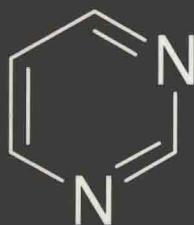
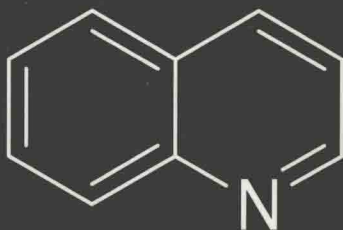
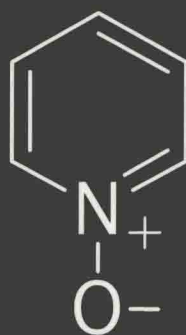
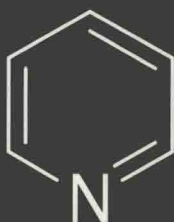
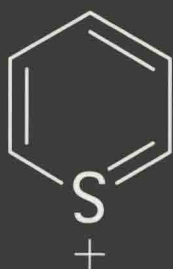


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HETEROCYCLIC CHEMISTRY

VOLUME **100**

Editor

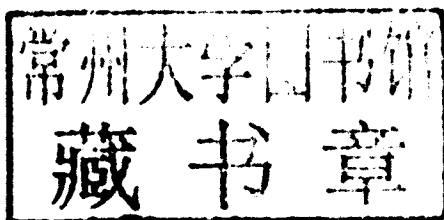
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PREFACE TO CELEBRATORY VOLUMES 99, 100 AND 101 OF ADVANCES IN HETEROCYCLIC CHEMISTRY

It is hard to believe that it is now 50 years since I conceived the concept of periodical volumes of these 'Advances' that would record progress in heterocyclic chemistry. In 1960, heterocyclic chemistry was slowly emerging from the dark ages; chemists still depicted purines by the archaic structural designation introduced (was it by Emil Fischer?) 50 years before that. Together with Jeanne Lagowski, I had published in 1959 a modern text on heterocyclic chemistry, the first that treated this subject in terms of structure and mechanism and attempted to logically cover significant methods of preparation and reactions of heterocyclic compounds as a whole, all in terms of reactivity.

The first two volumes of *Advances* contained extensive chapters on the tautomerism of various classes of heterocycles. Despite the great influence the precise structure of heterocyclic compounds has on chemical and biological properties (we only have to remember the base pairing of nucleotides to illustrate this), at that time the literature was replete with incorrectly depicted tautomers. The basis for the position of tautomeric equilibria was usually completely misunderstood. Although great progress has been made in the past 50 years, there still exist holdouts even among otherwise reputable chemists who persist in depicting 2-pyridone as '2-hydroxypyridine,' which is a very minor component of the tautomeric equilibrium under almost all conditions.

Over the years *Advances in Heterocyclic Chemistry* has indeed monitored many of the advances in the subject: the series is now boosted by *Comprehensive Heterocyclic Chemistry*, whose first edition was published in 1989 in 9 volumes followed by the second edition in 11 volumes and the third edition in 2008 in 18 volumes. Heterocyclic chemistry has now taken its place as one of the major branches (by several criteria the most important) of organic chemistry.

Chemistry has rapidly become the universal language of molecular interactions; it has essentially taken over biochemistry and is rapidly

gaining dominance in zoology, botany, physiology and indeed many branches of medicine.

Chemical structural formulae are quite basic to this progress and have enabled us to rationalize many natural phenomena and countless reactions both simple and exotic discovered in the laboratory.

Now we have reached the milestone of 100 volumes of the series. In place of a single volume we are offering the three-volume set 99, 100 and 101, which contain a fascinating variety of reviews covering exciting topics in heterocyclic chemistry.

Alan R. Katritzky
Gainesville, Florida

VOLUME PREFACE

Volume 100 of *Advances in Heterocyclic Chemistry* commences with a chapter by C. A. Ramsden (University of Keele, UK) on 1,2-benzoquinones as a precursor of a wide variety of heterocycles. Catherine L. Lucas and C. J. Moody (University of Nottingham, UK) provide a summary of naturally occurring 1,4-thiazines, a compound class that has been extensively investigated recently; much information on the synthesis and properties of important derivatives is included.

S. A. Raw (AstraZeneca, UK) and R. J. K. Taylor (University of York, UK) describe novel developments in the preparation and applications of 1,2,4-triazines, especially inverse electron demand Diels–Alder reactions. Heteroaryl radicals, with particular emphasis on pyridyl, indolyl, and thienyl radicals, in which the unpaired electron occupies an sp^2 orbital orthogonal to the π -system are covered by D. Mirizzi and K. Jones (Institute of Cancer Research, London, UK) and S. T. Hilton (School of Pharmacy, University of London, UK).

