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Microwave assisted DIC-promoted intramolecular cyclization for solid phase synthesis of trisubstituted imidazolidinones and pyrimidinones

Xiaobing Wang,[a] Seth Dixon,[b] Nianhuan Yao,[a] Mark J. Kurth[b] and Kit S. Lam[a,*]

[a]*Division of Hematology and Oncology, Department of Internal Medicine, UC-Davis Cancer Center, School of Medicine, 4501 X Street, Sacramento, CA 95817, USA*
[b]*Department of Chemistry, One Shields Avenue, UC-Davis, CA 95616, USA*

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Abstract—A convenient solid phase synthesis of trisubstituted imidazolidinones and pyrimidinones via microwave assisted DIC-promoted intramolecular cyclization is described. Intramolecular cyclization of a resin-bound thiourea prepared by acylation of a dipeptide with an aryl isothiocyanate was rapidly promoted with DIC under microwave to afford imidazolidinones and tetrahydropyrimidinones in good yield and purity.

Because of their interesting biological activities, low molecular weight heterocycles have attracted enormous attention in medicinal chemistry. Although numerous approaches have been reported for the synthesis of various heterocyclic compounds, there is a continuing need for the development of simple synthetic approaches for the solid phase synthesis of heterocycles under mild conditions.

Imidazolidinones and pyrimidinones represent a novel heterocyclic class of pharmacophores containing a guanidine unit. However, reports on the synthesis of multi-substituted imidazolidinones and pyrimidinones are very sparse.[1] Although copper(I) salts (CuX, X = Cl, Br, and I)[1a] and iodomethane[1b] were previously reported to promote the intramolecular cyclization of a thiourea, the reactions tend to be inconvenient and, importantly, not applicable to solid phase methods.

From a literature survey, it is clear that 1,4-diamines can be easily cyclized with an aryl isothiocyanate via mercury salt or DIC-promoted cyclization.[2] The mechanism is believed to proceed through a carbodiimide intermediate.[2,3] DIC (1,3-diisopropylcarbodiimide) is easy to handle and compatible with solid phase methods. Therefore, we envisioned appropriate conditions for a DIC-promoted mechanism to perform the intramolecular cyclization of 1-amide-4-thioureas. Since research opportunities in this area have not been thoroughly explored, we set out to investigate this opportunity and report herein a rapid DIC-promoted intramolecular cyclization method for the solid phase synthesis of trisubstituted imidazolidinones and pyrimidinones.

Our synthetic route to trisubstituted imidazolidinones and tetrahydropyrimidinones is depicted in Scheme 1. Rink amide resin was used for the synthesis. In route A to imidazolidinones, a resin-bound dipeptide in which the second residue is a α-L-amino acid was synthesized using Fmoc peptide chemistry. In route B to tetrahydropyrimidinones, the second residue of the resin-bound dipeptide is a racemic β-amino acid.[4] Upon Fmoc deprotection, the free N terminus of the dipeptide is acylated with an aryl isothiocyanate to generate a resin-bound thiourea. To probe the feasibility of the intramolecular cyclization, two conditions were tested: (i) DIC/CH_2Cl_2 at room temperature; and (ii) DIC/toluene/90 °C. These test reactions were carried out for two days. Upon 95% TFA cleavage of the resulting resin, the cleavage solution was analyzed using mass spectrometry, which showed that the cyclized product was achieved under the latter conditions. In contrast, the

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* Corresponding author. Tel.: +1 916 734 8012; fax: +1 916 734 7946; e-mail: kit.lam@ucdmc.ucdavis.edu

