Solution and soluble polymer syntheses of 3-aminoimidazoline-2,4-diones

Juyoung Yoon,† Chang-Woo Cho, Hyunsoo Han and Kim D. Janda*

Department of Chemistry, The Scripps Research Institute and The Skaggs Institute for Chemical Biology, 10550 N. Torrey Pines Road, La Jolla, CA 92037, USA. E-mail: kdjanda@scripps.edu

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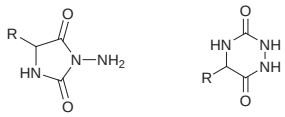
3-Aminoimidazoline-2,4-dione derivatives have been synthesized from a combination of α- and aza-amino acids by both solution phase and soluble polymer supported approaches; this soluble polymer methodology combines clean product isolation with recycling of the original matrix.

Molecular diversity based on combinatorial organic synthesis is now being used for rapid lead generation in both drug discovery and the development of biologically active compounds with potential therapeutic value.[1] Recently, solid-phase synthesis of heterocycles bearing one or more nitrogen atoms such as diketopiperazines,[2] diazines,[3] and hydantoins[4] has received considerable attention due to their medicinal importance. Hence, development of strategies for the mixture/parallel synthesis of additional heterocyclic structures either in solution or on a polymer support is of key interest.

The synthesis and structure assignment of hexahydro-1,2,4-triazine-3,6-dione **2**, isomeric with 3-aminoimidazoline-2,4-dione **1**, has been rather cryptic for over 30 years.[5–7] It has been demonstrated[6,7] that a hexahydro-1,2,4-triazine-3,6-dione could be prepared by the reaction of *N*-[*N*-(phenylthiocarbonyl)glycyl]-*N*′-(benzyloxycarbonyl)hydrazine with lead acetate.[8] A similar cyclization of ethyl semicarbazinoacetate [$H_2NNHC(O)NHCH_2CO_2Et$] with NaOEt[9] was discovered to lead to **1** rather than **2**. A more recent attempt[10] to synthesize 1,2,4-triazine-3,6-diones by the reaction of hydrazine with α-lactams gave mainly **1**.[11] If **1** or **2** could be made in a controlled

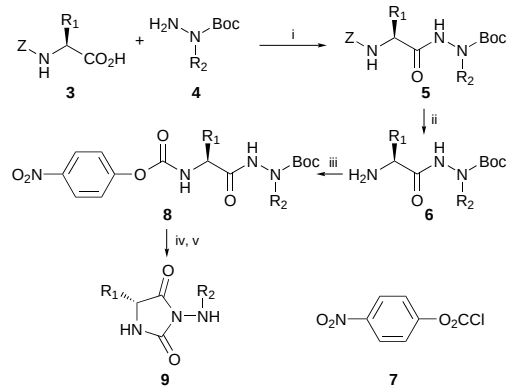


1 **2**

fashion they should make interesting targets for combinatorial synthesis/drug discovery as they are structurally rigid, possess ample hydrogen donor/acceptor functionality and contain two points for diversity generation. Herein we describe our synthetic approach to 3-aminoimidazoline-2,4-diones **1**, our application of this strategy to a soluble polymer support, and our ability to design a methodology that allows regeneration of the resin.

As detailed *vide supra* examples relating to the controlled syntheses of 3-aminoimidazoline-2,4-dione derivatives have been sparse. In 1985, a concise one step synthesis from α-amino acids and *tert*-butyl carbazate was reported by Lalezari,[12] however, this report also detailed a major problem with this synthetic tack which induced racemization of the product. To avoid this unwanted racemization, our solution phase approach utilized Et_3N or Pr^i_2NH at room temperature for the cyclization step, allowing optical activity‡ to be preserved.

As shown in Scheme 1, *N*-benzyloxycarbonyl protected amino acids were used as convenient starting materials in the solution phase synthesis. Thus, protected amino acids were coupled with our previously described Boc-protected aza-amino acids[13] using DCC and DMAP in typically 95% yield.



