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Solid-phase synthesis of 2,3,5-trisubstituted 4*H*-imidazolones

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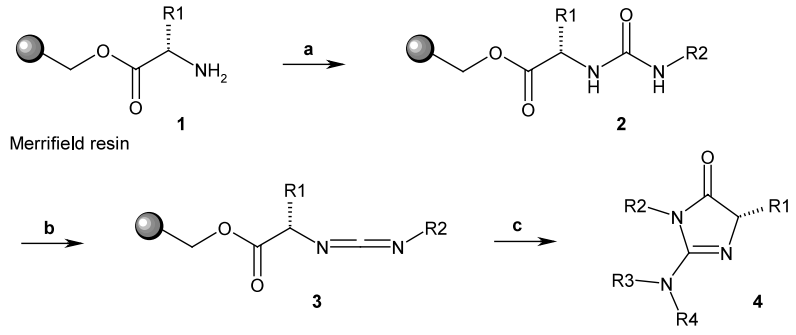
Abstract—The first solid-phase synthesis of 2,3,5-trisubstituted 4*H*-imidazolones suitable for automation using the dehydration of a urea as the key-step is described. The novel method is compared with other reported procedures. Furthermore, the formation of imidazolone diastereoisomers containing a chiral *C*,*N*-axis is discussed.

Imidazolones have received considerable attention over the last few years due to their interesting biological activities. Some imidazolones exhibited promising pharmacological activities,[1] others have been applied successfully in crop protection.[2] Hence these heterocycles, in particular 2,3,5-trisubstituted 4*H*-imidazolones, have become an attractive target for combinatorial chemistry groups involved in drug discovery and crop protection. Several approaches to access this class of compounds via solution or solid-phase synthesis have been reported.[3] In most solid-phase approaches the imidazolone ring is formed by an intramolecular nucleophilic attack of a guanidine moiety onto an ester or amide carbonyl. The guanidine is generated from an amine and a resin bound carbodiimide. This intermediate is either obtained from a thiourea moiety by formal extrusion of hydrogen sulphide[3c,d,f] or an azide via Staudinger reaction followed by reaction with an isocyanate.[3a,e] Jung and co-workers disclosed their preliminary results of a route that produced the requisite carbodiimide by dehydration of an urea.[3b]

The thiourea route involves the use of toxic mercury salts[3f] and can produce organo-sulphur compounds[3c,d] or even elemental sulphur as a difficult to detect by-product. Impurities of this type can interfere with certain biological assays.[4] The Staudinger reaction route requires an extensive washing step at the carbodiimide stage to remove the triphenylphosphine oxide by-product.[5] In a library synthesis a washing step of a labile intermediate can be capricious and jeopardize the purity of the desired products.

Our goal was to establish an automated solid-phase synthesis for 2,3,5-trisubstituted 4*H*-imidazolones that directly yields products pure enough for screening in biological assays.



Scheme 1. Solid-phase synthesis of substituted 2-aminoimidazolones: (a) R2-NCO; (b) Burgess reagent; (c) R3-NH-R4.

Keywords: solid-phase synthesis; combinatorial chemistry; 4*H*-imidazolones; atropo-isomers.

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Results and discussion

The synthetic approach employing the dehydration of a urea moiety as the key step seemed to be best suited for our purposes. The synthesis sequence is depicted in Scheme 1. Starting from inexpensive Merrifield resin loaded with an α-amino acid (**1**) urea **2** was obtained by reaction with an arylisocyanate. The dehydration of the urea moiety could easily be monitored by disappearance of the urea carbonyl stretch at 1650 cm^{-1} and the formation of a new carbondiimide signal at 2140 cm^{-1} in the IR spectrum.

