ORGANIC LETTERS

2003
Vol. 5, No. 22
4057−4060

Westphal Reaction in Solid-Phase

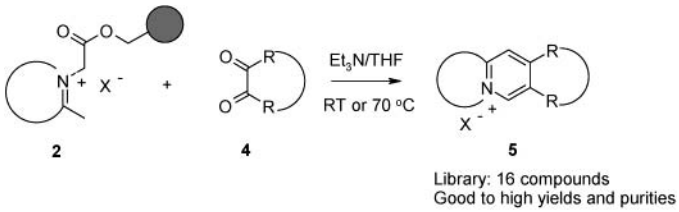
Francisca Delgado, M. Lourdes Linares, Ramón Alajarín, Juan J. Vaquero, and Julio Alvarez-Builla*

Departamento. de Química Orgánica, Universidad de Alcalá, Campus Universitario, 28871-Alcalá de Henares, Madrid, Spain

julio.alvarez@uah.es

Received July 28, 2003

ABSTRACT



A library of cycloimonium salts has been prepared through Westphal reaction in solid-phase. By reaction of solid-support-bound azolium or azinium acetates 2, 1,2-diketones 4, and base, cycloimonium salts 5 were synthesized in good to high yield and purities.

Combinatorial chemistry has emerged as a powerful tool in the drug discovery process. In particular, solid-phase synthesis methods drive reactions to completion, giving high yields and purities of products in a fast and productive manner.[1] Although solid-phase synthesis methods have been widely exploited in the last years, those involving charged molecules have been mainly directed to the preparation of polymer-supported reagents and scavengers or in intermediate steps involving phosphonium or sulfonium salts.[2] Those, however, going through or directed to the synthesis of charged heterocycles have been comparatively scarce.

To our knowledge the first reported solid-phase synthesis involving charged heterocycles has been the application of resin-bound pyridinium ylides to the synthesis of trisubstituted cyclopropanecarboxylates.[3] Later on, other uses of pyridinium methylides appeared. Thus, Tsuge reaction has been performed on solid-phase to give maleimide-fused indolizinium carboxylates.[4] In a related way, the Katritzky route to indolizines by formal [3 + 2] dipolar cycloaddition of a pyridinium salt with chalcones, followed by oxidation, has been achieved by polymer-assisted synthesis.[5] Another classical reaction applied on solid-phase is the Zincke reaction, which allowed preparation of ω-hydroxy pyridinium or isoquinolinium salts and pyridinium vesamicol analogues.[6] In another report, substituted pyridinium moieties have been introduced, through the Zincke reaction, during the solid-phase peptide synthesis of thyrotropin-releasing hormone analogues.[7]

Other works appeared in the literature in which azinium salts were prepared on solid-phase. A library of 1,3,5-trisubstituted pyridinium salts was synthesized from 5-bromonicotinic acid on Rink resin, through Suzuki coupling and further alkylation of the pyridine nitrogen.[8] Also, pyridinium-substituted azoles were obtained by alkylation of (3-pyridyl)-substituted azoles prepared on solid-phase.[9] Similarly, azinium (pyridinium and quinolinium) salts as asymmetric cyanine dyes have been obtained by solid-phase combina-

(1) Seneci, P. In *Solid-Phase Synthesis and Combinatorial Technologies*; John Wiley & Sons: New York, 2001.

(2) (a) Obrecht, D.; Villalgordo, J. M. In *Solid-Supported Combinatorial and Parallel Synthesis of Small-Molecular-Weight Compound Libraries*; Baldwin, J. E., Williams, R. M., Eds.; Pergamon: Elsevier Science: Oxford, 1998; Tetrahedron Organic Chemistry Series, Vol. 17. (b) Kirschning, A.; Monenschein, H.; Wittenberg, R. *Angew. Chem., Int. Ed.* **2001**, *40*, 650. (c) Thompson, L. A. *Curr. Opin. Chem. Biol.* **2000**, *4*, 324.

(3) Vo, N.-H.; Eyermann, C. J.; Hodge, C. N. *Tetrahedron Lett.* **1997**, *38*, 7951.

(4) Bicknell, A. J.; Hird, N. W.; Readshaw, S. A. *Tetrahedron Lett.* **1998**, *39*, 5869.

(5) Goff, D. A. *Tetrahedron Lett.* **1999**, *40*, 8741.

(6) (a) Eda, M.; Kurth, M. J.; Nantz, M. H. *J. Org. Chem.* **2000**, *65*, 5131. (b) Eda, M.; Kurth, M. J. *Tetrahedron Lett.* **2001**, *42*, 2063.

