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REGIOSPECIFIC SYNTHESIS OF α-(PHENYLTHIO)CYCLOALKENONES AND OF α-PHENYL-α-(PHENYLTHIO) KETONES VIA αα-ADDITION OF PHENYLSULPHENYL CHLORIDE TO α-DIAZOKETONES

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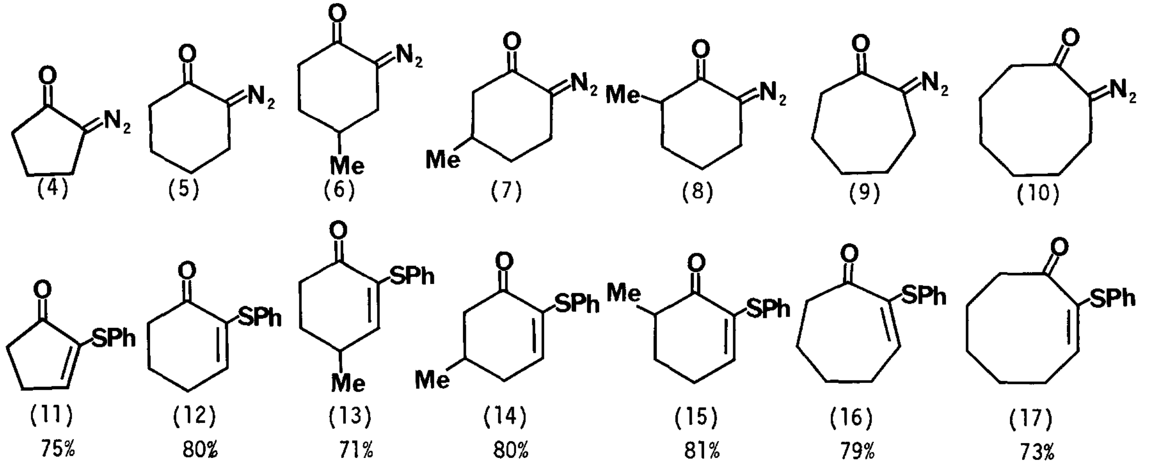
Summary Cyclic α-diazoketones react with phenylsulphenyl chloride at room temperature to furnish α-chloro-α-(phenylthio)cycloalkanones which undergo ready dehydrochlorination to α-(phenylthio)cycloalkenones when treated with triethylamine; acyclic, terminal α-diazoketones also furnish α-chloro-α-(phenylthio)adducts which are useful electrophiles in the synthesis of α-phenyl-α-(phenylthio)ketones.

In 1955 Weygand and Bestmann[1] reported that diazoacetophenone (1) and phenylsulphenyl chloride (2) react together at room temperature with evolution of nitrogen to yield the α-chloro-α-(phenylthio)adduct (3). Although this reaction represents an exceptionally mild, and potentially regiospecific way of functionalising a ketone at the α-position with a sulphur-containing substituent, no further work exploiting this aspect of the reaction has been reported. In recent times, the most widely used routes to α-sulphenylated carbonyl compounds have employed reactions of preformed enolates or carbanions with appropriate sulphenylating groups or reagents under strongly basic conditions.[2,3,4] However, we recently found that α-diazoketones can be used as dipolar enolate equivalents under essentially neutral conditions in rhodium(II)-catalysed, regiospecific reactions with thiophenol to produce α-(phenylthio)ketones[5], and we now demonstrate that addition of phenylsulphenyl chloride to cyclic and acyclic α-diazoketones produces regiodefined adducts which are ideally suited to other useful transformations in preparative organosulphur chemistry.

(1) (2) (3)

Diazoketones (4)-(10)[6] and phenylsulphenyl chloride (2) produced α-chloro-α-(phenylthio) adducts which could be dehydrochlorinated to α-(phenylthio)cycloalkenones (11)-(17), respectively, by treatment with triethylamine at room temperature. The following one-pot procedure for the conversion of 6-methyl-2-diazocyclohexanone (8)[6] into 6-methyl-2-(phenylthio) cyclohex-2-enone (15) is representative of the reactions summarised in Table 1 with the exception of that of diazoketone (6) for which the first stage was best conducted at 0°C; the yields recorded refer to analytically pure products whose structures have been confirmed by spectroscopic data.

TABLE 1



(4) (5) (6) (7) (8) (9) (10)

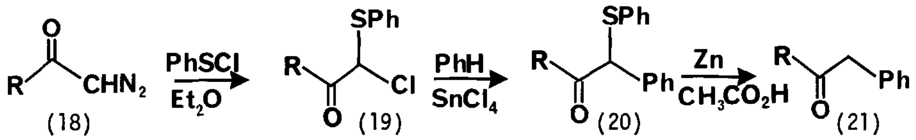
(11) 75%
(12) 80%
(13) 71%
(14) 80%
(15) 81%
(16) 79%
(17) 73%

To a stirred solution of 6-methyl-2-diazocyclohexanone (8) (0.42g) in ether (50 ml) was added a solution of phenylsulphenyl chloride (0.44g) in ether (10 ml) over 15 minutes at room temperature. After a further 15 minutes, triethylamine (0.31g) was added. The mixture was stirred overnight and then was filtered. Concentration of the filtrate followed by purification of the residue by PLC (silica gel, $CHCl_3$) furnished the enone (15) (0.54g,81%).

