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From cyclic dehydrodipeptides to uncommon acyclic peptide mimetics

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Abstract—1-Acetyl-3-arylmethylene-2,5-piperazinediones gave *N*-3-arylpyruvylamino esters by acid-promoted alcoholysis under thermal conditions or microwave irradiation. Compounds obtained from 1-acetyl-3-(*o*-nitro)arylmethylene-2,5-piperazinediones gave, after reduction of the nitro group and spontaneous cyclization, *N*-2-indolylcarbonylamino acid derivatives. A similar alcoholysis/reduction sequence applied to dehydrodipeptides bearing a 3(4)-nitroaryl substituent gave *N*-3(4)-aminophenyl-α-ketopropionylamino acid derivatives. Coupling of the free amino group with Boc-protected amino acids gave tripeptide mimetics with a 6-aminoindole-2-carboxylic or a 3(4)-aminophenyl-α-ketopropionic acid as the second residue.
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Cyclic dehydrodipeptides have been employed as chiral templates in the synthesis of α-amino acids,[1–3] but very little is known about their interest as intermediates for other synthetic objectives. We here report the acid-promoted alcoholysis of 1-acetyl-3-arylmethylene-2,5-piperazinediones to give *N*-3-arylpyruvylamino esters. The method was extended to nitroaryl derivatives taking part in the synthesis of tripeptide mimetics with an aminoindole-2-carboxylic acid or an aminophenyl-α-ketopropionic acid as the second residue.

Indoles are privileged structures in drug discovery[4] and, probably, represent the most relevant of all structural classes.[5] Indole-2-carboxamides, in particular, are important moieties of biologically active compounds such as the reverse transcriptase inhibitors, delaviridine and ateviridine[6,7] or antitumour agents.[8,9] Several synthetic procedures among the great number of alternatives leading to the indole ring system,[10] involve a cyclizative condensation between an amino and a carbonyl or an imine group.[11,12]

On the other hand, the α-ketoamide moiety is an important building block in neuroregenerative or immunosuppressive macrocyclic polyketides such as FK506 and rapamycin,[13] in the antitumour antibiotic lankacidin,[14] and in many transition-state protease inhibitors.[15–17] The development of the last compounds has become an important goal for the pharmaceutical industry where the search for novel peptide mimetic inhibitors is a very active field. Several of these inhibitors are based on the α-ketoamide linkage in which the affinity towards proteases is related to the nonplanarity of the dicarbonyl group.[18,19] From the synthetic point of view, α-ketoamides are usually prepared by Dess–Martin periodinane oxidation of the corresponding α-hydroxyamides,[15,16] oxidation of α-cyanoketones[20] and amidation of α-ketoacids.[21]

In the course of a project directed to the synthesis of tetrahydroisoquinoline antitumour antibiotics where compounds **1** are starting materials,[22] we observed that compounds **2** were N-deacetylated at room temperature upon standing in chlorohydric acid–methanol. In a detailed study of this process we isolated *N*-3-arylpyruvylamino esters **3** and methanol-adducts **4**. Formation of these minor products indicated that the enamine portion of compounds **2**, after protonation to give the corresponding *N*-acyliminium cations (**I**), can be attacked by nucleophiles at the iminium carbon atom to give adducts **4**, or at the *N*-carbonyl group leading to ring-opening and production of imine intermediates which hydrolyze to α-ketoamides **3** (Scheme 1). The last pathway represents the reversal of a protocol that has been applied for the synthesis of cyclic dehydrodipeptides.[23]

Given the significant yields of **3** that could be obtained when the acid-promoted alcoholysis was performed