(7) Prokai-Tatrai. K.; Perjési, P.; Zharikova, A. D.; Li, X.; Prokai, L. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 2171.

(8) Lago, M. A.; Nguyen, T. T.; Bhatnagar, P. *Tetrahedron Lett.* **1998**, *39*, 3885.

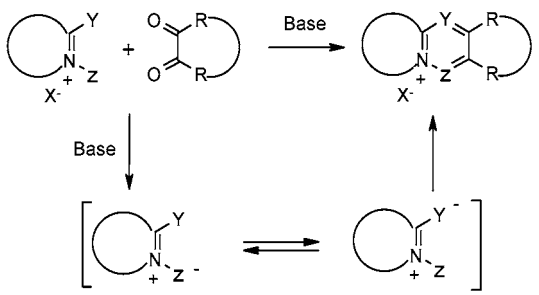
(9) Grosche, P.; Höltzel, A.; Walk, T. B.; Trautwein, A. W.; Jung, G. *Synthesis* **1999**, 1961.

10.1021/ol035417z CCC: $25.00
Published on Web 10/07/2003

torial synthesis.[10] Additionally, azolium ylides have been applied to a traceless solid-phase synthesis of 2-substituted azoles.[11]

An interesting class of charged heterocycles is polycyclic nitrogen bridgehead cycloimmonium salts. As an example, quinolizinium salts have shown DNA intercalative properties and antiproliferative activity.[12] An easy way to access to cycloimmonium and related salts is the Westphal condensation (Scheme 1). O. Westphal et al. reported in 1961 the

Scheme 1



condensation of a cycloimmonium salt, such as an *N*-alkyl-substituted 2-picolinium salt, acting as an 1,4-dinucleophile (C−C substrate) on 1,2-diketones in the presence of an organic base, to give the corresponding substituted quinolizinium salts.[13] Later on, A. N. Kost and co-workers published the first examples of the use of N−N substrates, in the condensation of 1,2-diaminopyridinium perchlorate with 1,2-diketones to give pyrido[1,2-*b*]triazinium perchlorates.[14] Since 1990, our group has been working on the Westphal condensation of N−C azinium and azolium substrates to afford diverse aza-quinolizinium and related cations.[15]

Our recent interest in solid-phase and parallel synthesis methods, as well as our long research in synthesis and reactivity of cycloimmonium salts, has been focused on developing the Westphal reaction in solid-phase.[16] The only precedent in the literature has been the preparation of polyquinoliziniums as cation-exchange resins, through Westphal reaction of poly-2-methyl-5-vinylpyridine-divinylbenzene or via polymerization of 2,3-dimethyl-7-vinylquinolizinium bromide.[17] Here we wish to report our results in the preparation of a library of cycloimmonium salts by Westphal condensation on solid-phase.

Initially, some heterocyclic building blocks **1a**−**h**, including five- and six-membered heterocycles, benzofused or not, were selected (Figure 1).

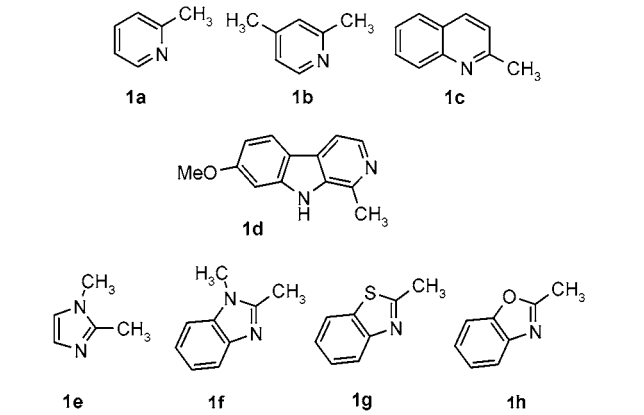
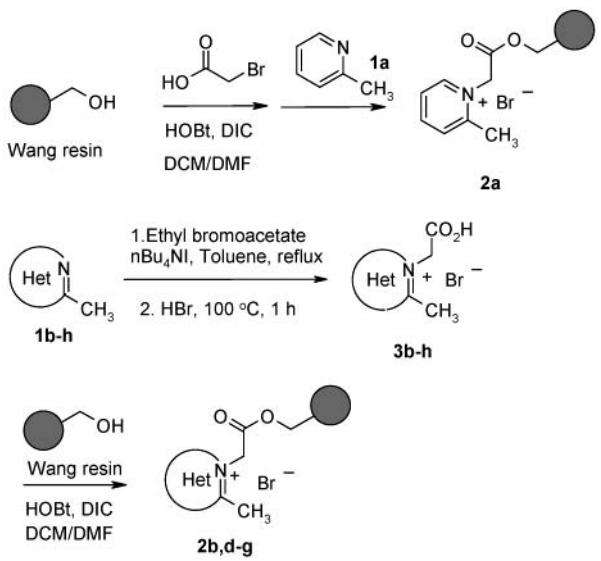


Figure 1. Heterocyclic building blocks **1a**−**h**.

