Intramolecular Aza-Wittig Reaction: A New Efficient Tool for the Construction of Piperazine 2,5-Dione Derivatives

K. C. Majumdar,* Krishanu Ray, Sintu Ganai

Department of Chemistry, University of Kalyani, Kalyani 741235, West Bengal, India
E-mail: kcm_ku@yahoo.co.in

Received 4 June 2010

Abstract: A new efficient approach for the synthesis of unsymmetricaly substituted piperazine 2,5-dione derivatives is described by using intramolecular aza-Wittig reaction as the key step. The reaction conditions are very simple, offer easy isolation, and excellent yields of the products.

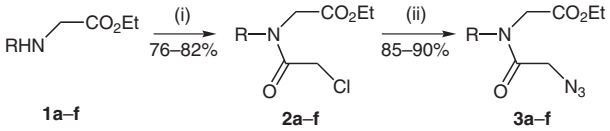
Key words: piperazine 2,5-dione, intramolecular aza-Wittig reaction, iminophosphorane, cyclization

2,5-Diketopiperazines, known as cyclic dipeptides, are frequently formed from both enzymatic and nonenzymatic processes of peptides/protein.[1] They are also well-known as byproducts that are formed during removal of temporal protecting group of secondary amino acids.[2] The piperazine-2,5-dione moiety occurs in a variety of drugs and natural products which show interesting biological activities[3] including antiviral,[4] antifungal,[5] antitumour,[6] antithrombic,[7] and antibacterial activities.[8] Additionally this heterocyclic system has found unique applications as an acceptor for organic anions or metal cations[9] and in material science.[10] While numerous approaches have been reported[11–14] for the synthesis of piperazine 2,5-diones there is still demand for more easier synthetic pathways. Generally, synthesis of 2,5-DKP starting from amino acids or amino esters requires protection, deprotection, and cyclization reactions which occur either in situ or at elevated temperatures.

The aza-Wittig reaction has become one of the most important synthetic method for the construction of C=N, N=N, and S=N double bonds especially in the preparation of nitrogen containing heterocycles. Iminophosphoranes, nitrogen analogues of phosphorus ylides, are versatile intermediates in modern synthetic chemistry.[15] Numerous research papers and reviews have appeared in the literature describing the general use of iminophosphorane as reagent and intermediate in organic synthesis,[16] including the synthesis of heterocyclic natural products by the aza-Wittig method.[17]

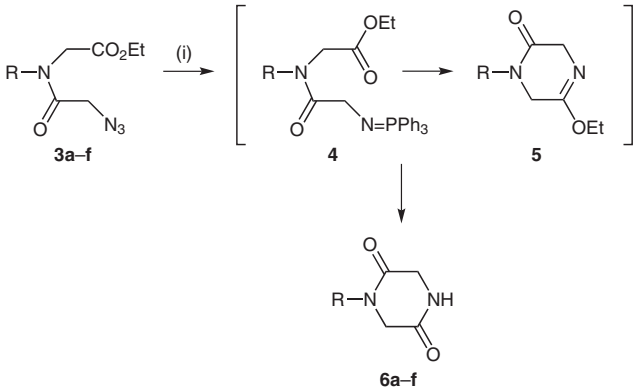
In continuation of our research interest in the synthesis of nitrogen heterocycles[18] we have undertaken a study to synthesize 2,5-diketopiperazine derivatives of biological interest from N-substituted amino esters using intramolecular aza-Wittig reaction as the key step, and the results are reported here.

The precursors **3a–f** required for our present study were synthesized from the amino esters **1a–f**. Treatment of **1a–f** with chloroacetyl chloride under phase-transfer-catalysis conditions gave the amides **2a–f**. The amide formation reaction under the PTC conditions proceeded at a much faster rate than any normal amide formation reaction. Compound **2a–f** were then treated with excess of sodium azide in DMF solution at 90 °C to afford the azide compounds **3a–f** in good to excellent yields (Scheme 1).



Scheme 1 *Reagents and conditions*: (i) chloroacetyl chloride, CH_2Cl_2–H_2O, K_2CO_3, r.t.; (ii) NaN_3, DMF, 90 °C.

Initially, the intramolecular aza-Wittig reaction was conducted with the substrate **3a**. When **3a** was treated with triphenylphosphine in THF at room temperature, product **6a** was afforded along with triphenylphosphine oxide. The intermediate iminophosphorane **4** was not isolated (Scheme 2).