B. Stanovnik and U. Grošelj (University of Ljubljana, Slovenia) review applications of acetone-1,3-dicarboxylates in heterocyclic synthesis with emphasis on pyrazole- and pyrimidine-derived ring systems. A. P. Sadimenko (University of Fort Hare, South Africa) reports on some of the remarkable advances in organometallic chemistry of heterocycles, which have occurred in the last decade.

The final chapter in this volume by G. Jones (University of Keele, UK) and B. Abarca (Universidad de Valencia, Spain) updates the chemistry of [1,2,3]triazolo[1,5-a]pyridines for the period 2001–2009.

Alan R. Katritzky
Gainesville, Florida

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Heterocycle-Forming Reactions of 1,2-Benzoquinones

Christopher A. Ramsden

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1. INTRODUCTION

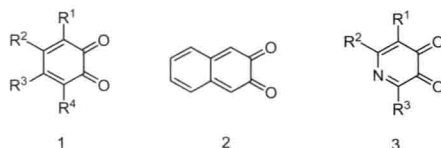
This review surveys heterocycle-forming reactions of 1,2-benzoquinones (*ortho*-quinones) **1** up to mid-2008. The main purpose of the review is to systematically analyse the modes of reaction of *ortho*-quinones **1** that lead to heterocycles and illustrate them using selected examples. We have attempted to provide comprehensive citation of the literature from 1980 to mid-2008. Some earlier papers are included but coverage of pre-1980 literature is not comprehensive. Often *ortho*-quinones are generated

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in situ by catechol oxidation and trapped without isolation and characterisation. This makes a full search of the literature difficult. However, the well-characterised examples discussed in the following sections give a representative overview of the main modes of reaction. We have not attempted to cover polycyclic or heteroquinones, for example **2** and **3**, but some examples are cited to illustrate the scope of certain reactions.

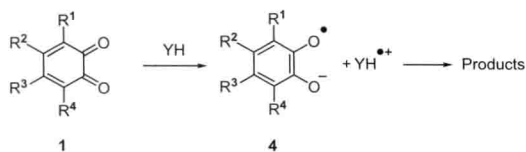


The 1,2-benzoquinones are often stable enough to be isolated and characterised, if necessary, but reactive enough to give products with a wide variety of reagents. This leads to a rich variety of transformations. Since they are associated with a particularly low-energy LUMO (lowest unoccupied molecular orbital), they are especially reactive towards electron-rich species. Figure 1 shows the properties of the LUMO and HOMO (highest occupied molecular orbital) of 1,2-benzoquinone calculated by the AM1 method (85JA3902).

A second general feature of *ortho*-quinone reactivity is the desire to achieve an aromatic sextet in the original carbocyclic benzoquinone ring. For these two reasons, the chemistry in this review is dominated by (i) addition and (ii) addition–elimination reactions of 1,2-benzoquinones with nucleophiles. The subdivision of the review is largely determined by the different ways in which an aromatic sextet can be achieved. However, although mechanistic aspects are emphasised in rationalising the formation of different products, some caution must be exercised in interpreting the detailed mechanisms of individual reactions. It must be born in mind that in addition to conventional nucleophilic attack, benzoquinones can also react by single-electron transfer (SET) to give a semiquinone intermediate **4** (Scheme 1), or by two-electron transfer to give a catechol dianion. In many cases any of these mechanisms can



Figure 1 The HOMO and LUMO of 1,2-benzoquinone calculated by the AM1 method.

**Scheme 1**

account for the same final product and little experimental evidence of mechanisms is available. Unless otherwise stated, general mechanisms in the following sections should be taken as guiding principles rather than experimental facts.

In addition to their chemical interest, some reactions of 1,2-benzoquinones are of biological significance. Dopaquinone **1** ($R^1=R^3=R^4=H$, $R^2=CH_2CH(NH_2)CO_2H$) is a precursor to the melanin pigments that are found widely in nature (92MI1, 04ME88, 06MI282, 07ARK23), and *ortho*-quinone formation may account for the toxic effects of some xenobiotic materials (04ME293). Examples of biologically significant heterocycle formation are emphasised wherever appropriate.