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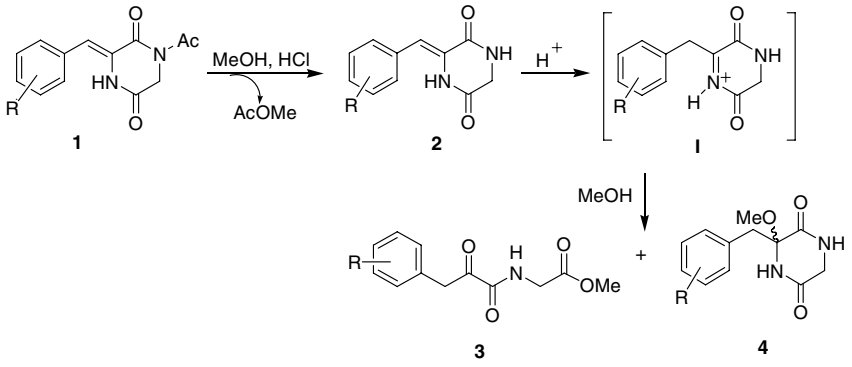
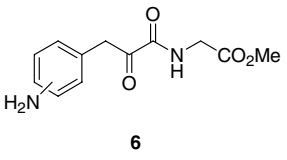
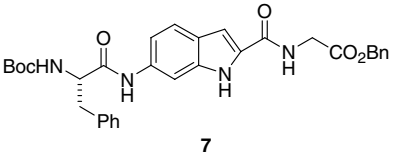
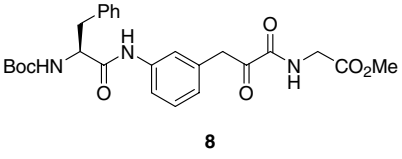


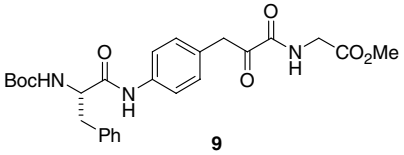
Scheme 1.

under reflux conditions and the accessibility of compounds **1**,[24] we explored this reaction with compounds bearing nitro groups at *o*-, *m*- or *p*-positions of the aryl substituent. The starting materials were obtained in very good yields by condensation of the corresponding nitrobenzaldehyde and *N*,*N*′-diacetyl-2,5-piperazinedione in the presence of potassium *tert*-butoxide. Condensation of aromatic aldehydes bearing an *o*-nitro group was performed in dichloromethane,[25] while tetrahydrofuran was a better solvent for *m*- and *p*-nitro derivatives.







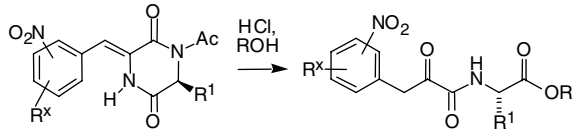


The success of the ring-opening reaction (**1** to **3**) in the first studied *o*-nitrophenyl compounds was highly dependent on the type of the alcohol employed (methanol, isopropanol or benzylic alcohol). Thus, while isopropanol or methanol gave the corresponding *N*-3-arylpyruvylamino esters in very low or moderate yields, benzylic alcohol gave these products in good to excellent yields (see compounds **3a**–**h** in Table 1).[26] Although these differences could be explained by steric reasons they are mainly due to the greater solubility in benzylic alcohol of *N*-deacetyl intermediates **2**. Application of this protocol to *m*- and *p*-nitrophenylmethylene derivatives, which were less soluble than the *o*-nitro compounds in the tested alcohols, gave very low yields for alcoholysis products under thermal conditions. Fortunately, the process worked better by applying microwave irradiation.[27]

Catalytic hydrogenation of the *o*-nitro group in compounds **3a**–**h** afforded in good yields, as it was planned, the corresponding *N*-indole-2-carbonylamino acid derivatives **5**.[28] Under these reaction conditions hydrogenolysis of the benzyl ester and aryl halide groups took place, although the benzyl ester group was maintained in **3g** to give **5d** (Table 2). The chiral compound **3h** gave indolecarboxamide **5e** without detection of epimerization.

Catalytic hydrogenation of the nitro group in compound **3i** and **3l** gave the corresponding aminophenyl-α-ketopropionylamino acid derivatives (**6i,l**). These products, as well as compound **5d**, were N-acylated[29] through standard procedures in peptide chemistry to give compounds **8**, **9** and **7**, respectively.