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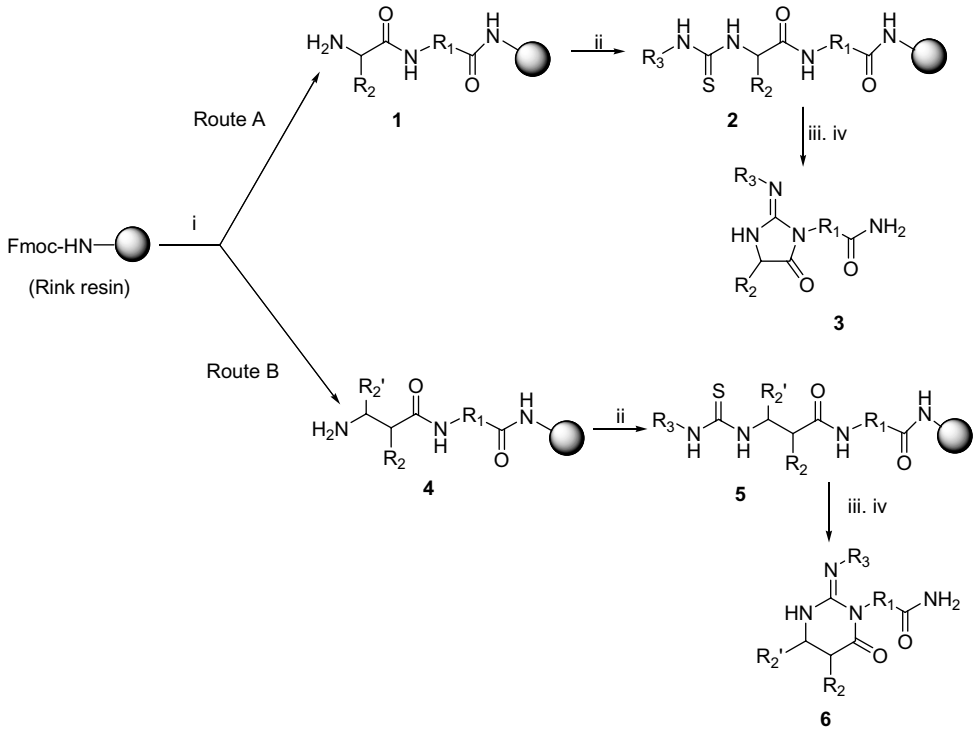


Scheme 1. Solid phase synthetic approaches to trisubstituted imidazolidinones and pyrimidinones. Reagents and conditions: (i): 25% piperidine, 15 min then assemble dipeptide using Fmoc peptide chemistry; (ii) aryl isothiocyanate (3 equiv), DIEA (6 equiv), 6 h; (iii) DIC (20 equiv)/DMF/MW, 4 min; (iv) 95% TFA/H_2O, 2 h.

former condition delivered a mass peak at 18 Da more than the expected product. This product resulted from the water adduct of the resulting carbodiimide intermediate while under TFA/water cleavage.

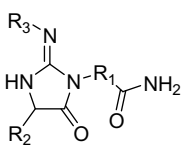
Since heating many resin samples in toluene to 90 °C for two days is rather inconvenient, we turned to a microwave assisted strategy for these intramolecular cyclizations. Two model resin-bound compounds were tested in a conventional microwave for 4 min, and the resulting resins were then released for MS detection. These MS data showed that the cyclized products were achieved in satisfactory purity.

With these successful experiments in hand, a diverse set of dipeptides and aryl isothiocyanates were explored for the synthesis of trisubstituted imidazolidinones and pyrimidinones. Since in route B, the second residue of the dipeptide was a racemic β-amino acid, we intentionally coupled a non-chiral amino acid[5] as the first residue. The results are illustrated in Table 1. All products were obtained in high yield (>90%) with satisfactory purity (>70%) even if the second residue is a cyclic amino acid (compound **3d** and **6d**).

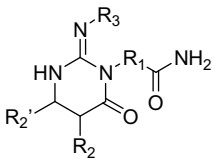
In conclusion, we have developed a microwave assisted solid phase DIC-promoted intramolecular cyclization method that can be used to efficiently synthesize trisubstituted imidazolidinones and pyrimidinones. To our knowledge, this is the first report of the DIC-promoted intramolecular cyclization of 1-amide-4-thiourea under microwave. Since the reaction conditions are as mild as peptide synthesis chemistry, in principle, the synthesis can be easily automated. Furthermore, a number of the starting materials can be efficiently prepared using diverse α- or β-amino acids and aryl isothiocyanates meaning that large libraries of imidazolidinone or pyrimidinone with three diversity points can be easily constructed using parallel or combinatorial synthetic approach.