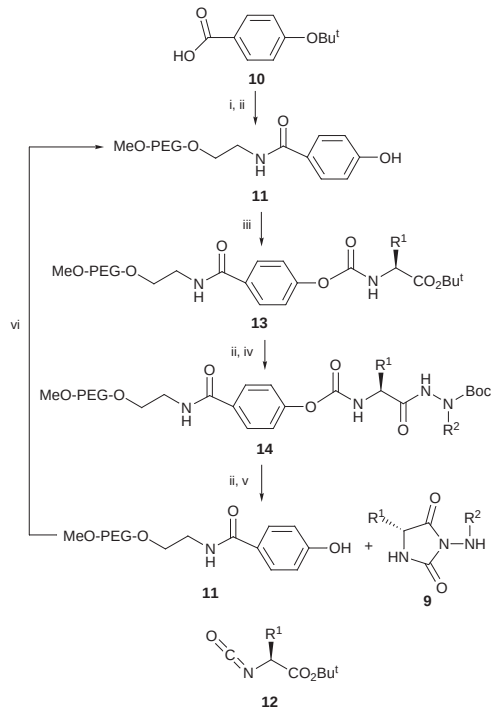
Scheme 1 *Reagents and conditions*: i, DCC, DMAP; ii, H_2/Pd-C; iii, **7** (1.1 equiv.), Et_3N (1.1 equiv.); iv, TFA–CH_2Cl_2 (1:1 v/v); v, dilution, Et_3N (1.1 equiv.).

After removal of the benzyloxycarbonyl (Z) group, nitrophenyl chloroformate was introduced to generate an activated intermediate for the cyclization reaction. Removal of the Boc group was performed using TFA–CH_2Cl_2 (1:1), followed by cyclization in Et_3N–CH_2Cl_2 (1:100 v/v) at 25 °C, and the desired unracemized 3-aminoimidazoline-2,4-diones **9** were obtained in approximately 75% yield.

With a sound solution phase strategy in hand we extended our methodology to a soluble polymer supported synthesis. In this scenario linear homopolymer [polyethylene glycol monomethyl ether (MeO-PEG)] served as our carrier for polymer synthesis and purification. We have demonstrated the advantages of using liquid phase synthesis through the construction of both peptide/small molecule combinatorial libraries[14] and as a reagent/catalyst support.[15]

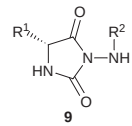
Linker **10** was prepared *via* the oxidation of 4-(*tert*-butoxy)benzaldehyde with Ag_2O. This acid was coupled to MeO-PEG5000-amine and upon deprotection with TFA gave phenol **11** which was now ready for the first diversity step coupling (Scheme 2). The amino acid was introduced in the form of isocyanate **12**[16] and this building block was attached to **11** granting **13**; the second point of diversity, Boc-aza-amino acid **4** was added to deprotected **13** providing PEG-**14**. It should be stressed that the unique physical properties of the MeO-PEG homopolymer allowed each coupling/deprotection reaction to be purified by precipitation of the modified homopolymer. Furthermore, reaction progress was conveniently monitored by ^1H and ^{13}C NMR spectroscopy. Finally, after removal of the Boc group, **14** could be base-cyclized and thus cleaved from the support generating a variety of 3-aminoimidazoline-2,4-diones in greater than 90% purity and in 62–80% yield (Table 1). The structures of the products were confirmed by ^1H, ^{13}C NMR and FAB mass as well as IR spectroscopy.§ For example, ^1H NMR analysis of **9d** in [$^2H_6$]DMSO clearly shows a doublet at δ 2.49 for NCH_3 and a quartet for NH at δ 5.43. Also, all of the compounds showed distinct peaks in their IR spectra at 1775 and 1725 cm^{-1} which is indicative of a 3-aminoimidazoline-2,4-dione structure.[5] Lastly, it was possible to regenerate PEG-**11** and reapply this material in another round of synthesis. This was accomplished by simple treatment of the isolated reaction PEG-**11** with 1 M NaOH which in effect removed any previous

† Present address: Department of Chemistry, Silla University, 1-1 San, Kwaebop-dong, Sasang-gu, Pusan, 617-736 Korea.