In our hands the reagent combination reported earlier using *para*-toluenesulphonyl chloride (pTsCl) and ethyldiisopropylamine (DIEA)[3b,6] gave good but incomplete conversion in the dehydration step (entry 1, Table 1) resulting in moderate yields of the desired imidazolones and unreacted secondary amines as contaminants. A screening of alternative dehydrating reagents led to an optimized procedure. The results are summarized in Table 1. The use of pTsCl and cesium carbonate[7] was less effective (entry 2). Dehydration of the urea moiety with trifluoroacetic acid anhydride and ethyldiisopropylamine (entry 3)[8] was comparable to the original procedure. Efficient conversion to the desired carbodiimide was finally achieved with the combination carbon tetrabromide, triphenylphosphine and triethylamine (entry 4)[9] or the Burgess reagent (entry 5).[10] The Burgess reagent is known as a very mild, non-basic dehydrating agent compatible with various functional groups.[11] To avoid the formation of difficult to remove by-products like triphenylphosphine oxide we chose this dehydration method over the carbon tetrabromide/triphenylphosphine alternative. Reaction of the carbodiimide **3** with a substoichiometric amount of a secondary amine resulted in the formation of the corresponding guanidine intermediate which upon cyclative cleavage[12] directly gave the desired imidazolone **4**. Some typical examples are listed in Table 2.

Table 1. Optimization of the dehydration step

Entry	Reagent	Result[a]
1	pTsCl, DIEA	+
2	pTsCl, Cs_2CO_3	−
3	$(CF_3CO)_2O$, DIEA	+
4	CBr_4, PPh_3, NEt_3	++
5	Burgess reagent	++

[a] Conversion of the urea to the corresponding carbodiimide, analyzed by IR: ++ efficient, + good, − low.

Cyclic secondary amines generally gave better yields than acyclic amines (cf. entries 5–14 and 1–4, Table 2). Acyclic amines with α-substituents tended to be less reactive than the α-unsubstituted amines (cf. entries 1–3 and 4, Table 2). Primary amines reacted equally well giving a mixture of tautomers.[13] This protocol[14] was implemented on an automated synthesizer[15] and used for the production of a library containing several hundred imidazolones in purities directly suitable for screening.

When 2-substituted arylisocyanates with bulky substituents were used the imidazolones were obtained as a mixture of atropo-isomers with a chiral *C*,*N*-axis in the 3-position. A detailed NMR study was done on the chloro-substituted derivative depicted in Fig. 1. It was

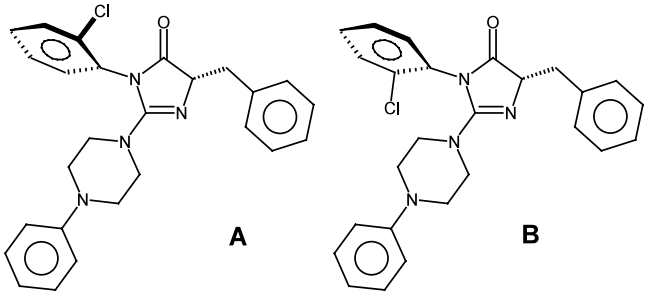

Figure 1. Diastereomeric 4*H*-imidazolones containing a chiral *C*,*N*-axis.

Table 2. 2,3,5-Trisubstituted 4*H*-imidazolones **4**

Entry	R^1	R^2	$-NR^3R^4$	Yield (%)[a]	Purity (%)[b]
1	Isopropyl	Phenyl	Cyclopropylisopropylamino	54	>95
2	Isopropyl	2-Chlorophenyl	Cyclopropylisopropylamino	47	90
3	Isopropyl	2,4-Dimethoxyphenyl	Cyclopropylisopropylamino	48	80
4	Benzyl	2-Chlorophenyl	*N*-Ethyl-*N*-propylamino	71	>90
5	Isopropyl	Phenyl	4-Phenylpiperazin-1-yl	81	>90
6	Isopropyl	2-Chlorophenyl	4-Phenylpiperazin-1-yl	79	75
7	Isopropyl	2,4-Dimethoxyphenyl	4-Phenylpiperazin-1-yl	90	90
8	Benzyl	2-Chlorophenyl	4-Phenylpiperazin-1-yl	78	90
9	Isopropyl	phenyl	4-Ethoxycarbonylpiperazin-1-yl	80	>95
10	Isopropyl	2-Chlorophenyl	4-Ethoxycarbonylpiperazin-1-yl	71	90
11	Isopropyl	2-Fluorophenyl	4-Ethoxycarbonylpiperazin-1-yl	70	90
12	Isopropyl	2,4-Dimethoxyphenyl	4-Ethoxycarbonylpiperazin-1-yl	89	>90
13	Benzyl	Phenyl	4-Ethoxycarbonylpiperazin-1-yl	93	85
14	Benzyl	2,4-Dimethoxyphenyl	4-Ethoxycarbonylpiperazin-1-yl	82	90

[a] Overall yields.
[b] Determined by RP-HPLC at 214 nm.

obtained as a 1.5:1 mixture of diastereomers as was determined by RP-HPLC and ^{1}H NMR.