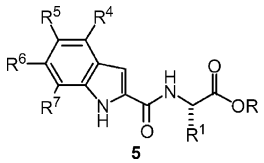
Table 1. Synthesis of *N*-3-arylpyruvylamino esters **3**



Product	Yield (%)	R^x	R^1	R	Nitro group position
3a	59[a]	H	H	Me	2′
3b	93[a]	H	H	Bn	2′
3c	95[a]	6-Cl	H	Bn	2′
3d	66[a]	3,6-$(MeO)_2$	H	Bn	2′
3e	98[a]	4,5-$(MeO)_2$	H	Bn	2′
3f	11[a]	4,5-$(MeO)_2$	H	^{i}Pr	2′
3g	50[a]	4-NO_2	H	Bn	2′
3h	80[a]	H	Me	Bn	2′
3i	8[a]	H	H	Me	3′
3j	12[a]	H	H	Et	3′
3k	16[a]	H	H	Bn	3′
3i	41[b]	H	H	Me	3′
3l	61[b]	H	H	Me	4′

[a] Reflux time: 2.5 h.
[b] Microwave irradiation time: 5 min.

Table 2. Synthesis of *N*-(indole-2-carbonyl)amino acids **5**



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Starting compound	Product (yield %)	R^4	R^5	R^6	R^7	R	R^1
3a	**5a** (76)	H	H	H	H	H	H
3b	**5a** (83)	H	H	H	H	H	H
3c	**5a** (94)	H	H	H	H	H	H
3d	**5b** (79)	MeO	H	H	MeO	H	H
3e	**5c** (94)	H	MeO	MeO	H	H	H
3g	**5d** (60)	H	H	NH_2	H	H	Bn
3h	**5e** (92)	H	H	H	H	Me	H

In conclusion, the regioselective ring opening of the readily available compounds **1** is the key-step in the synthesis of *N*-3-arylpyruvylamino esters. These compounds may be subsequently derived to tripeptide mimetics bearing an aminoindole-2-carboxylic acid or an aminophenyl-α-ketopropionic acid as the intermediate residue. Further research on the application of this protocol to the synthesis of more complex peptide mimetics are in progress in our laboratories.

Acknowledgements

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.07.095.

