Westphal Reaction in Solid-Phase

5 AUTHORS, INCLUDING:

Ramon Alajarin
University of Alcalá
36 PUBLICATIONS **419** CITATIONS

SEE PROFILE

Julio Alvarez-Builla
University of Alcalá
**240** PUBLICATIONS **2,467** CITATIONS

SEE PROFILE

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

ABSTRACT

Library: 16 compounds
Good to high yields and purities
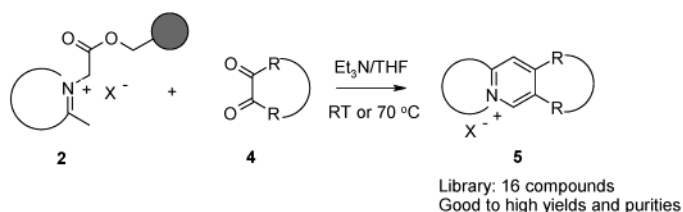
A library of cycloimonium salts has been prepared through Westphal reaction in solid-phase. By reaction of solid-support-bound azolium or azinium acetates 2, 1,2-diketones 4, and base, cycloimonium salts 5 were synthesized in good to high yield and purities.

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.

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
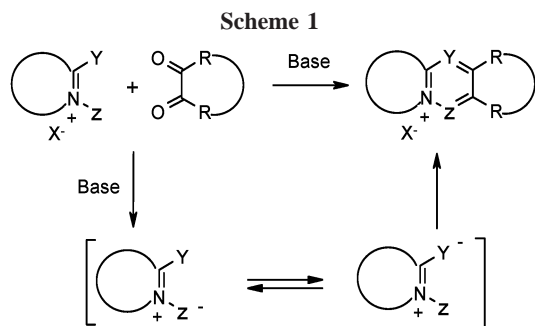
condensation of a cycloimmonium salt, such as an *N*-alkyl-substituted 2-picolinium salt, acting as an 1,4-dinucleophile (C−C substrate) on 1,2-diketones in the presence of an organic base, to give the corresponding substituted quinolizinium salts.[13] Later on, A. N. Kost and co-workers published the 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).
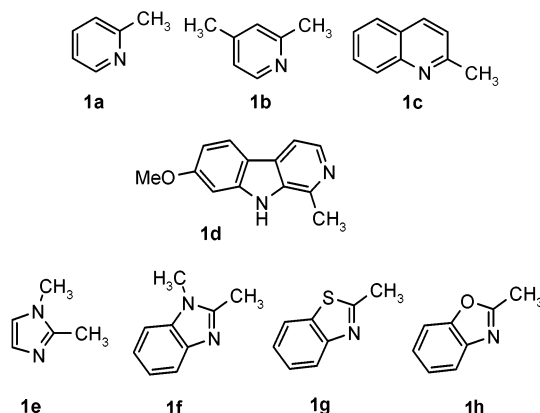

Figure 1. Heterocyclic building blocks **1a−h**.

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$_2$Cl$_2$.

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
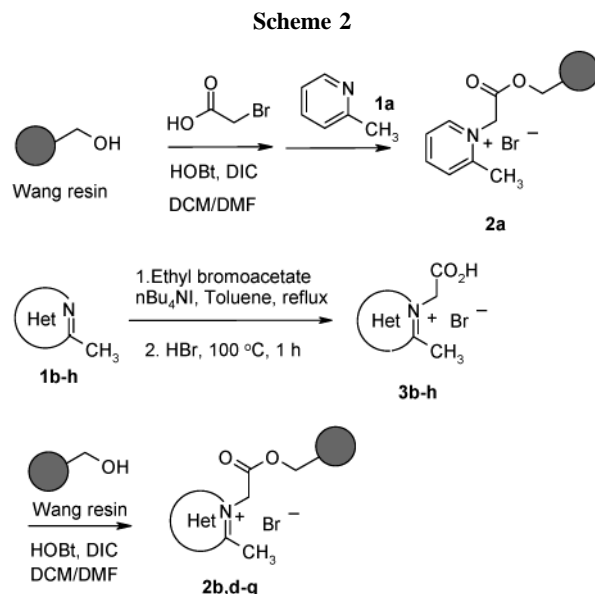
(10) Isacsson, J.; Westman, G. *Tetrahedron Lett.* **2001**, *42*, 3207.

(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.
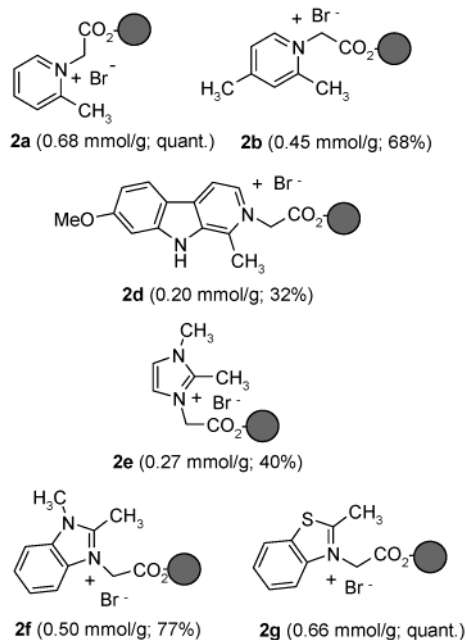

Figure 2. Resin building blocks **2**.