In order to look for slow chemical exchange, a 2D-ROESY experiment was performed with the mixture of diastereomers in DMSO-d_6 at room temperature. Within the ROE spin lock time of 1 s, no exchange cross peaks between the two methine signals of the 4*H*-imidazolone protons of the diastereomers could be observed. At elevated temperatures up to 100°C no coalescence of these signals occurred. This proton did, however, undergo a slow H/D-exchange in DMSO-d_6/D_2O at room temperature within 96 h. These observations are consistent with a hindered rotation of the chiral axis and a labile stereocenter at the 5-position of the 4*H*-imidazolone. Furthermore, the 2D-ROESY experiment showed ROEs between the 6-proton of the 2-chloro-phenyl moiety and the aromatic 2- and 6-protons of the benzyl moiety of the main stereoisomer. On the basis of these effects and the up-field-shift of the 6-proton signal of the 2-chloro-phenyl ring due to the anisotropic effect caused by the aromatic ring of the benzyl moiety structure **A** (Fig. 1) could be assigned to the main stereoisomer.

In the main stereoisomer the benzyl moiety and the chloro-atom of the 2-chlorophenyl moiety were on opposite sides of the 4*H*-imidazolone ring. The new chiral *C*,*N*-axis could either be formed under stereocontrol of the chiral amino acid building block or the diastereomeric ratio could be obtained later by epimerization at C-5 of the imidazolone. It could be envisaged that a chiral amine in the 2-position would have a much stronger effect on the stereochemistry of the chiral *C*,*N*-axis and could be used for an asymmetric induction. This intriguing option lay, however, beyond the scope of this study, which was directed towards the synthesis biologically active compounds. No attempts have been made yet to exploit this chemistry for the asymmetric synthesis of 4*H*-imidazolones containing a chiral *C*,*N*-axis.

Summary

A novel solid-phase synthesis for 2,3,5-trisubstituted 4*H*-imidazolones has been developed that avoids unwanted by-products like transition metal salts, organo-sulphur compounds or elemental sulphur. The protocol has been used successfully for an automated synthesis of a medium sized library. The desired products were obtained in good yields. The cyclative cleavage in the final step gave the desired imidazolones in purities good enough for the direct use of the compounds in biological assays without further purification.

The formation of diastereomeric 4*H*-imidazolones containing a chiral *C*,*N*-axis in the 3-position was described, the relative stereochemistry of the main stereoisomer was determined by a 2D-ROESY experiment and techniques for asymmetric induction were suggested.

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14. Representative procedure: Merrifield resin bound phenylalanine (loading 0.8 mmol/g, 290 mg, 0.23 mmol) was reacted with 2-chlorophenylisocyanate (138 mg, 0.9 mmol) at room temperature in dichloromethane (DCM, 5.8 mL) for 12 h. After washing (4×DCM) the urea was dehydrated with Burgess reagent (164 mg, 0.69 mmol) in DCM (5.8 mL) at room temperature for 12 h. After washing (2×DCM, 3×NMP, 3×DCM) the carbodiimide was reacted with *N*-phenylpiperazine (22.4 mg, 0.138 mmol) in DCM (5.8 mL) at room temperature for 12 h. Filtration and concentration in vacuo gave the desired 5-benzyl-3-(2-chlorophenyl)-2-(*N*′-phenyl-*N*-piperazinyl)-4*H*-imidazolone (yield: 48 mg, 0.108 mmol, 78%, 90% purity by RP-HPLC at 214 nm).
15. The library synthesis was performed on a Bohdan automated synthesizer.