References and notes

1. Hashimoto, Y.; Aoyagi, H.; Waki, M.; Kato, T.; Izumiya, N. *Int. J. Protein Res.* **1983**, *21*, 11–15.
2. Oba, M.; Terauchi, T.; Owari, Y.; Imai, Y.; Motoyama, I.; Nishiyama, K. *J. Chem. Soc., Perkin Trans. 1* **1998**, 1275–1281.
3. Kukula, P.; Prins, R. Diastereoselective hydrogenation in the preparation of Fine Chemicals. In *Topics in Catalysis*; Springer-Science+Business media B., 2003; Vol. 25, pp 29–42.
4. Horton, D. A.; Bourne, G. T.; Smythe, M. L. *Chem. Rev.* **2003**, *103*, 893–930.
5. For summary of the applications of indoles, see: Gribble, G. W. Five-membered rings with one heteroatom and fused carbocyclic derivatives. In *Comprehensive Heterocyclic Chemistry*; 2nd ed. Bird, C. W., Katrizky, A. R., Rees, C. W., Scriven, E. F. V., Eds.; Pergamon Press: Oxford, 1995; Vol. 2, pp 207–257.
6. Williams, T. M.; Ciccarone, T. M.; MacTough, S. C.; MacTough, S. C.; Rooney, C. S.; Balani, S. K.; Condra, J. H.; Emini, E. A.; Goldman, M. E.; Greenlee, W. J.; Kauffman, L. R.; O'Brien, J. A.; Sardana, V. V.; Schleif, W. A.; Theoharides, A. D.; Anderson, P. S. *J. Med. Chem.* **1993**, *36*, 1291–1294.
7. Romero, D. L.; Morge, R. A.; Biles, C.; Berrios-Peña, N.; May, P. D.; Palmer, J. R.; Johnson, P. D.; Smith, H. V.; Busso, M.; Tan, Ch.-K.; Voorman, R. L.; Reusser, F.; Althaus, I. W.; Downey, K. M.; So, A. G.; Resnick, L.; Tarpley, W. G.; Aristoff, P. A. *J. Med. Chem.* **1994**, *37*, 999–1014.
8. Ichimura, M.; Ogawa, T.; Takahashi, K.; Kobayashi, E.; Kawamoto, I.; Yasuzawa, T.; Takahashi, I.; Nakano, H. *J. Antibiot.* **1990**, *43*, 1037–1038.
9. Kobayashi, E.; Okamoto, A.; Asada, N.; Okabe, M.; Nagamura, S.; Asai, A.; Saito, H.; Gosni, K.; Hirata, T. *Cancer Res.* **1994**, *54*, 2404–2410.
10. Gribble, G. W. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1045–1075.
11. Moody, C. J.; Rahimtoola, K. F. *J. Chem. Soc., Perkin 1* **1990**, 673–679.
12. Tsuji, Y.; Kotachi, S.; Huhm, K.-T.; Watanabe, Y. *J. Org. Chem.* **1990**, *55*, 580–584.
13. Schreiber, S. L. *Science* **1991**, *251*, 283–287.
14. Kende, A. S.; Liu, K.; Kaldor, I.; Dorey, G.; Koch, K. *J. Am. Chem. Soc.* **1995**, *117*, 8258–8270.
15. Han, W.; Hu, Z.; Jiang, X.; Decicco, C. P. *Bioorg. Med. Chem.* **2000**, *10*, 711–713.
