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Solid-phase synthesis of 2-aminoimidazolinones

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Abstract

The synthesis of 2-aminoimidazolinones from resin-bound amino acids is described. Reaction of resin-bound amino acids with isothiocyanates followed by treatment of the thioureas with Mukaiyama's reagent afforded the corresponding carbodiimides, which reacted with amines to give 2-aminoimidazolinones in good yield and purity through a cyclization reaction that cleaves the product from the resin.

Small ring heterocycles occupy an important place in pharmaceutical and agrochemical research due to their relative ease of synthesis, the possibility of modulating their biological properties through different substitution patterns, and their minimum impact in terms of molecular weight as scaffolds.[1] We became particularly intrigued by the solid-phase synthesis of 2-aminoimidazolinones, because this scaffold combines three points of diversity together with interesting hydrogen bond donor and acceptor characteristics. Based on our continued interest in the utility of polymer-bound carbodiimides as versatile intermediates,[2] and a recent literature report[3] detailing the application of carbodiimide chemistry to the synthesis of 2-aminoimidazolinones from azidoesters (Scheme 1), we decided to exploit a similar route for a solid-phase synthesis of this class of compounds. In addition, the success of a related route to quinazolinones employing a polymer-supported carbodiimide and a cyclization-release strategy encouraged us.[4]

In spite of the importance of unsymmetrical carbodiimides in synthetic organic chemistry, one finds that there are relatively few methods available for the synthesis of such versatile compounds. The principal routes include the formal hydrogen sulfide extrusion from disubstituted thioureas, and the aza-Wittig reaction of iminophosphoranes with isocyanates. Recently, an interesting method based on tin(II)-mediated heterocumulene metathesis appeared in the literature.[5]

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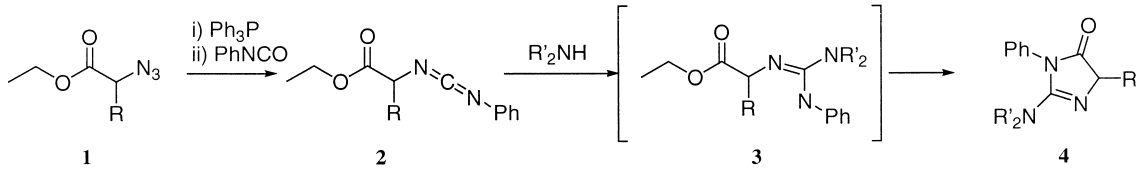
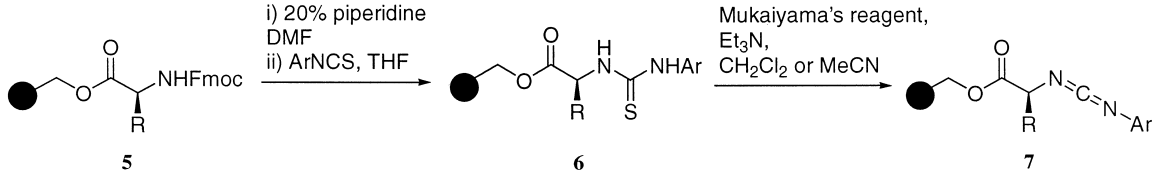


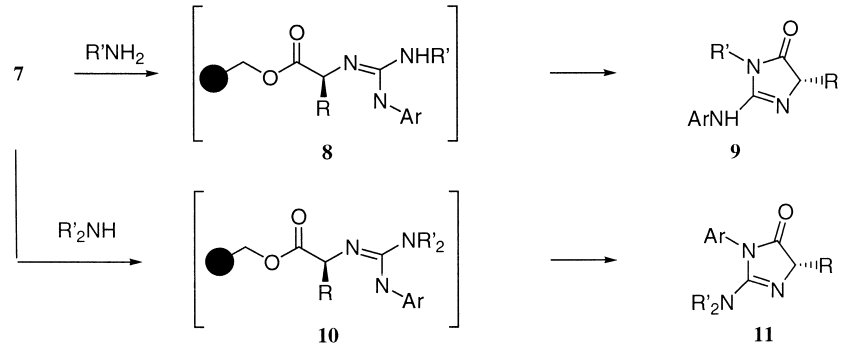
Scheme 1.

We decided to follow the hydrogen sulfide extrusion route, because the ready availability of aminoacids would permit us to explore one diversity position quite rapidly, and the increased stability of isothiocyanates with respect to isocyanates would be an advantage to the development of the route (Scheme 2).



