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A traceless solid-phase synthesis of 2-imidazolones

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Abstract—A traceless solid-phase synthesis of 2-imidazolones has been developed. Polymer-bound glycerol resin was reacted with bromoacetaldehyde diethyl acetal to give the cyclic acetal bromide on the solid support. Amination of the resin-bound acetal bromide followed by urea formation by reaction with isocyanates afforded the resin-bound urea acetals. The aldehyde urea intermediate, which was released from the resin upon treatment with TFA, immediately cyclized to afford the desired 2-imidazolones in good yield and purity.

Construction of heterocyclic ring systems on solid support continues to be of considerable interest in combinatorial organic synthesis.[1] In this context, developing methodologies that provide access to these heterocyclic systems without leaving any trace of the linker used for tethering the starting building blocks to the solid support is one of the greatest challenges.[2] As part of our program to develop heterocyclic systems using solid phase organic synthesis (SPOS), we found the intramolecular cyclization of *N*-acyliminium ions of acetal amides (or ureas) on the solid support to be a useful method for building heterocyclic systems without leaving a linker trace.[3] Herein we describe a convenient synthesis of 2-imidazolones using this strategy.

Table 1. 2-Imidazolones via traceless solid-phase synthesis

Entry	R_1	R_2	Yield[a]
1	$PhCH_2CH_2$	Ph	55
2	$PhCH_2CH_2$	*m*-CF_3Ph	46
3	$PhCH_2CH_2$	*m*-MeOPh	62
4	$PhCH_2CH_2$	Et	61
5	*n*-Bu	Ph	60
6	Ph	*n*-Bu	10
7	*n*-Bu	*m*-CF_3Ph	61
8	*n*-Bu	*m*-MeOPh	56
9	Bn	Ph	55
10	Bn	Et	62
11	Bn	*m*-MeOPh	61

[a] Isolated yield based on the starting glycerol resin (Aldrich, loading 1.38 mmol/g). All products were purified by preparative TLC and gave satisfactory ^{1}H NMR and ESIMS data.

2-Imidazolones have long been known to possess some interesting biological activities.[4] Several synthetic procedures have been reported in the literature.[5] The most convenient one is the intramolecular *N*-acyliminium ion cyclization. It is well known that *N*-acyliminium ions spontaneously deprotonate to afford the enamides in the absence of any nucleophiles.[6] This chemistry has been successfully used to prepare 2-imidazolones and related compounds in the solution phase.[3] We envisioned that if the acetal functionality was mounted onto a polymer, the latter could serve as both a solid support and a protecting group. Upon deprotection of the polymer-bound acetal functionality under acidic conditions, the released amide (or urea) aldehyde intermediate would spontaneously undergo cyclization to form an *N*-acyliminium ion that would deprotonate to afford the desired 2-imidazolones.

We investigated several previously reported approaches to polymer-bound acetal functionalities,[7] including Wang resin and glycerol-resin based acetals. Although Wang resin gave similar results as glycerol resin (vide infra), it is not as good as glycerol resin in terms of product purity and yields. IR analysis indicated the presence of unreacted hydroxyl groups in the case of Wang resin was used, probably due to incomplete conversion. Therefore the reaction was conducted using glycerol resin.[8] Acetal exchange of bromoacetaldehyde diethyl acetal under acidic condition with polymer-bound glycerol afforded the polymer-bound bromide (**2**). The following acids were tested: camphorsulfonic

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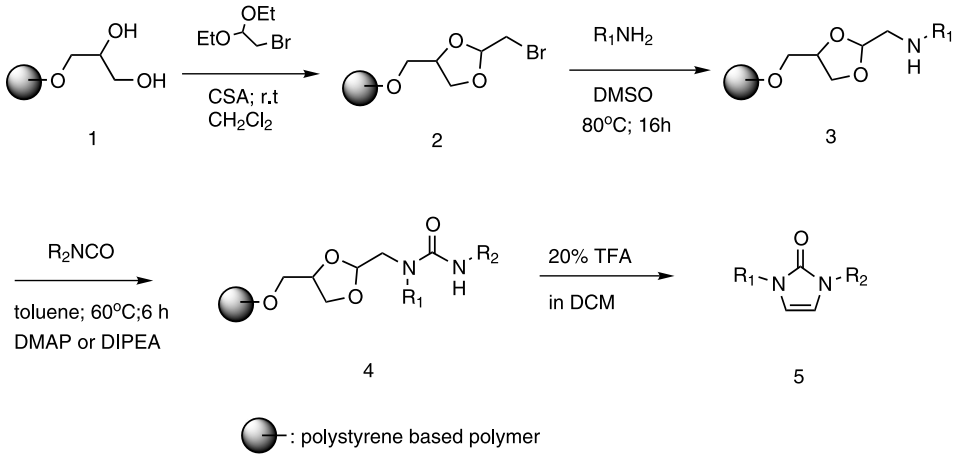

