atmosphere, final flash chromatography of the target) are unusual, to our knowledge, in the solution-phase strategy. Therefore we tested the suitability of the conditions for parallel reactions paying particular attention to the identification of side products (Scheme 1). One of the major contaminants is the β-lactam ring arising from an intramolecular Staudinger-type cyclization [9, 10] *versus* intermolecular Diels-Alder reaction. In order to minimise the

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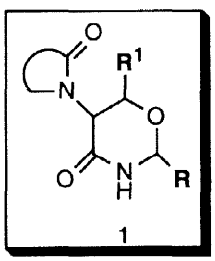
Staudinger-type side reaction a slight excess of dienophilic aldehyde was used. This excess was removed by the SER technique [11] using, as trapping agent, the aminomethylpolystyrene resin. In a blank experiment no decomposition of the target compound, submitted to the trapping conditions of excess-aldehyde, was observed. Table 1 reports the results obtained. The set of reactions performed has been classified into three major groups: **G**, **S** and **U** depending on the yield and purity of the target [**G** (good): yield and purity from 60 up to 80%; **S** (satisfactory): yield and purity from 40 to 60%; **U** (unsatisfactory): yield and purity from 0 to 40%]. It must be stressed that no optimisation studies have been performed.

Table 1: Set of Oxazin-4-ones 1 prepared.

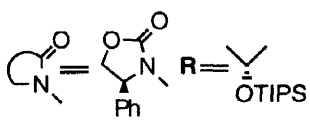
Entry	Oxazin-2-ones **1** (%)	β-lactam **5** (%)	amides **6a, 6b** (%)	bis adduct **7** (%)	Purity class
A 1	80	traces	traces	-	**G**
A 2	65	5	5	-	**G**
A 3	55	5	15	-	**S**
A 4	40	10	30	-	**U**
A 5	65	30	traces	-	**G**
A 6	50	10	30	-	**S**
A 7	55	10	25	-	**S**
A 8	30	5	15	-	**U**
A 9	70	5	15	-	**G**
A 10	60	10	25	-	**G**
B 1	35	15	10	0	**U**
B 2	60	5	5	15	**G**
B 3	35	10	20	10	**U**
B 4	70	15	10	0	**G**
B 5	45	20	25	10	**S**
B 6	50	20	5	20	**S**
B 7	60	15	20	traces	**G**
B 8	80	traces	traces	15	**G**
B 9	45	traces	35	15	**S**
B 10	30	10	30	15	**U**
C 1	70	10	10	traces	**G**
C 6	10	25	25	20	**U**
C 7	15	30	30	10	**U**
C 9	50	25	20	traces	**S**

Identification keys for Table 1

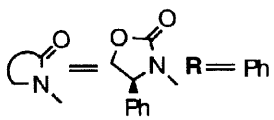


R^1= **1**, Me; **2**, *i*-Pr; **3**, Cyclohexyl; **4**, Ph; **5**, 2-Naphthyl; **6**, 4-OMe-Phenyl; **7**, 4-Nitrophenyl; **8**, 3-Pyridyl; **9**, 2-Furyl; **10**, 2-Thienyl.

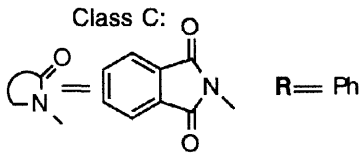
Class **A**:



Class B:



Class C:

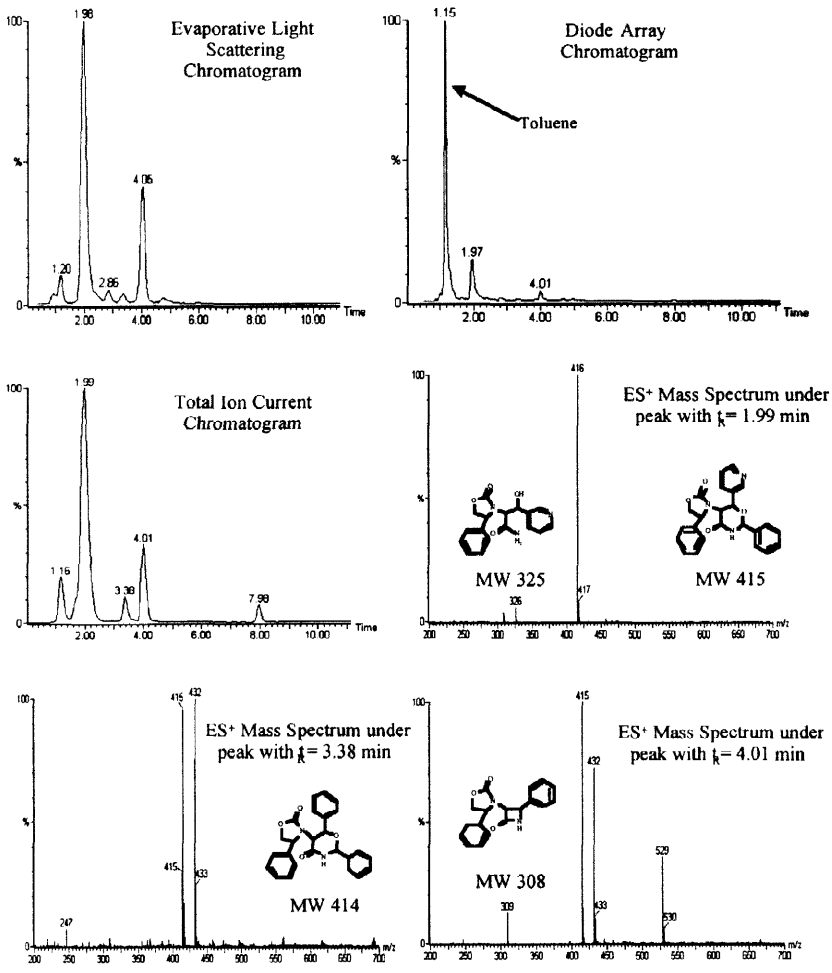


Analytical characterization:

HPLC analysis revealed material of high to satisfactory purity and LC-MS confirmed that in most cases the principal component had a molecular ion corresponding to the appropriate perhydrooxazin-4-one and showed fragmentation peaks compatible with the assigned structures. In some cases (purity group **G**) the library components were unambiguously characterised by ^{1}H NMR spectra which were superimposable with those obtained by classical

organic methodology [12]. For the scope of this preliminary paper no studies were performed on the stereochemical ratio of diastereomeric mixtures. The impurities were all identified and, as discussed above, were essentially constituted by the β-lactam ring **5**, by the open-amides **6a** and **6b**, arising from traces of moisture (Scheme 1), and by the bis-adduct **7** (only when PhCHO was used for the preparation of silylimine **3**).
As a typical example, the full characterization of compound **B8** is provided (HPLC/ELS/DAD/MS detection, MS spectra of individual peaks) in Fig. 1.

Fig. 1



General procedure for the preparation of perhydro-1,3-oxazin-4-ones
The azadiene **4** was prepared from acyl chloride **8** (2.88 mmol) and the silylimine **3** (2.4 mmol) according to the published procedure [8]. The clear residue thus obtained was dissolved in dry dichloromethane (12 mL) and 1 mL (0.2 mmol) was distributed to ten vials (5 mL), equipped with a rubber septum and a stirring bar, under nitrogen. The vials were cooled to -78 °C and ten different aldehydes (0.22 mmol), dissolved in dry DCM (0.2 mL), were added dropwise immediately followed by a solution of $BF_3.Et_2O$ (0.025 mL, 0.2 mmol/vial) in dry dichloromethane (1 mL). The mixture was stirred at -78 °C for 3 h then slowly warmed to rt and stirred overnight.

Parallel purification:
The crude products, diluted to 4 mL with DCM, were poured into ten manifold supported polypropylene syringes (15 mL) equipped with a bottom frit and a stopcock. Extraction with sat. $NaHCO_3$ aqueous solution (2x4 mL) and brine (6 mL) gave an organic phase which was dried ($MgSO_4$) by vigorously shaking the resulting suspension for 5 min. After filtration, solvents and volatiles were removed using a vacuum centrifuge. The crude products dissolved in dry THF/trimethylorthoformate (TMOF) 1/1 (1 mL) were purified from unreacted aldehydes using an aminomethylated polystyrene resin (AM resin; 200-400 mesh; 1.2 mmol/g; Novabiochem; 167 mg; 0.2 mmol). After shaking overnight, the resin was filtered and washed with THF and DCM (2 x 1 mL). The organic solutions were evaporated to dryness in a vacuum centrifuge.

While the library described above is only of small size, its purpose is purely illustrative. The range of side chains included in the perhydrooxazinone core for this small library demonstrates the versatility and scope of this procedure. Given the range of aldehydes used, one can readily visualize a diverse range of potential library substrates and products. Finally we are currently involved in adding versatility to our perhydrooxazinones combinatorial library through its elaboration, according to a published procedure [8], to an α-amino-β-hydroxy acid library.

The practical ease with which 1,3-perhydrooxazinone libraries can be prepared is worth stressing. The majority of reported combinatorial library syntheses involves solid supported methodologies that require specialised techniques, equipments and financial investments with which academic and industrial chemists may be unfamiliar. In contrast, the use of the solution phase library synthesis described herein would require little specialised knowledge.

The use of known procedures would also allow to switch this synthetic strategy to a solid support by use of resin bound Evan's oxazolidinones [14, 15], thus opening the route to larger and more diverse perhydrooxazinone libraries. Further efforts in this area are currently ongoing.

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