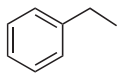
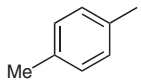
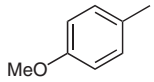
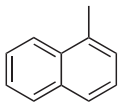
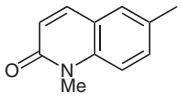
Scheme 2 *Reagents and conditions*: (i) Ph_3P, THF, r.t.

In this case the iminophosphorane **4** formed during the reaction readily underwent cyclization to form the intermediate **5** followed by enol ether cleavage in moist THF (not anhydrous) to give the final product **6a**[19] in 96% yield. The other solvents, acetonitrile, dichloromethane, and toluene, were also effective in the cyclization but THF

SYNLETT 2010, No. 14, pp 2122–2124
Advanced online publication: 27.07.2010
DOI: 10.1055/s-0030-1258519; Art ID: G13910ST

was the best choice as it gave the maximum yield of **6a**. Accordingly the other substrates **3b–f** were similarly treated to give the desired cyclized products **6b–f** in 88–96% yields. The results are summarized in Table 1.

Table 1 Summarized Results of the Intramolecular Aza-Wittig Reaction

Entry	R	Substrate	Time (min)	Product	Yield (%)
1		**3a**	30	**6a**	96
2		**3b**	30	**6b**	92
3		**3c**	30	**6c**	94
4		**3d**	30	**6d**	95
5		**3e**	30	**6e**	92
6		**3f**	30	**6f**	88

Although a recent report[20] in the literature shows a one-pot preparation of symmetrically 1,4-substituted piperazine 2,5-diones but our methodology provides the synthesis of 1-substituted piperazine 2,5-diones which can be converted into pyrazino[2,1-*b*]quinazoline-3,6-dione,[21] an important scaffold, present in a several families of natural products such as the fiscalins,[22] the fumiquinazolines,[23] and *N*-acetylardeemin.[24] However, this 1-substituted piperazinones can also be used as other important scaffolds by protection of the second nitrogen atom and performing further substitution at C2/C5 position.

In summary we have developed a strategy to generate different mono-*N*-substituted piperazine 2,5-diones starting from easily available amino esters using intramolecular aza-Wittig reaction as the key step. The method allows mild reaction conditions, easy separation of products, and affords the products in excellent yields.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

Acknowledgment

We thank (New Delhi) and CSIR (New Delhi) for financial assistance. Two of us (K.R. and S.G.) are grateful to CSIR (New Delhi) for their research fellowships.