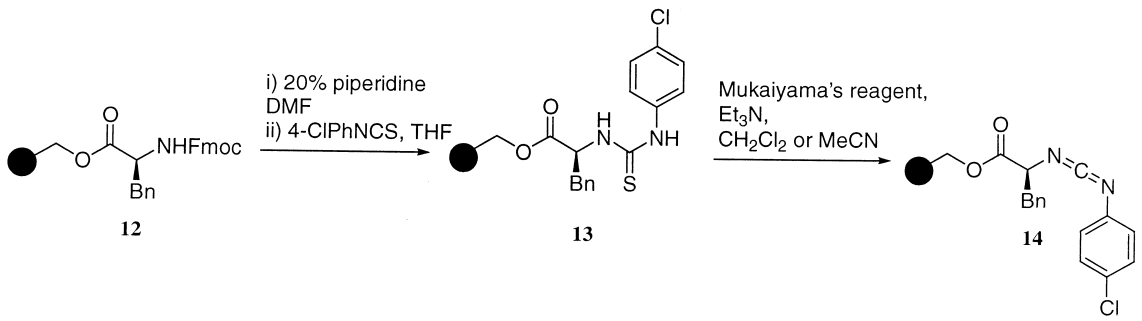
Scheme 2.

We reasoned that it should be possible to react carbodiimide **7** with a series of primary and secondary amines (Scheme 3) and that the obtained guanidines **8** and **10** would afford the desired trisubstituted 2-aminoimidazolinones **9** and **11**, respectively, in a cyclization–cleavage process. Indeed, we found that the reaction of the carbodiimide **7** with primary amines afforded the cyclized product **9**, and the reaction with secondary amines provided the corresponding products **11**. These reactions proceeded overnight at room temperature.



Scheme 3.

A specific example is depicted in Scheme 4, in which phenylalanine–Wang resin was reacted with 4-chlorophenylisothiocyanate to afford a thiourea, and Mukaiyama's reagent[6] was used in the carbodiimide formation step. Reaction of *p*-toluenesulphonyl chloride[7] and triethylamine with the thiourea also afforded, albeit more slowly and with a less clean reaction, the carbodiimide **14**, while the use of the triphenylphosphine/carbon tetrachloride/triethylamine system[8] did not afford the desired carbodiimide.



Scheme 4.

Carbodiimide formation could be followed easily by IR of the resin beads (difference spectra), looking for disappearance of the C=S stretching band (1340 cm^{-1}) and appearance of the strong N=C=N band at 2132 cm^{-1}.

Representative examples of the carbodiimide reaction with primary and secondary amines are reported in Table 1, together with the isolated yields. Purity was uniformly high, due to the cyclization–cleavage strategy. Only material that arrives successfully at the guanidine stage can be cleaved.

Table 1

amine	product	yield%[a]	MH+
Ph_2CHNH_2	**9a**	62[b]	480
$cyHexCH_2NH_2$	**9b**	34[b], 31[c]	396
$Me_2N(CH_2)_3NH_2$	**9c**	52[b], 46[c]	385
$BnNH_2$	**9d**	44[b], 39[c]	390
$MeOCH_2CH_2NH_2$	**9e**	52[b], 39[c]	358
$MeNH_2$	**9f**	55[b], 60[c]	314
Bn_2NH	**11a**	46[b], 44[c]	480
4-Ph-piperazine	**11b**	51[b], 49[c]	445
piperidine	**11c**	94[b]	368
2-Ethylpiperidine	**11d**	69[b]	396
Et_2NH	**11e**	80[b]	356

[a] all compounds were detected as the major peak (>90% of total peak area, desired molecular weight) by HPLC/MS with diode array detection
[b] isolated yield, gravimetric analysis
[c] yield determined by NMR with 2,5-dimethylfuran (DMFu) as an internal standard[9]

We found it convenient to use a slight excess of amine with respect to the theoretical amount of carbodiimide. An excess of isocyanate resin[10] could be added directly to the cleaved 2-amino-imidazolinone and Wang resin suspension as an amine scavenger. The final product was then obtained by filtration to remove the resins, and solvent evaporation.

Experimental procedures. Compound **7**: Commercially available Fmoc-Phe-Wang resin (Novabiochem, 2.5 g, 1.0 mmol/g) was treated with 30% piperidine in DMF (25mL) for 1 hour, then washed with THF, MeOH, and CH_2Cl_2, and dried. The resin was then treated with 20 mL of a 0.5 M solution of 4-chlorophenylisothiocyanate for 15 hours, washed (THF, DMF, MeOH, CH_2Cl_2), and dried. A suspension of the resin and 2-chloro-1-methylpyridinium iodide (12 mmol,

3.1 g) in 60 mL of CH_2Cl_2 was treated with triethylamine (22.5 mmol, 3.1 mL) and the mixture was heated at 45°C for 3.5 hours. The reaction was then cooled and washed extensively with DMF and CH_2Cl_2.