Anchoring of **1a**−**h** was performed in two different ways (Scheme 2). Wang resin (PS-DVB 1%, 0.80 mmol/g; ArgoGel, 0.40 mmol/g) was chosen as a solid support. For **1a**, the method reported by Hodge was performed, but it was slightly modified by adding *N*-hydroxybenzotriazole (HOBt) as an activator, in a mixture of DIC in DMF/CH_2Cl_2.

Then, the suspension was shaken overnight at room temperature to give **2a**. This method, however, was not suitable for **1b**−**h**, since low loadings of resins **2** were obtained. These building blocks were first reacted with ethyl

Scheme 2



(10) Isacsson, J.; Westman, G. *Tetrahedron Lett.* **2001**, *42*, 3207.
(11) Deng, Y.; Hlasta, D. J. *Org. Lett.* **2002**, *4*, 4017.
(12) (a) Pastor, J.; Siro, L.; García-Navío, J. L.; Vaquero, J. J.; Rodrigo, M. M.; Ballesteros, M.; Alvarez-Builla, J. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 3043. (b) Molina, A.; Vaquero, J. J.; García-Navío, J. L.; Alvarez-Builla, J.; de Pascual-Teresa, B.; Gago, F.; Rodrigo, M. M. *J. Org. Chem.* **1999**, *64*, 3907. (c) Fontana, A.; Benito, E. J.; Martín, M. J.; Sánchez, N.; Alajarín, R.; Vaquero, J. J.; Alvarez-Builla, J.; Lambel-Giraudet, S.; Leonce, S.; Pierré, A.; Caignard, D. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 2611.
(13) Westphal, O.; Jahn, K.; Heffe, W. *Arch. Pharm. (Weinheim, Ger.)* **1961**, *294*, 37.
(14) Baranova, N.; Sheinkman, A. K.; Kost, A. N. *Khim. Geterotsikl. Soedin.* **1970**, *8*, 1148; *Chem. Abstr.* **1971**, *75*, 63840.
(15) Matía, M. P.; García Navío, J. L.; Vaquero, J. J.; Alvarez-Builla, J. *J. Heterocycl. Chem.* **1990**, *27*, 661.
(16) (a) Vaquero, J. J.; Alvarez-Builla, J. *Adv. Nitrogen Heterocycl.* **2000**, *4*, 159. (b) Martínez-Barrasa, V.; Burgos, C.; Izquierdo, M. L.; Alvarez-Builla, J.; Vaquero, J. J. *Tetrahedron Lett.* **1999**, *40*, 4115. (c) Díaz, A.; Matía, M. P.; Ezquerra, J.; García Navío, J. L.; Vaquero, J. J.; Alvarez-Builla, J. *J. Org. Chem.* **1994**, *59*, 8294.

bromoacetate, in refluxing toluene and then hydrolyzed in refluxing 48% HBr for 1 h to give azinium or azolium acetic acids **3b**−**h**. Compound **3h** was not fully characterized since it decomposed under LC-MS conditions. Then, anchoring to Wang resin was performed using DIC/HOBt to give resins **2b**,**d**−**g**. Compound **3c** was not anchored under their conditions, and **3h** decomposed when cleaved from the resin with TFA. The substitution level for **2a**,**b**,**d**−**g** was quantified by TFA cleavage and subsequent mass balance of isolated **3**. Resin building blocks **2** prepared are shown in Figure 2.

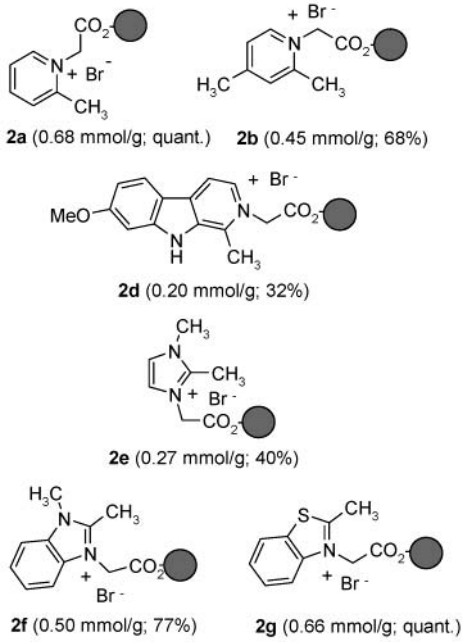


Figure 2. Resin building blocks **2**.