References and Notes

(1) Prasad, C. *Peptides* **1995**, *16*, 151.
(2) (a) Rothe, M.; Mazanek, R. B. *Liebigs Ann. Chem.* **1974**, 439. (b) Rovero, P.; Vigano, S.; Pegoraro, S.; Quartara, L. *Lett. Peptide Sci.* **1995**, *2*, 319. (c) Chiva, C.; Vilaseca, M.; Giralt, E.; Albericio, F. *J. Pept. Sci.* **1999**, *5*, 131. (d) Borsuk, K.; van Delft, F. L.; Eggen, I. F.; ten Kortenaar, P. B. W.; Petersen, A.; Rutjes, F. P. J. T. *Tetrahedron Lett.* **2004**, *45*, 3585.
(3) (a) Martins, M. B.; Carvalho, I. *Tetrahedron* **2007**, *63*, 9923. (b) Li, W.-R.; Yang, J. H. *J. Comb. Chem.* **2002**, *4*, 106. (c) McCleland, K.; Milne, P. J.; Lucieto, F. R.; Frost, C.; Brauns, S. C.; Venter, M. V. D.; Plessis, J. D.; Dyason, K. *J. Pharm. Pharmacol.* **2004**, *56*, 1143.
(4) Sinha, S.; Srivastava, R.; De Clercq, E.; Singh, R. *Nucleosides, Nucleotides Nucleic Acids* **2004**, *23*, 1815.
(5) (a) Houston, D. R.; Synstad, B.; Eijsink, V. G. H.; Stark, M. J. R.; Eggleston, I. M.; van Aalten, D. M. F. *J. Med. Chem.* **2004**, *47*, 5713. (b) Byun, H.-G.; Zhang, H.; Mochizuki, M.; Adachi, K.; Shizuri, Y.; Lee, W.-J.; Kim, S.-K. *J. Antibiot.* **2003**, *56*, 102. (c) Park, Y. C.; Gunasekera, S. P.; Lopez, J. V.; McCarthy, P. J.; Wright, A. E. *J. Nat. Prod.* **2006**, *69*, 580.
(6) (a) Nicholson, B.; Lloyd, G. K.; Miller, B. R.; Palladino, M. A.; Kiso, Y.; Hayashi, Y.; Neuteboom, S. T. C. *Anti-Cancer Drugs* **2006**, *17*, 25. (b) Kozlovsky, A. G.; Vinokurova, N. G.; Adanin, V. M.; Burkhardt, G.; Dahse, H.-M.; Grafe, U. *J. Nat. Prod.* **2000**, *63*, 698.
(7) Lucietto, F. R.; Milne, P. J.; Kilian, G.; Frost, C. L.; Van De Venter, M. *Peptides* **2006**, *27*, 2706.
(8) (a) Huberman, L.; Gollop, N.; Mumcuoglu, K. Y.; Breuer, E.; Bhusare, S. R.; Shai, Y.; Galun, R. *Med. Vet. Entomol.* **2007**, *21*, 127. (b) Clark, B.; Capon, R. J.; Lacey, E.; Tennant, S.; Gill, J. H. *J. Nat. Prod.* **2005**, *68*, 1661. (c) Fdhila, F.; Vazquez, V.; Sanchez, J. L.; Riguera, R. *J. Nat. Prod.* **2003**, *66*, 1299.
(9) Fuji, K.; Takasu, K.; Miyamoto, H.; Tanaka, K.; Taga, T. *Tetrahedron Lett.* **1996**, *37*, 7111.
(10) Li, W.-R.; Kao, K.-C.; Yo, Y.-C.; Lai, C. K. *Helv. Chim. Acta* **1999**, *82*, 1400.
(11) Perez-Picaso, L.; Escalante, J.; Olivo, H. F.; Rios, M. Y. *Molecules* **2009**, *14*, 2836.
(12) Bossio, R.; Marcos, C. F.; Marcaccini, S.; Pepino, R. *Tetrahedron Lett.* **1997**, *38*, 2519.
(13) Marcaccini, S.; Pepino, R.; Pozo, M. C. *Tetrahedron Lett.* **2001**, *42*, 2727.
(14) Falorni, M.; Giacomelli, G.; Porcheddu, A.; Taddei, M. *Eur. J. Org. Chem.* **2000**, 1669.
(15) For recent contributions, see: (a) Cossío, F. P.; Alonso, C.; Lecea, B.; Ayerbe, M.; Rubiales, G.; Palacios, F. *J. Org. Chem.* **2006**, *71*, 2839. (b) Cassidy, M. P.; Oezdemir, A. D.; Padwa, A. *Org. Lett.* **2005**, *7*, 1339. (c) Ding, M.-W.; Huang, N.-Y.; He, H.-W. *Synthesis* **2005**, 1601. (d) Snider, B. B.; Zhon, J. *J. Org. Chem.* **2005**, *70*, 1087. (e) Gil, C.; Bräse, S. *Chem. Eur. J.* **2005**, *11*, 2680. (f) Alajarín, M.; Sánchez-Andrada, P.; Vidal, A.; Tovar, F. *J. Org. Chem.* **2005**, *70*, 1340.
(16) For reviews, see: (a) Palacios, F.; Alonso, C.; Aparicio, D.; Rubiales, G.; de los Santos, J. M. *Tetrahedron* **2007**, *63*, 523. (b) Palacios, F.; Aparicio, D.; Rubiales, G.; Alonso, C.; de los Santos, J. M. *Curr. Org. Chem.* **2006**, *10*, 2371. (c) Eguchi, S. *Top. Heterocycl. Chem.* **2006**, *6*, 113. (d) Arqués, A.; Molina, P. *Curr. Org. Chem.* **2004**, *8*, 827. (e) Wamhoff, H.; Richardt, G.; Stölben, S. *Adv. Heterocycl. Chem.* **1995**, *64*, 159. (f) Molina, P.; Vilaplana, M. J. *Synthesis* **1994**, 1197. (g) Nitta, M. *Reviews on Heteroatom Chemistry*, Vol. 9; Oae, S., Ed.; MYU K. K.: Tokyo, **1993**,

87. (h) Gololobov, Y. G.; Kasukhin, L. F. *Tetrahedron* **1992**, *48*, 1353. (i) Barluenga, J.; Palacios, F. *Org. Prep. Proced. Int.* **1991**, *23*, 1.

