

The First Example of an Intramolecular Westphal Reaction. Synthesis of a New Aza-Quinolizinium Type System.

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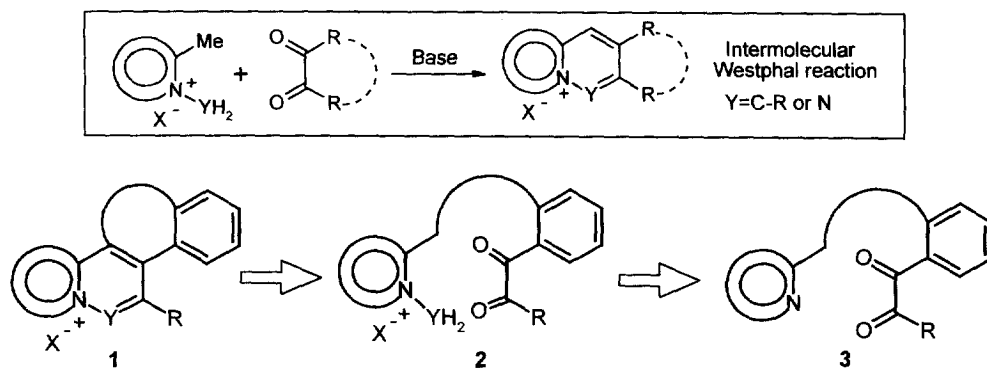
Abstract

The first example of an intramolecular Westphal condensation is described. To test the utility of this reaction, new benz(*f*)azino[2,1-*a*]phthalazinium salts have been prepared from appropriate dicarbonyl precursors.

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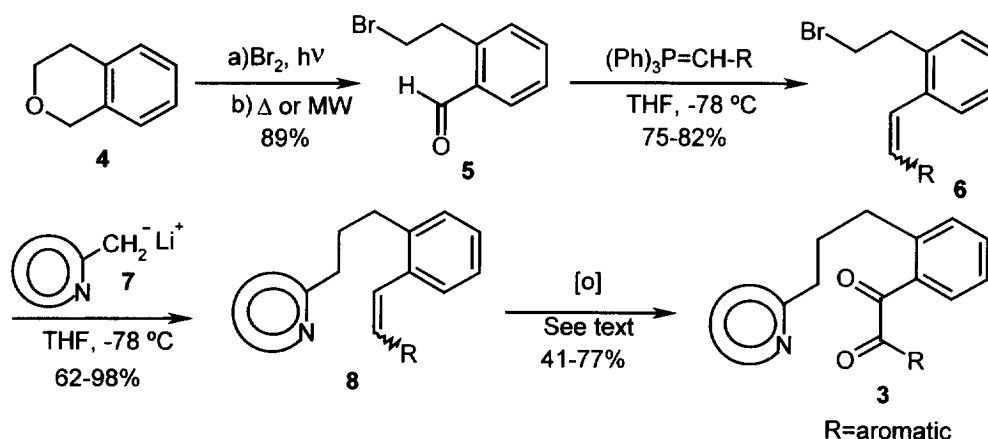
Keywords: Westphal; condensations; quinolizinium ions; phthalazines.

In a current research project focused on the synthesis and biochemistry of novel DNA intercalators based on quinolizinium and aza-quinolizinium chromophores [1-4], the Westphal reaction [5] has proved to be a useful tool for preparing these polycyclic systems containing a bridgehead quaternary nitrogen. Although the procedure has been described for C-C [5-7], N-N [8-11] and N-C [12-15] substrates, it had always being used in its intermolecular version.



Scheme 1: Westphal reaction and retrosynthetic analysis of the aza-quinolizinium cation 1

In an attempt to extend this simple and straightforward methodology to the preparation of new aza-quinolizinium systems, we decided to explore the viability of the intramolecular process and here we communicate the first successful example, applied to the synthesis of the benz(*f*)azino[2,1-*a*]phthalazinium system **1**, a new cationic tetracyclic system not available by the classical intermolecular process. The aza-quinolizinium cation **1** is a benzo-analogue of the known pyrido[2,1-*a*]phthalazinium ion, which has been recently prepared [16] by acid catalysed ring closure of 1-amino-2-(2'-[1,3]dioxolan-2-yl-phenyl)pyridinium salt. The parent compound of the latter, pyrido[1,2-*b*]pyridazinium has been previously described [12]. The retrosynthesis of **1** is outlined in Scheme 1 and involves the intramolecular condensation of the aminated salt **2**, with the diketone **3** being the key intermediate.



Scheme 2: Preparation of dicarbonyl compounds **3**.