16. Sun, D. X.; Liu, L.; Heinz, B.; Kolykhalov, A.; Lamar, J.; Johnson, R. B.; Wang, Q. M.; Yip, Y.; Chen, S. *Bioorg. Med. Chem.* **2004**, *14*, 4333–4338.
17. Chen, K. X.; Njoroge, F. G.; Arasappan, A.; Venkatraman, S.; Vibulbhan, B.; Yang, W.; Parekh, T. N.; Pichardo, J.; Prongay, A.; Cheng, K.; Butkiewicz, N.; Yao, N.; Madison, V.; Girijavallabhan, V. *J. Med. Chem.* **2006**, *49*, 995–1005.
18. Bach, R. D.; Mintcheva, I.; Kronenberg, W. J.; Schlegel, H. B. *J. Org. Chem.* **1993**, *58*, 6135–6138.
19. Kahn, K.; Bruice, T. C. *Bioorg. Med. Chem.* **2000**, *8*, 1881–1891.
20. Yang, Z.; Zhang, Z.; Meanwell, N. A.; Kadow, J. F.; Wang, T. *Org. Lett.* **2002**, *4*, 1103–1105.
21. Nakamura, M.; Inoue, J.; Yamada, T. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 2807–2910.
22. González, J. F.; Salazar, L.; de la Cuesta, E.; Avendaño, C. *Tetrahedron* **2005**, *61*, 7447–7455.
23. Li, W.; Peng, S. *Tetrahedron Lett.* **1998**, *39*, 7373–7376.
24. González, J. F.; de la Cuesta, E.; Avendaño, C. *Synth. Commun.* **2004**, *34*, 1589–1597.
25. *Condensation procedure.* Synthesis of **1a**: To a solution of *N*,*N*′-diacetyl-2,5-piperazinedione (2 g, 10 mmol) in anhydrous CH_2Cl_2 (10 mL), under Ar atmosphere, were added *o*-nitrobenzaldehyde (1.66 g, 11 mmol) and 1 equiv of a 1 M solution of potassium *tert*-butoxide in *tert*-butyl alcohol. The reaction was stirred at room temperature for 5 h. After addition of hexane (10 mL), the condensation product precipitated. The filtrate was first washed with water and then with hexane giving **1a** (2.83 g, 98%): mp 173–174 °C, IR (NaCl, film): 1693, 1640 and 1524 cm^{-1}; ^1H (250 MHz, $CDCl_3$): δ, ppm 8.24 (d, 1H, $J = 8.2$ Hz), 7.95 (ws, 1H), 7.73 (dd, 1H, $J = 8.0$ and 7.8 Hz), 7.62 (dd, 1H, $J = 8.0$ and 7.8 Hz), 7.46 (d, 1H, $J = 8.2$ Hz), 7.44 (s, 1H), 4.48 (s, 2H), 2.69 (s, 3H); ^{13}C (63 MHz, $CDCl_3$): δ, ppm 172.5, 162.7, 158.9, 147.9, 134.4, 130.6, 128.1, 127.0, 126.0, 116.4, 46.1, 27.3. Anal. Calcd for $C_{13}H_{11}N_3O_5$: C, 53.98; H, 3.83; N, 14.53. Found: C, 53.63; H, 3.87; N, 14.18.
26. *Acid-promoted alcoholysis under thermal conditions.* Synthesis of **3b**: To a solution of **1a** (500 mg, 1.75 mmol) in benzyl alcohol (50 mL), was added 5 N HCl (5 mL). The reaction was refluxed for 2.5 h, the solvent was distilled in vacuo to dryness, and the solid residue was purified by