Scheme 2 *Reagents and conditions*: i, MeO-PEG-$CH_2CH_2NH_2$, DCC, DMAP; ii, TFA–CH_2Cl_2 (1:1 v/v); iii, **12**, Et_3N; iv, **4**, DCC; v, dilution, Pr^i_2NEt (1.1 equiv.), vi, 1 M NaOH.

Table 1 3-Aminoimidazoline-2,4-diones generated *via* Scheme 2



Compound	R^1	R^2	Yield (%)[a]
9a	H	Me	62
9b	Me	Me	73
9c	Pr^i	Me	75
9d	Bu^s	Me	78
9e	Bn	Me	80
9f	Bn	*p*-$MeOC_6H_4CH_2$	78
9g	Bn	Bu^i	74
9h	Me	H	60
9j	Bu^i	H	67
9k	Bn	H	67

[a] Yields are based on the conversion of **11** to **9** and are isolated yields.

materials that had accumulated during the synthesis of **9**. We could use this PEG-**11** again without any significant reduction in loading or yield, which was confirmed by ^{1}H NMR analysis.

In conclusion, we have shown both solution and liquid phase methodologies for the controlled stepwise synthesis of 3-aminoimidazoline-2,4-diones. In our strategy we have provided a method that allows for the incorporation of two points of diversity which can be drawn from a large pool of building blocks. Finally, our approach allows for polymer regeneration and its reuse.

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Notes and references

‡ Optical rotation values for **9b**,**c**,**e**–**g**,**j** are reported in their characterization data (see below). In the case of **9b**, there was no significant change in its optical rotation value after a first and second recrystallization from EtOH. This supports our assumption that there was no sign of racemization in our synthetic scheme. {before recrystallization: $[\alpha]_D^{24}$ −39.0 (*c* 1.06, MeOH), after first recrystallization: $[\alpha]_D^{24}$ −38.8 (*c* 1.06, MeOH), after second recrystallization: $[\alpha]_D^{24}$ −40.3 (*c* 1.04, MeOH)}