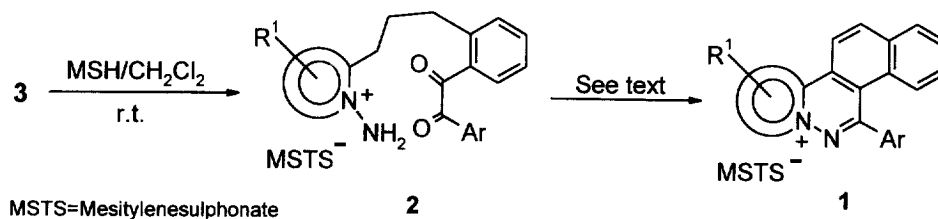
Scheme 2 displays the preparation of the diketones **3**, starting from isochroman **4**. Bromination of commercially available **4** in the presence of sunlight, followed by thermolysis gives **5** [17,18], but better results were obtained during the course of this work by microwave irradiation (1 min at 362 watts) of the bromination product of **4** adsorbed on silica gel [19]. Wittig olefination of **5** was carried out by treatment with the corresponding phosphonium salt and *n*-BuLi, (THF, -78°C) to yield a *cis/trans* mixture of alkenes **6**. Nucleophilic displacement of bromide in **6**, by α -azinyllithium reagents **7** [20] produced **8** in excellent yield.

The 1,2-dicarbonyl system in **3** (R= Ar) was then smoothly generated by oxidation of the styryl moiety in **8** using various DMSO-reagents (HBr/DMSO, I₂/DMSO and PdCl₂/DMSO) [21-24]¹. Other non DMSO-based oxidative systems, such as Katritzky's reagent [25], were

¹These methods can be successfully applied when R is an aromatic substituent, providing the corresponding 1,2-diketones **3** under mild conditions. However they are not suitable reagents for preparative oxidation of alkyl olefins when arylcarboxylic acids and aldehydes were found in the main reaction products.

also tried, although they did not provide satisfactory results.

The preparation of the N-aminoazinium salts **2** was performed by direct amination of the dicarbonylazine compounds **3**, using (*o*-mesitylenesulfonyl)hydroxylamine (MSH), in CH₂Cl₂ at room temperature [13,26] (Scheme 3). Having the substrates in hand, we performed the intramolecular condensation using different bases and solvents, with sodium acetate/acetone [12] and triethylamine/ethanol [1], giving the best yields.² Results are summarised in Table 1.



Scheme 3: Preparation of compounds **2** and **1**.

Table 1

Benz(*f*)azino[2,1-*a*]phthalazinium salts **1** prepared by intramolecular Westphal reactions.

Entry	Azine	R ¹	Ar	Yield(%) ^a	
				2	1
1		H	C ₆ H ₅	92	65 ^b
2		4-Me	C ₆ H ₅	76	28 ^b
3		6-Me	C ₆ H ₅	83	50 ^c
4		6-Me	4-EtO-C ₆ H ₄	92	28 ^c
5		H	C ₆ H ₅	92	75 ^b
6		H	4-EtO-C ₆ H ₄	75	29 ^c
7		6-Me	C ₆ H ₅	95	50 ^b
8		6-Me	4-EtO-C ₆ H ₄	84	50 ^b

^aYields refer to isolated pure products. All products were identified by spectroscopic and/or literature data

^bSodium acetate/acetone, reflux.

^cEt₃N/EtOH, reflux.

²Typical experimental procedure: Sodium acetate (0.075 g, 0.91 mmol) was added to a solution of **2** (0.91 mmol) in acetone (20 mL) and the mixture was heated at reflux for 6 h. The solvent was evaporated under vacuum and the residue washed with AcOEt and Et₂O to give **1** (Azine= pyridine, R¹= H, Ar= C₆H₅), as a yellow solid, which was crystallised from EtOH/Et₂O (Yield: 65%, m.p. = 140-142°C). δ_H(300 MHz, CD₃OD) 9.59(d, *J* 6.9 Hz, 1H), 9.51(d, *J* 9.5 Hz, 1H), 9.04(d, *J* 9.1 Hz, 1H), 8.78(t, *J* 9.1 Hz, 2H), 8.30(t, *J* 7.3 Hz, 1H), 8.26(d, *J* 9.1 Hz, 1H), 7.85-7.63(m, 7H), 7.44(t, *J* 6.9 Hz, 1H), 6.79(s, 2H), 2.60(s, 6H), 2.23(s, 3H). Analysis: for C₃₁H₂₆N₂SO₃, calculated C 73.49, H 5.17, N 5.53; found C 73.20, H 4.98, N 5.78.

In conclusion benz(*f*)azino[2,1-*a*]phthalazinium derivatives **1** can be obtained through a six-step sequence, using as the key step the first example of an intramolecular Westphal condensation. The methodology is currently being extended to the preparation of other related systems and results will be described in relation with their DNA intercalating properties.

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