(17) (a) Eguchi, S. *ARKIVOC* **2005**, *(ii)*, 98. (b) Fresneda, P. M.; Molina, P. *Synlett* **2004**, 1. (c) Eguchi, S.; Okano, T.; Okawa, T. *Recent Res. Dev. Org. Chem.* **1997**, 337.

(18) (a) Majumdar, K. C.; Ray, K.; Ganai, S. *Tetrahedron Lett.* **2010**, *51*, 1736. (b) Majumdar, K. C.; Ray, K.; Ganai, S.; Ghosh, T. *Synthesis* **2010**, 858. (c) Majumdar, K. C.; Ray, K.; Ganai, S. *Synthesis* **2010**, 2101. (d) Majumdar, K. C.; Chakravorty, S.; Ghosh, T.; Sridhar, B. *Synlett* **2010**, 3127. (e) Majumdar, K. C.; Taher, A.; Ponra, S. *Synlett* **2010**, 735.

(19) **General Procedure for the Preparation of Compound 6a**
To a solution of compound **3a** (100 mg, 0.36 mmol) in THF (5 mL) was added Ph_3P (142 mg, 0.54 mmol). The mixture was stirred at r.t. for 30 min. After completion of the reaction (as monitored by TLC), THF was completely evaporated, and the crude product was purified by column chromatography over silica gel (60–120 mesh) using PE–EtOAc (1:1) as eluant to give the pure product **6a** in 96% yield.
Yield 96%, solid, mp 208–210 °C. IR (KBr): ν_{max} = 1655, 1689, 3243 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.27–7.38 (m, 5 H), 6.26 (br s, 1 H), 4.61 (s, 2 H), 4.10 (s, 2 H), 3.86 (s, 2 H). ^{13}C NMR (125 MHz, DMSO-d_6): δ = 44.4, 48.2, 49.0, 127.4, 127.8, 128.5, 136.2, 164.3, 165.5. HRMS: *m/z* calcd for $C_{11}H_{12}N_2O_2$: 227.0797 [M^+ + Na]; found: 227.0797 [M^+ + Na].

(20) O'Reilly, E.; Pes, L.; Paradisi, F. *Tetrahedron Lett.* **2010**, *51*, 1696.

(21) Hernández, F.; Morales, V.; Buenadicha, F. L.; Söllhuber, M.; Avendaño, C. *Tetrahedron: Asymmetry* **2004**, *15*, 3045.

(22) (a) Wong, S.-M.; Musza, L. L.; Kydd, G. C.; Kullnig, R.; Gillum, A. M.; Cooper, R. *J. Antibiot.* **1993**, *46*, 545. (b) Fujimoto, H.; Negishi, E.; Yamaguchi, K.; Nishi, N.; Yamazaki, M. *Chem. Pharm. Bull.* **1996**, *44*, 1843.

(23) (a) Numata, A.; Takahashi, C.; Matsushita, T.; Miyamoto, T.; Kawai, K.; Usami, Y.; Matsumura, E.; Inoue, M.; Ohishi, H.; Shingu, T. *Tetrahedron Lett.* **1992**, *33*, 1621. (b) Takahashi, C.; Matsushita, T.; Doi, M.; Minoura, K.; Shingu, T.; Kumeda, Y.; Numata, A. *J. Chem. Soc., Perkin Trans. 1* **1995**, 2345.

(24) (a) Karwowski, J. P.; Jackson, M.; Rasmussen, R. R.; Humphrey, P. E.; Poddig, J. B.; Kohl, W. L.; Scherr, M. H.; Kadam, S.; McAlpine, J. B. *J. Antibiot.* **1993**, *46*, 374. (b) Hochlowski, J. E.; Mullally, M. M.; Spanton, S. G.; Whittern, D. N.; Hill, P.; McAlpine, J. B. *J. Antibiot.* **1993**, *46*, 380.