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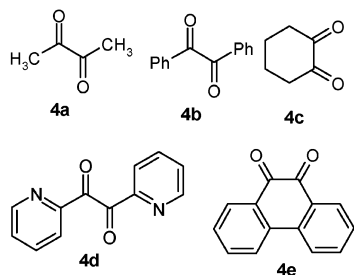

Figure 3. Diketone building blocks **4**.

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$_3$N. [c] E: acetone. F: ethanol. G: DMF. H: CH$_2$Cl$_2$. 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
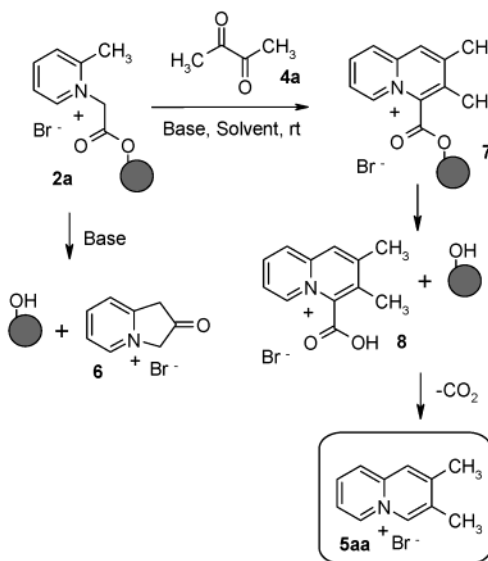
reaction conditions, hydrolyzed to **8**, which spontaneously gave **5aa** by decarboxylation. This sequence of hydrolysis−decarboxylation has usually been observed in conventional Westphal condensations in solution.[17] When triethylamine

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
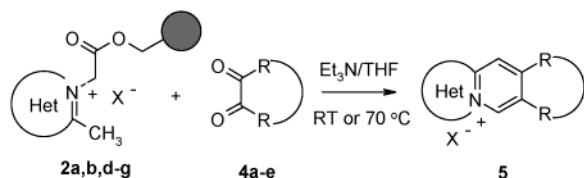
When reactions were performed at room temperature, using the optimized conditions, results were not quite successful. Thus, the same process was performed at 70 °C overnight, using a parallel format. After filtering and washing the resins, solvent was evaporated, and the crude products were treated with 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

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

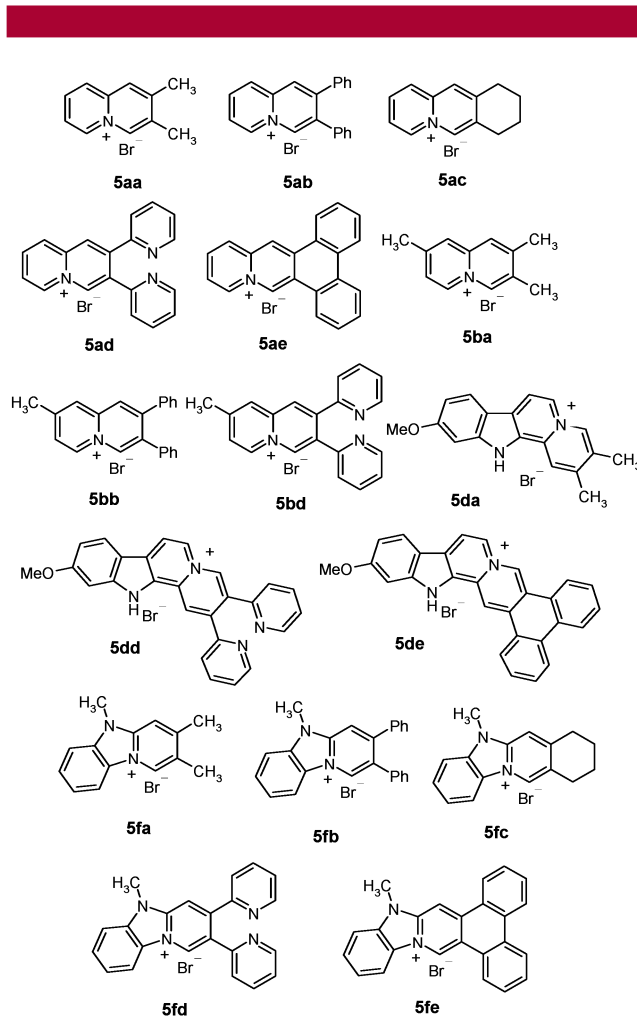(18) Purities are given at 220 nm. The members of the library were characterized by HRMS and NMR.

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.

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

OL035417Z