§ *Selected data* for **9a**: mp 189–191 °C; δ_H([$^2H_6$]DMSO, 400 MHz) 8.00 (br s, 1H), 5.40 (br s,1H), 3.87 (d, 2H), 2.51 (d, 3H); δ_C([$^2H_6$]DMSO, 101 MHz) 169.8, 156.5, 44.5, 36.9; ν($CHCl_3$)/cm^{-1} 3024, 1772, 1724, 1211; HRMS [FAB, (M + 1)$^+$]: calc. 130.0617, found 130.1612. For **9b**: mp 182–185 °C; δ_H(CD_3OD, 400 MHz) 3.99 (q, 1H), 2.55 (s, 3H), 1.27 (d, 3H); δ_C(CD_3OD, 101 MHz) 172.5, 155.1, 50.1, 34.9, 14.8; ν($CHCl_3$)/cm^{-1} 3006, 1768, 1724, 1214; HRMS [FAB, (M + 1)$^+$]: calc. 144.0773, found 144.0766; $[\alpha]_D^{24}$ −39.0 (*c* 1.06, MeOH). For **9c**: mp 138–140 °C; δ_H($CDCl_3$, 400 MHz) 6.73 (br s, 1H), 4.32 (br s, 1H), 3.90 (d, 1H), 2.72 (s, 3H), 2.23 (m, 1H), 1.04 (d, 3H), 0.91 (d, 3H); δ_C($CDCl_3$, 101 MHz) 171.3, 156.9, 60.9, 38.0, 30.2, 18.6, 15.9; ν($CHCl_3$)/cm^{-1} 3024, 1774, 1718, 1208; HRMS [FAB, (M + Na)$^+$]: calc. 194.0905, found 194.0914; $[\alpha]_D^{24}$ −73.0 (*c* 0.69, $CHCl_3$). For **9d**: δ_H(DMSO, 400 MHz) 8.17 (s, 1H), 5.53 (q, 1H), 3.97 (d, 1H), 2.49 (d, 3H), 1.77 (m, 1H), 1.18–1.34 (m, 2H), 0.90 (d, 3H), 0.84 (t, 3H); δ_C(CD_3OD, 101 MHz) 169.6, 154.2, 57.3, 34.3, 33.6, 20.8, 11.2, 8.0; ν($CHCl_3$)/cm^{-1} 3024, 2986, 1774, 1718, 1214; HRMS [FAB, (M+1)$^+$]: calc. 186.1242, found 186.1239. For **9e**: mp 210–213 °C; δ_H($CDCl_3$, 400 MHz) 7.30 (m, 5H), 5.45 (br s, 1H), 4.26 (q, 1H), 4.23 (m, 1H), 3.28 (dd, 1H), 2.90 (dd, 1H), 2.58 (d, 3H) ; δ_C($CDCl_3$, 101 MHz) 170.6, 155.5, 134.6, 129.4, 128.9, 127.6, 61.0, 56.9, 37.8; ν($CHCl_3$)/cm^{-1} 3011, 1762, 1724, 1227; HRMS [FAB, (M + 1)$^+$]: calc. 220.1086, found 220.1094; $[\alpha]_D^{24}$ −63.9 (*c* 0.39, MeOH). For **9f**: mp 125–128 °C; δ_H($CDCl_3$, 400 MHz) 7.30 (m, 5H), 7.16 (d, 2H), 6.86 (d, 2H), 5.24 (s, 1H), 4.35 (br s, 1H), 4.15 (m, 1H), 3.95 (d, 2H), 3.78 (s, 3H), 3.23 (dd, 1H), 2.69 (dd, 1H); δ_C($CDCl_3$, 101 MHz) 170.6, 159.4, 155.6, 134.9, 130.7, 129.3, 128.9, 127.7, 127.5, 113.8, 56.9, 55.2, 53.9, 37.8; ν($CHCl_3$)/cm^{-1} 3011, 1755, 1737, 1215; HRMS [FAB, (M + Na)$^+$]: calc. 348.1324, found 348.1335; $[\alpha]_D^{24}$ −76.0 (*c* 0.42, MeOH). For **9g**: δ_H($CDCl_3$, 400 MHz) 7.28 (m, 5H), 6.21 (s, 1H), 4.26 (q, 1H), 4.21 (m, 1H), 3.21 (dd, 1H), 2.94 (dd, 1H) 2.53 (t, 2H), 1.55 (m, 1H), 0.90 (d, 3H); δ_C($CDCl_3$, 101 MHz) 170.9, 156.1, 134.5, 129.5, 128.8, 127.5, 58.4, 56.8, 37.5, 26.6, 20.3; ν($CHCl_3$)/cm^{-1} 3440, 3023, 1774, 1731, 1214; HRMS [FAB, (M+H)$^+$]: calc. 262.1556, found 262.1563; $[\alpha]_D^{24}$ −66.7 (*c* 0.59, MeOH). For **9h**: mp 134–136 °C; δ_H(CD_3OD, 400 MHz) 3.99 (q, 1H), 1.26 (d, 3H); δ_C(CD_3OD, 101 MHz) 173.1, 156, 50.1 14.9; ν($CHCl_3$)/cm^{-1} 3021, 1784, 1726, 1208; HRMS [FAB, (M + 1)$^+$]: calc. 130.0616, found 130.0612. For **9j**: mp 150–153 °C; δ_H(CD_3OD, 400 MHz) 3.95 (m, 1H), 1.71 (m, 1H), 1.54 (m, 1H), 1.39 (m, 1H), 0.84 (d, 6H); δ_C(CD_3OD, 101 MHz) 171.3, 154.7, 51.3, 37.9, 21.6, 19.4, 17.1; ν($CHCl_3$)/cm^{-1} 3023, 1793, 1724, 1208; HRMS [FAB, (M + 1)$^+$]: calc. 172.1086, found 172.1080; $[\alpha]_D^{24}$ −78.1 (*c* 0.64, MeOH). For **9k**: mp 201–203 °C; δ_H(CD_3OD, 400 MHz) 7.16 (m, 5H), 4.23 (m, 1H), 3.03 (dd, 1H), 2.89 (dd, 1H); HRMS [FAB, (M + 1)$^+$]: calc. 206.0930, found 206.0924.

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