Efficient Solid-Phase Synthesis of Disubstituted 1,3-Dihydro-imidazol-2-ones

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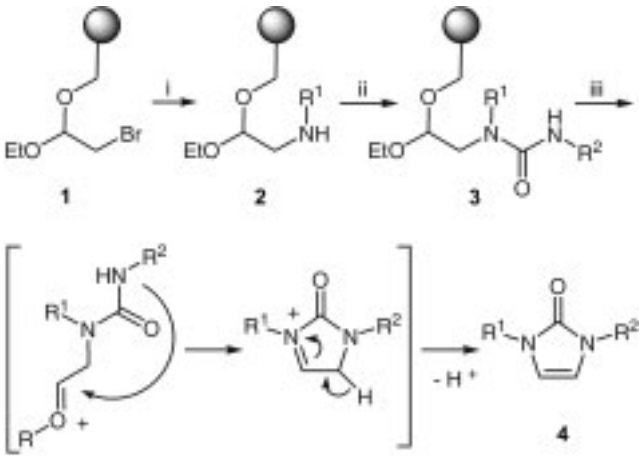
Abstract: A bromoacetal linker was used to achieve the synthesis of ureas on a solid support. The resulting ureido acetals were treated with TFA and were converted in an intramolecular cyclization via *N*-acyliminium ion to disubstituted 1,3-dihydro-imidazol-2-ones.

Key words: heterocycles, acetals, solid-phase synthesis, nucleophiles, cyclizations

The synthesis of heterocyclic ring systems on solid support to rapidly generate collections of small molecules useful in medicinal chemistry programs is of considerable interest.[1] In the search for novel methodologies, we investigated the application of intramolecular cyclization via *N*-acyliminium ion[2] on solid support.[3] An important side reaction in *N*-acyliminium ion chemistry is the formation of enamides.[4] We report herein the solid-phase synthesis of 1,3-dihydro-imidazol-2-ones using this strategy.

Substituted 1,3-dihydro-imidazol-2-ones are found in many synthetic compounds that exhibit for example activities as central nervous system depressant[5] as well as properties desirable in the treatment of thrombosis,[6] Alzheimer disease[7] and obesity.[8] Due to their broad biological activities several synthetic procedures have been reported.[9] The synthetic strategy using bromoacetaldehyde dimethylacetal as starting material is especially attractive. Following this strategy, 1,3-dihydro-imidazol-2-ones are obtained in a three step synthesis involving the displacement of the bromine with primary amines, their conversion to ureido-acetals and an acidic treatment to generate the oxonium functionality. The activated aldehyde then reacts spontaneously with the urea to form an *N*-acylimium ion, which in the absence of nucleophiles deprotonates to form the 1,3-dihydro-imidazol-2-one. To be successful, this synthetic pathway requires the purification of each intermediates and is therefore not appropriate for the preparation of combinatorial libraries. A solid-phase synthesis strategy will avoid the purification steps. Since we have made a bromoacetal resin available,[3a] we realized that this three-step synthetic pathway is ideally suited for a solid-phase synthesis.

The synthesis started with the reaction of bromoacetal resin **1**[10] with primary amines in a mixture of DMSO–NMP at 80 °C to afford the amino acetal resins **2** (Scheme 1). Whilst the reaction proceeded well with non-aromatic amines, the nucleophilic substitution with anilines failed to give the desired products. The ureido-acetal resin **3** was obtained by reacting resin **2** in NMP at 70 °C with either isocyanates or with amines, which were pretreated with *N*,*N*′-carbonyldiimidazoles (CDI). The activation of aliphatic or aromatic amines with CDI represented a simple and inexpensive method for the formation of ureas when the desired isocyanates were not commercially available.



Scheme 1 (i) R^1-NH_2, DMSO–NMP 1:1, 80 °C; (ii) R^2-NCO or R^2-NH_2–CDI, NMP, 70 °C; (iii) TFA, 16 h.

Table 1 *N*-Acyliminium Cyclization Yielding **4a**–**k**

R^1	R^2	Product	Yield (%)[a]
Bn	Ph	**4a**	37
Bn	5-*tert*-butyl-1*H*-3-aminopyrazole	**4b**	77
Bn	Et	**4c**	25
Bn	Bn	**4d**	53
Me	4-Cl-Ph	**4e**	42
Me	Ph	**4f**	24
$(Ph)_2CH$	Et	**4g**	11
$(CH_3)_2N$-CH_2CH_2-	4-Cl-Ph	**4h**	89
$(CH_3)_2N$-CH_2CH_2-	Ph	**4i**	76
$(CH_3)_2N$-CH_2CH_2-	3,4,5-$(MeO)_3$-Ph	**4j**	73
$(CH_3)_2N$-CH_2CH_2-	Bn	**4k**	71

[a] Yields in % of purified products are based on the initial loading of bromoacetal resin (1.6 mmol/g). A purity >90% was observed for all examples described as determined by LC-MS, detecting at 220 nm.