flash chromatography (CH_2Cl_2 as eluant) to give **3b** (580 mg, 93%): mp 92–93 °C, IR (NaCl, film): 3382, 1750, 1689 and 1524 cm^{-1}; ^1H (250 MHz, $CDCl_3$): δ, ppm 8.17 (dd, 1H, $J = 8.1$ and 1.2 Hz), 7.63 (dt, 1H, $J = 7.5$ and 1.3 Hz), 7.50 (dt, 1H, $J = 8.1$ and 1.5 Hz), 7.44 (ws, 1H), 7.37 (s, 5H), 7.32 (dd, 1H, $J = 7.5$ and 1.2 Hz), 5.22 (s, 2H), 4.64 (s, 2H); 4.16 (d, 2H, $J = 5.7$ Hz). ^{13}C (63 MHz, $CDCl_3$): δ, ppm 193.2, 168.5, 159.7, 148.6, 134.9, 133.8, 133.7, 129.4, 128.7, 128.6, 128.4, 125.4, 67.5, 42.5, 41.2. Anal. Calcd for $C_{18}H_{16}N_2O_6$: C, 60.67; H, 4.53; N, 7.85. Found: 60.82; H, 4.70; N, 7.65.

27. *Acid-promoted alcoholysis under microwave irradiation.* Synthesis of **3l**: The microwave instrument used in this experiment was the CEM, Discover. To **1l** (100 mg, 0.35 mmol) in methanol (5 mL), was added 5 N HCl (1 mL) and the mixture was placed in a MW test tube (10 mL) containing a magnetic stirring bar. The tube was sealed and irradiated at 130 °C for 5 min. After cooling to room temperature, the solution was filtered and the solvent evaporated in vacuo. To the residue was added EtOAc (50 mL). The organic solution was washed with brine (50 mL), dried over sodium sulfate, filtered and concentrated. The crude product was purified by flash chromatography (hexane–EtOAc, 7:3 as eluant), to give **3l** (60 mg, 61%): mp 80–81 °C, IR (NaCl, film): 3397, 1750, 1688 and 1519 cm^{-1}; ^1H (250 MHz, $CDCl_3$): δ, ppm 8.22 (d, 2H, $J = 8.8$ Hz), 7.45 (d, 2H, $J = 8.8$ Hz), 4.37 (s, 2H), 4.12 (d, 2H, $J = 5.7$ Hz), 3.81 (s, 3H). ^{13}C (63 MHz, $CDCl_3$): δ, ppm 193.7, 167.0, 159.5, 147.2, 139.9, 130.8, 123.8, 52.6, 42.9, 41.0. Anal. Calcd for $C_{12}H_{12}N_2O_6$: C, 51.43; H, 4.32; N, 10.00. Found: C, 51.29; H, 4.15; N, 9.82.
28. *Reductive cyclization of compounds* **3**. Synthesis of **5a**: A mixture of **3b** (160 mg, 0.45 mmol), in a suspension of Pd–C (20 mg) in EtOAc (30 mL), was hydrogenated at room temperature for 5 h. After filtration over celite and evaporation of the solvent under reduced pressure, the solid residue was purified by flash chromatography (EtOAc as eluant) to give **5a** (82 mg, 83%): mp 158–159 °C, IR (NaCl, film): 3371, 3275, 1738, 1642 and 1552 cm^{-1}; ^1H (250 MHz, DMSO-d_6): δ, ppm 11.63 (s, 1H), 8.96 (t, 1H, $J = 5.7$ Hz), 7.62 (d, 1H, $J = 7.9$ Hz), 7.42 (d, 1H, $J = 8.1$ Hz), 7.18 (dd, 1H, $J = 8.1$ and 7.5 Hz), 7.03 (dd, 1H, $J = 7.9$ and 7.5 Hz), 7.11 (s, 1H), 2.02 (d, 2H, $J = 5.7$ Hz). ^{13}C (63 MHz, DMSO-d_6): δ, ppm 170.7, 161.7, 136.7, 131.2, 127.2, 123.7, 121.8, 120.0, 112.6, 103.2, 41.0. Anal. Calcd for $C_{11}H_{10}N_2O_3$: C, 60.55; H, 4.62; N, 12.84. Found: C, 60.34; H, 4.23; N, 12.60.
29. N-Acylation. Synthesis of compound **8**: To a solution of **6i** (17 mg, 0.66 mmol), *N*-Boc-L-phenylalanine (175 mg, 0.66 mmol), 1-hydroxy-7-azabenzotriazole (HOAt) (103 mg, 0.73 mmol), and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC) hydrochloride (152 mg, 0.79 mmol), in anhydrous DMF (10 mL) under Ar atmosphere at 0 °C, was added 4-methylmorpholine (NMM) (0.22 mL, 1.98 mmol). After being stirred at 0 °C for 2 h, the reaction mixture was kept in a freezer overnight (16 h) and it was then warmed at room temperature. EtOAc (300 mL), brine (50 mL) and 5% H_3PO_4 (50 mL) were added and the layers were separated. The organic solution was washed consecutively with a 1 N solution of sodium bicarbonate (50 mL) and water (50 mL), dried with sodium sulfate, filtered and concentrated to afford **8** (195 mg, 63%) as a white solid. An analytical sample was obtained through flash chromatography (hexane–EtOAc, 7:3 as eluant): mp 64–65 °C, IR (NaCl, film): 3312, 2977, 1752 and 1682 cm^{-1}; ^1H (250 MHz, $CDCl_3$): δ, ppm 7.39 (t, 1H, $J = 7.5$ Hz), 6.89 (d, 1H, $J = 7.5$ Hz), 5.01 (m, 1H), 4.49 (m, 1H), 4.08 (s, 2H), 4.01 (d, 2H, $J = 5.7$ Hz), 3.70 (s, 3H), 3.05 (m, 2H), 1.33 (s, 9H). ^{13}C (63 MHz, $CDCl_3$): δ, ppm 194.6, 169.6, 169.2, 162.4, 159.9, 137.5, 136.5, 133.2, 129.2, 129.1, 128.7, 127.0, 125.9, 121.3, 118.9, 80.8, 56.6, 52.6, 42.9, 40.9, 38.3, 28.3. Anal. Calcd for $C_{26}H_{31}N_3O_7$: C, 62.76; H, 6.28; N, 8.45. Found: C, 62.48; H, 6.15; N, 8.32.