Scheme 1. A traceless solid-phase synthesis of 2-imidazolones.

acid (CSA), *p*-toluenesulfonic acid (PTS) and pyridinium *p*-toluenesulfonate (PPTS). CSA was the most efficient and gave the cleanest product.[9] IR analysis and weight change of the resin confirmed the formation of bromide on the solid support. Amination of the intermediate bromide with primary amine[10] afforded the desired amine (**3**) on the solid support. IR analysis showed the appearance of NH absorption.

Reaction of the resin-bound amine **3** with isocyanates gave the desired urea (**4**) under a variety of conditions. The reaction went smoothly in THF, CH_2Cl_2 or toluene and in the presence or absence of bases as evidenced by the successful formation of the final products. In order to ensure the complete reaction with relatively unreactive isocyanates or sterically hindered amines, the reaction was conducted at 60°C in toluene in the presence of DMAP or DIPEA. Finally, treatment of the acetal urea (**4**) with 20% TFA in CH_2Cl_2 released the aldehyde, which spontaneously cyclized to give 2-imidazolones **5** in good yields and purity (Table 1).

The reaction sequence toward 2-imidazolones shown in Scheme 1 is extremely simple. The overall yield seems to be affected only by the efficiency of formation of resin-bound acetal, not by amination or urea formation. While a variety of aliphatic amines and all isocyanates worked well under these conditions, aromatic amines ($R_1 = Ar$) were not as efficient as aliphatic amines. For example, when aniline ($R_1 = Ph$) reacted with resin-bound bromide **2** followed by reaction of the resulting amine with *n*-BuNCO, only a small amount of the desired product *N*-butyl-*N*′-phenyl-2-imidazolone (Table 1, entry 6) was obtained (ca. 10% yield). Although the same product was obtained in 60% yield (Table 1, entry 5) simply by switching the reagents, the current condition may not the best for preparing *N*,*N*′-diarylimidazolones.

In summary, a new and straightforward traceless solid-phase synthesis of 2-imidazolones has been developed. The reaction conditions are amenable to the synthesis of large combinatorial libraries and the purity of the final product is excellent.

General procedure: Glycerol resin[8] (250 mg, 1.38 mmol/g) was suspended in dichloromethane (3 mL) in a 10 mL tube with frit and screw cap. Camphor sulfonic acid (1 equiv.) was added followed by 2-bromoacetaldehyde diethyl acetal (10 equiv.). The suspension was shaken in a shaker at room temperature for 12 h. The solvent was drained, and the resin was washed with DMF (3×6 mL), MeOH (3×6 mL) and CH_2Cl_2 (3×6 mL) and dried under vacuum at room temperature. The dried resin was suspended in DMSO (3 mL). Benzylamine (6 mmol) was added, and the reaction suspension was heated in an oven shaker at 80°C for 6–16 h. The solvent was drained and the resin was washed and dried as described above to give the resin-bound amine. To the polymer-bound amine suspended in toluene (3 mL) was added *m*-methoxyphenylisocyanate (10 equiv.) and DMAP (1 equiv.). The suspension was heated to 60°C in the oven shaker for 6 h. After washing and drying, the resin was cleaved with 20% TFA in dichloromethane followed by 50% TFA in H_2O afforded the crude product. Further purification by preparative TLC (30% ethyl acetate in hexanes) gave the *N*-benzyl-*N*′-(3′-methoxylphenyl)-2-imidazolone in 61% yield. ^1H NMR ($CDCl_3$) δ 7.5 (d, 1H), 7.3 (m, 6H), 7.0 (m, 2H), 6.4 (d, 1H), 6.2 (d, 2H), 4.8 (s, 2H), 3.8 (s, 3H). ESIMS: m/z 281 (M+H), $C_{17}H_{16}N_2O_2$.

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