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Treatment of the ureido-acetal resin **3** with TFA afforded the 1,3-dihydro-imidazol-2-ones **4**. The monitoring of the final cleavage step by LC-MS analysis showed a rapid cleavage of the compounds from the resin and a subsequent slow intramolecular cyclization, which required 16 hours for completion. The compounds **4** were purified by preparative reverse-phase LC-MS and obtained in good yields (Table 1). All new compounds were characterized by LC-MS, ^{1}H- and ^{13}C NMR analysis.[11]

In summary, we have developed an expedient and straightforward approach to synthesize disubstituted 1,3-dihydro-imidazol-2-ones. The use of high loading resin was particularly useful for rapidly preparing combinatorial libraries of **4** in good quality and sufficient amounts for biological, physicochemical and eADME evaluation.

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(10) Bromoacetal resin has been prepared as described in ref.[3a]. Bromoacetal linker attached on TentaGel or polystyrene resin is now commercially available from Novabiochem (www.novabiochem.com), Rapp Polymers (www.rapp-polymer.com) and LCC Technologies (http://www.chemsupply.ch).

(11) The synthesis of **4a** and **4b** are representative of the procedure used for the parallel synthesis of the libraries. **Benzyl-amino-acetal Resin (2a)**: Bromoacetal LCC-Dynosphere polystyrene resin (100 mg, 0.16 mmol, 203 μ, batch#F-BAS/270-F146.1, 1.6 mmol/g as determined by elemental analysis, from LCC Engineering, Switzerland) was swollen once with NMP (5 mL). A mixture of DMSO–NMP 1:1 (2 mL) was added followed by benzylamine (257 μL, 2.4 mmol). The reaction mixture was shaken for 16 h at 80 °C, filtered off, washed three times with DMF (3 mL), three times with *i*-PrOH (3 mL) and four times with DMF (3 mL) each. A sample of the resin was washed five times with *i*-PrOH (3 mL) and dried under high vacuum: 94% conversion based on elemental analysis. Anal. Found: N, 2.03; Br, 0.33.
1-Benzyl-3-phenyl-1,3-dihydro-imidazol-2-one (4a): NMP (2 mL) and phenylisocyanate (285 μL, 2.4 mmol) were successively added to resin **3a** (0.16 mmol). The reaction mixture was shaken for 7 h at 70 °C, filtered off, washed three times with DMF (3 mL), three times with *i*-PrOH (3 mL) and five times with CH_2Cl_2 (3 mL) each. After drying the resin for 30 min under vacuum (ca. 20 mbar house vacuum), TFA (3 mL) was added and the reaction mixture was shaken for 17 h. This eluate and one subsequent wash with TFA (2 mL) were collected and combined. The solvent was evaporated and the residue was purified by preparative LC-MS with a Waters Fractionlynx system (YMC Pack Pro C_{18} column, 5 μ, 120Å, 50 × 20 mm) using a gradient of H_2O and MeCN (in 7 min from 5% MeCN to 85% MeCN, in 0.1 min from 85% MeCN to 95% MeCN, 1.2 min at 95% MeCN, in 0.1 min from 95% MeCN to 5% MeCN, flow: 35 mL/min, an autoblend method was used to ensure a concentration of 0.1% TFA throughout the complete run). Compound **4a**: 21 mg (37%). ESI-MS: *m/z* (%) = 251.1 (100) $[M + H]^+$. ^{1}H NMR (300 MHz, DMSO-d_6): δ = 7.65 (d, *J* = 2.6 Hz, 2 H), 7.23–7.47 (m, 8 H), 6.59 (d, *J* = 1.0 Hz, 1 H), 6.28 (d, *J* = 1.0 Hz, 1 H), 6.40 (s, 1 H), 4.90 (s, 2 H). ^{13}C NMR (150 MHz, DMSO-d_6): δ = 151.1, 137.3, 137.1, 128.7, 128.3, 126.7, 121, 112.2, 109.8, 66.1.
1-Benzyl-3-(5-tert-butyl-1*H*-pyrazol-3-yl)-1,3,-dihydro-imidazol-2-one (4b): 5-tert-butyl-1*H*-3-aminopyrazol (334 mg, 2.40 mmol) was dissolved in NMP (2.4 mL). CDI (389 mg, 2.40 mmol) was dissolved in NMP (2.4 mL) and then added to the aminopyrazole solution. The solution was shaken for 10 min and added to the resin **3a** (0.16 mmol). The reaction mixture was shaken for 7 h at 70 °C and filtered off. Washing of the resin, cleavage of the compound from the resin and purification using LC-MS were performed as described for **4a**. Compound **4b**: 51 mg (77%). ESI-MS: *m/z* (%) = 297.2 (100) $[M + H]^+$. ^{1}H NMR (600 MHz, DMSO-d_6): δ = 7.34–7.36 (m, 2 H), 7.27–7.30 (m, 3 H), 6.91 (d, *J* = 1.0 Hz, 1 H), 6.72 (d, *J* = 1.0 Hz, 1 H), 6.40 (s, 1 H), 4.78 (s, 2 H), 1.28 (s, 9 H). ^{13}C NMR (150 MHz, DMSO-d_6): δ = 150.4, 137.7, 128.5, 127.4, 119.5, 112.5, 107.6, 91.1, 46.1. 30.7, 29.8.