Typical synthetic approach to imidazolidinones: synthesis of 3-(5-oxo-2-phenylamino-4,5-dihydro-imidazol-1-yl)-propionamide **3a**. DMF-swollen Rink amide resin (0.1 mmol) was deprotected with 25% piperidine in DMF for 15 min. The washed resin was coupled with *N*-Fmoc-β-alanine (3.0 equiv) in the presence of HOBt (3.0 equiv)/DIC (3.0 equiv). After Fmoc deprotection with 25% piperidine in DMF twice for 15 min, the resulting resin was further coupled with *N*-Fmoc-glycine (3.0 equiv) in the presence of HOBt (3.0 equiv)/DIC (3.0 equiv). After Fmoc deprotection with 25% piperidine in DMF, phenyl isothiocyanate (3 equiv) was incubated with the resin in the presence of *N*,*N*′-diisopropylethylamine (6 equiv) for 6 h. The Kaiser test was used to monitor each step of the reaction. The resulting resin was thoroughly washed with DMF (3×10 mL) and CH_2Cl_2 (3×10 mL), dried in vacuo for 1 h, and then added to a small glass tube. After addition of DIC (20 equiv) and DMF (2 mL), the tube was loosely capped, and heated in a conventional microwave for 4 min on high power. The resulting resin was drained, thoroughly washed, and dried in vacuo. Finally, the resin was incubated with 95% TFA/H_2O (2 mL) for

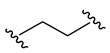
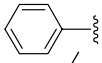
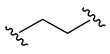
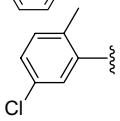
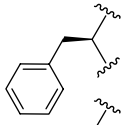
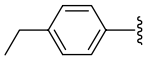
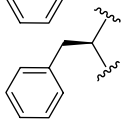
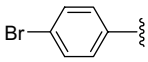
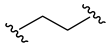
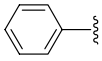
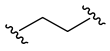
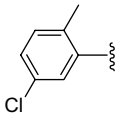
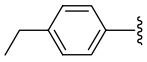
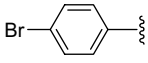
Table 1. Synthesis of trisubstituted imidazolidinones (**3a–d**) and pyrimidinones (**6a–d**) via Scheme 1



3a-d

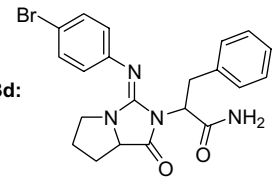


6a-d

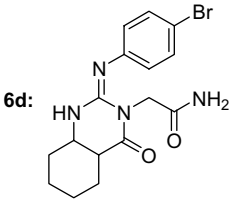
Entry	R_1	R_2	R_3	Yield[a] (%)	Purity[b] (%)	MS[c] (M^+) found (calcd)
3a				95	77	246.7 (246)
3b				94	88	336.7 (336)
3c				99	84	406.6 (406)
3d[d]				90	99	440.8 (440)
6a		$R_2 = H$ $R_2' = H$		98	73	260.5 (260)
6b		R_2 = benzyl $R_2' = H$		92	81	398.2 (398)
6c		$R_2 = H$ R_2' = phenyl		95	97	350.7 (350)
6d[d]				94	74	378.8 (378)

[a] Yield of the crude product was based on Rink resin loading.
[b] Purity was measured by RP-HPLC at $\lambda = 254$ nm.
[c] Molecular weight was measured by ES-MS.
[d] Chemical structure of the products:

3d:



6d:



2 h. The cleavage solution was filtered and evaporated to dryness. Yield: 95%; purity: 77%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.43 (t, 2H), 7.35 (m, 2H), 7.21 (s, 2H), 7.06 (t, 1H), 6.33 (s, 1H), 3.58 (s, 2H), 3.44 (t, 2H), 2.51 (t, 2H). ^{13}C NMR (400 MHz, DMSO-d_6): δ 175.6, 172.5, 150.1, 149.2, 131.2 (2 carbons), 127.9, 124.3 (2 carbons), 50.5, 36.4, 34.4.

Typical synthetic approach of pyrimidinones: synthesis of 3-(6-oxo-2-phenylimino-tetrahydropyrimidin-1(2*H*)-yl)-propanamide **6a**. The procedure described above was followed except the second coupling amino acid was *N*-Fmoc-alanine instead of *N*-Fmoc-glycine. Yield: 98%; purity: 67%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.38 (t, 2H), 7.31 (m, 2H), 7.18 (s, 2H), 7.06 (t, 1H), 6.26 (s, 1H), 3.48 (t, 2H) 3.02 (t, 2H), 2.48 (t, 2H), 2.33 (t, 2H). ^{13}C NMR (400 MHz, DMSO-d_6): δ 175.6, 175.2, 166.1, 152.3, 130.1 (2 carbons), 127.7, 122.5 (2 carbons), 37.8, 33.8, 33.1, 30.4.

Acknowledgments

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References and notes

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