This simple procedure makes readily available a range of α-(phenylthio)cycloalkenones. Of the examples listed in Table 1, the cyclopentenyl system (11) has been synthesised already in 50% yield by the action of phenylsulphenyl chloride on cyclopentanone.[7] The direct approach however, is peculiar to cyclopentanone and is not applicable to the cyclohexenyl or cycloheptenyl systems (5) and (9) for which the only other published route requires the corresponding α-(phenylthio)cycloalkanones as intermediates.[8] It is worth noting that the regiochemistry displayed by examples (14) and (15) is established by the regiospecificity of formylation of 2- and 3-methylcyclohexanone prior to diazoketone formation.[6] Recent examples of the efficacy of the cyclopentenyl system (11) in Diels-Alder reactions[9], Michael additions[10], and as a source of regiodefined enolates[11], suggest that α-(phenylthio)cycloalkenones may be generally useful as synthetic intermediates.

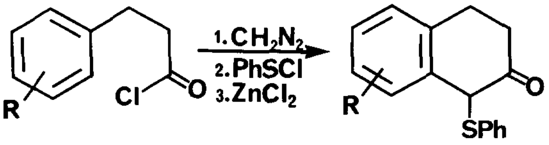
A second aspect of the synthetic utility of the diazoketone-phenylsulphenyl chloride reaction is illustrated by the conversion of acyclic, terminal diazoketones into α-phenyl-α-(phenylthio)ketones (Table 2), the key step being the Friedel-Crafts alkylation of benzene using an α-chloro-α-(phenylthio)ketone as the electrophile. Since terminal α-diazoketones, e.g. (18a)-(18d), can be obtained in excellent yield from acyl chlorides and diazomethane, the route to α-phenyl-α-(phenylthio)ketones (20a)-(20d) in Table 2 does not depend on the availability of the parent ketone, nor does it require regiospecific enolate or α-haloketone production for the introduction of the phenylthio group.[12] Furthermore the operations involved are ideally suited to a one-pot procedure. Thus, diazoacetone (18a), prepared in 95% yield from acetyl chloride and diazomethane in ether and used without purification, was treated with phenylsulphenyl chloride in ether at room temperature to afford the α-chloro-α-(phenylthio)adduct (19a) in essentially quantitative yield; although purification was unnecessary prior to the next stage, the pure compound (83%) could be isolated by column chromatography. The crude adduct (19a) was then exposed to stannic chloride in dry benzene at room temperature to yield 1-phenyl-1-(phenylthio)propanone (20a) (85%), mp 65.5-66.5^{o}C. Diazoketones (18b)-(18d) in Table 2 were also prepared from the acid chlorides and were converted using the above sequence into the

TABLE 2



	R	%	%	%	%
(a)	CH$_3$	95	83	85	93 (68)
(b)	Ph	94	81	84	88 (65)
(c)	PhCH$_2$	98	93	89	92 (68)
(d)	PhCH$_2$CH$_2$	89	96	70	86 (61)

(22) R=H
(23) R= 4-Me
(24) R= 2-Me
(25) R= 4-MeO
(26) R= 2-MeO



(27) R=H
(28) R=4-Me
(29) R= 2-Me
(30) R= 4-MeO
(31) R= 2-MeO

α-phenyl-α-(phenylthio)ketones shown; the yields quoted refer to purified intermediates and products. As expected, compounds (20a)-(20d) were easily desulphurised (Zn/acetic acid) to the corresponding benzyl ketones (21a)-(21d), and the final set of yields in parenthesis in Table 2 are those realised for the overall transformation when the diazoketones were carried through to benzyl ketones without purification of intermediates.

The intramolecular version of the process in Table 2 can be applied very successfully to the production of substituted β-tetralones, though here zinc chloride was found to be the more appropriate catalyst for the alkylation stage. Thus, dihydrocinnamoyl chloride (22), and its 4-methyl-, 2-methyl-, 4-methoxy-, and 2-methoxy- derivatives, (23), (24), (25), and (26), were each treated sequentially with diazomethane, phenylsulphenyl chloride, and zinc chloride in dichloromethane, to produce the 1-(phenylthio)-2-tetralones, (27)(73%), (28) (81%), (29) (80%), (30) (79%), and (31) (76%), respectively, which were readily desulphurised by zinc in acetic acid.

References and Footnotes

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