Having resins **2** on hand, symmetric diketones **4** were selected bearing alkyl, aryl, and heteroaryl groups, either acyclic or constrained cyclic (Figure 3).

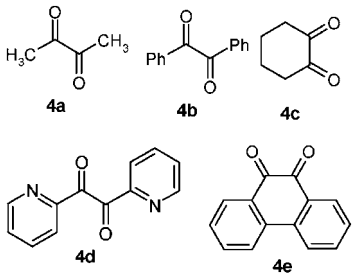


Figure 3. Diketone building blocks **4**.

Then, Westphal reaction conditions were optimized for **2a** and **4a** as a model (Table 1). All experiments were performed at room temperature. Initially, conventional condi-

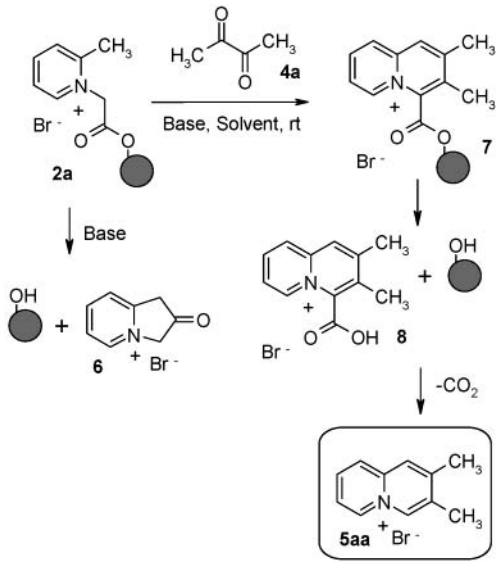
Table 1. Optimization of Westphal Reaction on Solid-Phase

entry	resin[a]	**4a** (equiv)	base (equiv)[b]	solvent[c]	**5aa**/**6**[d]
1	A	3	C (3)	E/F (1:1)	1/1
2	B	3	C (3)	E/F (1:1)	1/1
3	A	5	C (3)	E/F (1:1)	1/1
4	A	3	C (5)	E/F (1:1)	1/1
5	A	5	C (10)	E/F (1:1)	1/1
6	A	10	C (5)	E/F (1:1)	1/1
7	A	3	C (3)	F	1/1
8	A	3	C (3)	E	1/1
9	A	3	D (3)	G	1/0
10	A	5	D (5)	G	1/0
11	A	3	D (3)	H	
12	A	3	D (3)	I	1/0

[a] A: PS-Wang. B: ArgoGel-Wang. [b] C: AcONa. D: Et_3N. [c] E: acetone. F: ethanol. G: DMF. H: CH_2Cl_2. D: THF. [d] Entries 1−8: **5aa** (19−22%). Entries 9, 10, and 12: **5aa** (80%).

tions using sodium acetate as a base and acetone and/or ethanol as solvents were explored for resin **2a**, prepared from PS-Wang or ArgoGel-Wang solid supports. Variation of the number of equivalents of **4a** and sodium acetate, as well as the solvent, gave in every case low yields of a mixture of quinolizinium derivative **5aa** and **6** in a 1:1 ratio. This set of reactions was performed in parallel on either PS and ArgoGel solid supports. Both resins have the same behavior. PS-Wang resin, being cheaper, was finally selected. Under these conditions, **2a** gave **6** as a byproduct through cyclization-assisted cleavage. On the other hand, Westphal condensation took place to give **7** (Scheme 3), which, under the

Scheme 3

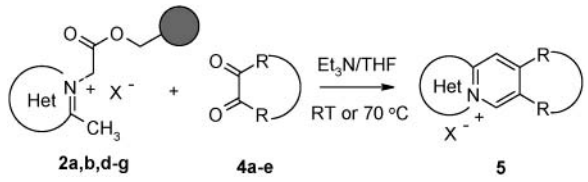


reaction conditions, hydrolyzed to **8**, which spontaneously gave **5aa** by decarboxylation. This sequence of hydrolysis−decarboxylation has usually been observed in conventional Westphal condensations in solution.[17] When triethylamine

was used as a base, **5aa** was the only product detected, either in THF or DMF, while no product was detected in CH_2Cl_2. Only 3 equiv of base were necessary to perform the conversion. THF was the solvent of choice, since **5aa** was then isolated easily in higher purity.