Compound **9b**: Carbodiimide resin (75 mg, theoretical loading 1.0 mmol/g, 75 μmol) was suspended in THF (1 mL) and cyclohexylmethylamine (11 μL, 82 μmol) was added. The reaction was shaken at room temperature for 24 hours, diluted with CH_2Cl_2 (3 mL) then treated with polymer-supported isocyanate scavenger resin (17.5 μmol). The reaction was shaken for 6 hours, the resins were removed by filtration, and the filtrate concentrated to afford the product as a pale yellow oil (10 mg, 34% yield by gravimetric analysis; 23.3 μmol, 31% yield by ^{1}H NMR with 2,5-dimethylfuran as an internal standard). ^{1}H NMR (CD_3OD, 300 MHz): δ 7.34 (m, 5H), 7.19 (d, 2H, J = 6.3 Hz), 6.93 (d, 2H, J = 8.5 Hz), 4.37 (t, 1H, J = 4.2 Hz), 3.28 (m, 2H), 3.09 (m, 2H), 1.63 (m, 5H), 1.10 (m, 4H), 0.79 (m, 2H).

Compound **11b**: Carbodiimide resin (75 mg, theoretical loading 1.0 mmol/g, 75 μmol) was suspended in THF (1 mL) and treated with 1-phenylpiperazine (12.5 μL, 82 μmol). The reaction was shaken at room temperature for 24 hours, diluted with CH_2Cl_2 (3 mL) then treated with polymer-supported isocyanate scavenger resin (17.5 μmol). The scavenging reaction was shaken for 6 hours, the resins were removed by filtration, and the filtrate concentrated to afford the product as a pale yellow oil (17 mg, 51% yield by gravimetric analysis; 36.7 μmol, 49% yield by 1H NMR with 2,5-dimethylfuran as an internal standard). ^{1}H NMR (CD_3OD, 300 MHz): δ 7.43 (d, 2H, J = 8.7 Hz), 7.2 (m, 7H), 6.86 (m, 5H), 4.57 (t, 1H, J = 4.4 Hz), 3.34 (m, 4H), 3.17 (m, 2H), 2.96 (m, 4H).

In summary, 2-aminoimidazolinones of general structure **9** and **11** can be prepared by reaction of primary or secondary amines, respectively, with a carbodiimide formed from a resin bound amino acid. Cyclization-induced cleavage leads to products of high purity because any unreacted intermediates such as uncapped amino acid and thiourea cannot cyclize and thus remain resin-bound. This three-step sequence also illustrates the utility of Mukaiyama's reagent for the preparation of resin-bound carbodiimides from thioureas.

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References

1. Fecik, R. A.; Frank, K. E.; Gentry, E. J.; Menon, S. R.; Mitscher, L. A.; Telikepalli, H. *Med. Res. Rev.* **1998**, *18*, 149.
2. Drewry, D. H.; Gerritz, S. W.; Linn, J. A. *Tetrahedron Lett.* **1997**, *38*, 3377.
3. Ding, M.-W.; Tu, H.-Y.; Liu, Z.-J. *Synth. Commun.* **1997**, *27*, 3657.
4. Chucholowski, A.; Masquelin, T.; Obrecht, D.; Stadlwieser, J.; Villagordo, J. M. *Chimia* **1996**, *50*, 525.
5. Babcock, J. R.; Sita, L. R. *J. Am. Chem. Soc.* **1998**, *120*, 5585.
6. Shibanamu, T.; Shiono, M.; Mukaiyama, T. *Chemistry Lett.* **1977**, 575. Yong, Y. F.; Kowalski, J. A.; Lipton, M. A. *J. Org. Chem.* **1997**, *62*, 1540.
7. Weishenker, N. M.; Shen, C. M. *Org. Synth., Coll. Vol. VI* **1988**, 951.
8. Appel, W.; Kleinstück, R.; Ziehn, K.-D. *Chem. Berichte* **1971**, *104*, 1335.
9. Gerritz, S. W.; Sefler, A. M. *J. Comb. Chem.* **2000**, *2*, 39.
10. Kaldor, S. W.; Siegel, M. G.; Fritz, J. E.; Dressman, B. A.; Hahn, P. J. *Tetrahedron Lett.* **1996**, *37*, 7193.