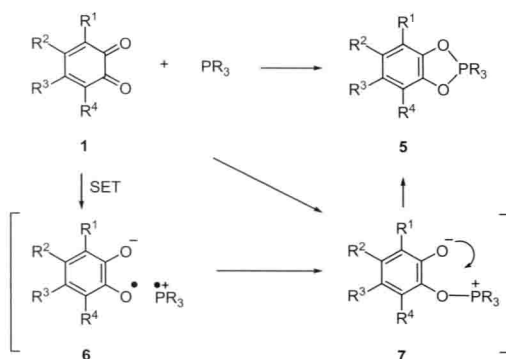
2. ADDITION REACTIONS

2.1 Intermolecular cycloadditions

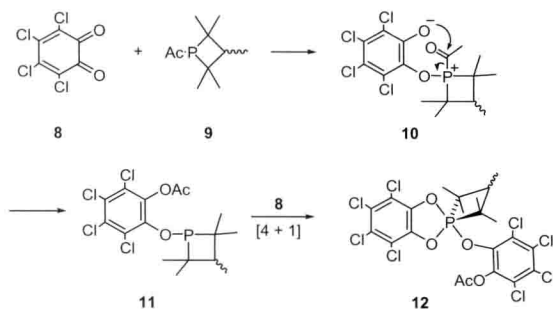
2.1.1 [4+1] Cycloadditions

2.1.1.1 Phosphorus. 1,2-Benzoquinones **1** react with a wide range of trivalent phosphorus reagents to give the [4+1] cycloadducts **5** (Scheme 2). The formation of the 1,2,5-phosphodioxole derivatives **5** is often strongly exothermic and good to excellent yields are usually obtained. Representative examples are given in Table 1.

The most plausible mechanism for these reactions is nucleophilic attack by phosphorus on oxygen to give the zwitterionic intermediates **7**. Although nucleophilic attack on electronegative oxygen is counter-intuitive, a driving force for this step is the formation of the aromatic phenolate ion, and this mode of reaction is comparable to reaction of nitro groups with trialkyl phosphites. A variation involving initial attack at carbon and C–O rearrangement to give the zwitterions **7** has been proposed based on kinetic studies (70JA4670, 83T3189, 84CJC2179). Cyclisation of the dipolar intermediates **7** can then occur giving the products **5** in a step comparable to oxyphosphetane formation in the Wittig reaction. There is some evidence that semiquinones **4** can be formed in these reactions (73JOC3423, 74REC69, 91JCS(D)19). It is possible that in some reactions SET gives a radical pair **6**, or a similar species, which then collapses to the zwitterion **7** (Scheme 2).



Scheme 2



Scheme 3

Evidence for the formation of dipolar intermediates was provided when the *P*-acetylphosphetane **9** was reacted with 3,4,5,6-tetrachloro-1,2-benzoquinone (*ortho*-chloranil) **8** (75JCS(P1)1220). The product obtained was the 2:1 adduct **12**, which occurs *via* acetyl transfer in the dipolar intermediate **10** to give the phosphite **11** (Scheme 3). A second [4+1] addition then gives the product **12**.

Because of its stability and ease of handling, many of these oxidative cyclisations of phosphorus reagents have been carried out using 3,4,5,6-tetrachloro-1,2-benzoquinone **8** (m.p. 126–129 °C). These includes reactions of diphosphanes [R_2PPR_2] (90ZNB1177), diphosphenes [$\text{RP}=\text{PR}$] (01HAC300), phosphines [R_3P] (75JCS(P1)1220, 80CB1406, 90AG689, 91JCS(D)19), aminophosphines [$\text{R}_2\text{P}-\text{NR}_2$] (90T2381, 90AG659), chlorophosphines [R_2PCl] (73CB2733, 91JCS(D)19), triheterophosphines [X_3P] (02RJC1764, 02HCA1364), phosphites [$(\text{RO})_3\text{P}$] (68JOC20, 75PS73, 90JA7475, 91JGU2298, 93RJC17, 95JCS(P1)2945), chlorophosphites [$(\text{RO})_2\text{PCl}$] (74JCS(P1)2125, 79TL193, 94T6989),

Table 1



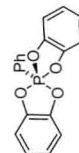
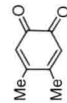
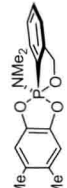

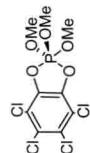

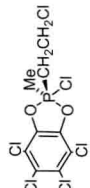

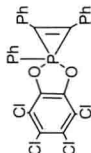

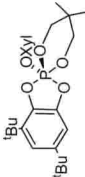



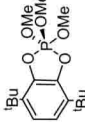
					
Benzoquinone	Product	Conditions	Yield (%)	m.p. (°C)	References
		Ether, room temp.	74	111	(68TL5333)
		Toluene, 0°C	72	126–129	(81JCS(P1)2239)
		Benzene, 70°C	> 80	65–66	(68JOC20)
		Benzene, reflux	100	65	(73CB2733)
		Toluene, room temperature	58	143.5 (d)	(06JOC5448)

Table 1 (Continued)

Benzoquinone	Product	Conditions	Yield (%)	m.p. (°C)	References
		no solvent, 100 °C	75	88–90	(90JA6095)
		Benzene, 70 °C	100	85–86	(82CB901)
		CH ₂ Cl ₂ , room temperature	–	not reported	(86PS119)