The optimized reaction conditions were then applied to the synthesis of a library of cycloimmonium salts **5** (Scheme 4).

Scheme 4



When reactions were performed at room temperature, using the optimized conditions, results were not quite successful. Thus, the same process was performed at 70 °C overnight, using a parallel format. After filtering and washing the resins, solvent was evaporated, and the crude products were treated with Et_2O/CH_2Cl_2 to give **5** as solids, in high yield and good purities (Figure 4, Table 2). For **2e**, complex

Table 2. Yields and Purities (%, in Parentheses) for Compounds **5**

	2a	**2b**	**2d**	**2f**
4a	**5aa** 80(100)	**5ba** 95(100)	**5da** 98(90)	**5fa** 97(84)
4b	**5ab** 64(97)	**5bb** 82(75)	**5db** mixture	**5fb** 86(88)
4c	**5ac** 80(98)	**5bc** mixture	**5dc** mixture	**5fc** 90(93)
4d	**5ad** 95(90)	**5bd** 90(78)	**5dd** 90(92)	**5fd** 95(93)
4e	**5ae** 69(100)	**5be** mixture	**5de** 99(83)	**5fe** 97(84)

mixtures were obtained in every case. The library was analyzed by HPLC and fully characterized.[18]

In summary, a solid-phase Westphal reaction has been developed for 1,4-dinucleophile azinium or azolium salts (C−C substrates) and a library of nitrogen bridgehead cycloimmoniun salts has been prepared in high yields and

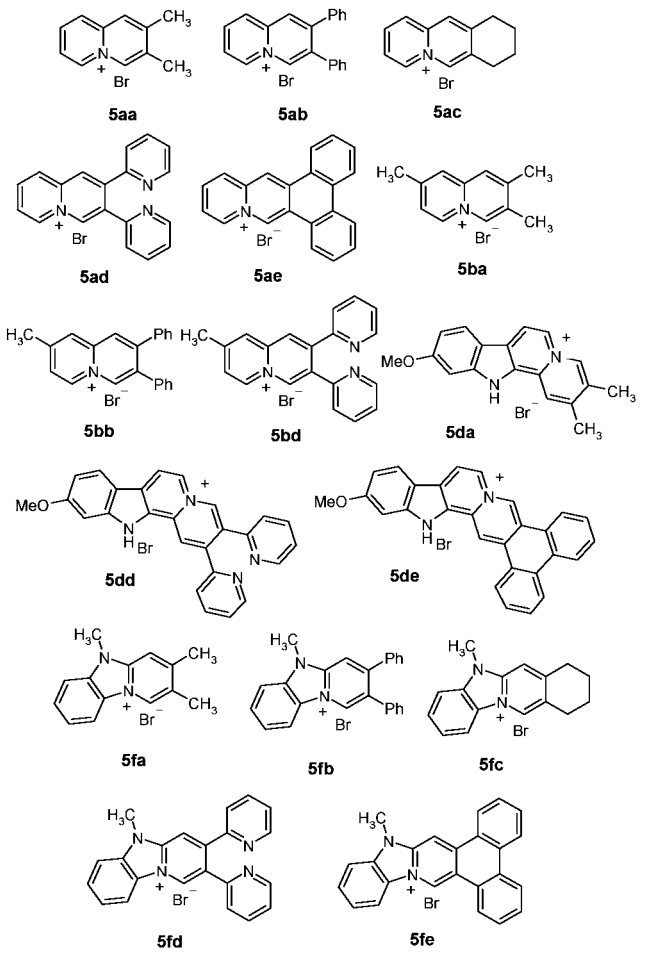


Figure 4. Library synthesized.

purities. Now, work is in progress to prepare new libraries using N−C substrates to apply the methodology to the synthesis of new DNA intercalators and antitumor agents.

Acknowledgment. We thank the Universidad de Alcalá (UAH2002/052) and the Comisión Interministerial de Ciencia y Tecnología (CICYT, BQU2001-1508 and BQU 2002-03578) for funding the project. We also thank Dr. J. L. García-Navío for helpful comments and Mr. Alberto Fontana (JANSSEN-CILAG, Toledo, Spain) for LC-MS analysis.

Supporting Information Available: Experimental procedures and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

OL035417Z

(17) Costin, C. R. U.S. Pat. 4046766, 1977; *Chem. Abstr.* **1977**, *87*, 152907.

(18) Purities are given at 220 nm. The members of the library were characterized by HRMS and NMR.