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Studies on organophosphorus compounds: reactions of benzosuberones with 2,4-bis(*p*-methoxyphenyl)-1,3,2,4-dithiadiphosphetane-2,4-disulfide (Lawesson's reagent)

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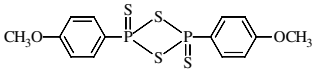
Abstract—6-Arylidene-3-methyl-6,7,8,9-tetrahydro-5*H*-benzo[*a*]cyclohepten-5-ones (**2a**–**h**), obtained by the condensation of 3-methylbenzocyclohepten-5-one **1** with appropriate aromatic aldehydes, on reaction with Lawesson's reagent in xylene yielded phosphorus containing compounds **3a**–**h**. A number of these compounds showed promising anti-inflammatory activity.

Among the most effective thionating reagents known at present is the dimeric anhydride of *p*-methoxyphenyl-dithiophosphinic acid-2,4-bis(*p*-methoxyphenyl)-1,3,2,4-dithiadiphosphetane-2,4-disulfide, known in the literature as Lawesson's reagent (LR).[1]



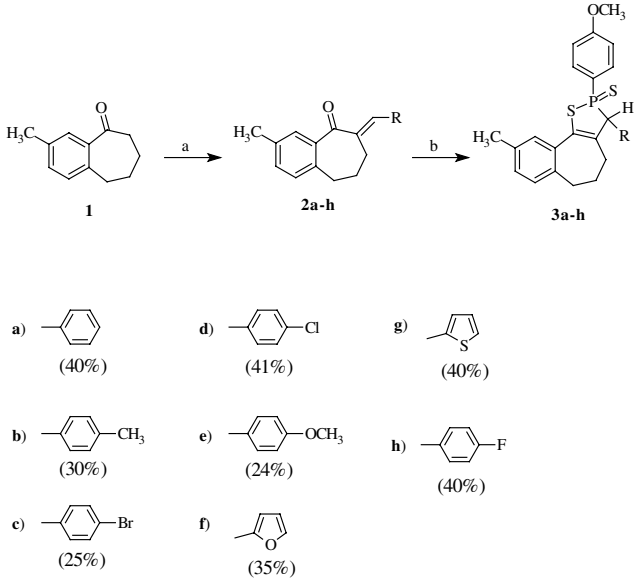
Lawesson's reagent (LR)

The attractiveness of LR is associated with its ready availability, simplicity and convenience of use, high yields of sulfur-containing reaction products, and comparative ease of isolation from reaction mixtures.

Lawesson's reagent has also been utilized in the synthesis of five- and six-membered phosphorus heterocycles such as oxathiaphospholes,[2] oxathiazaphospholidine-2-thiones,[3] benzodioxaphospholane-2-sulfides,[4] oxazaphosphorine-4-thione-2-sulfides,[5] thiazaphosphorin-4-one-2-sulfides,[6] benzoxathiaphosphorin-4-thione-2-sulfides, their oxo analogues,[7] 2-substituted-3,5-diaryl-Δ^4-1,2-thiaphospholene-2-sulfides[8] and sulfur-containing heterocycles.[9–13]

2,4-Bis-(*p*-methoxyphenyl)-1,3,2,4-dithiadiphosphetane-2,4-disulfide was found to be an effective thionation reagent for α,β-unsaturated ketones and cyclic ketones.[14,15] Accordingly, the reaction of LR with 6-arylmethylene derivatives **2a**–**h** has been studied and the results reported here.

6-Arylidene-3-methyl-6,7,8,9-tetrahydro-5*H*-benzo[*a*]-cyclohepten-5-one **2** has proved to be a useful intermediate for conversion into new heterocycles. 6-Arylidene-3-methyl-6,7,8,9-tetrahydro-5*H*-benzo[*a*]cyclohepten-5-ones (**2a**–**h**, Scheme 1) were obtained by condensation of



Scheme 1. Reagents and conditions: (a) alc KOH, aromatic aldehydes, rt; (b) Lawesson's reagent, xylene, 150 °C.

Keywords: Benzosuberone; Lawesson's reagent.
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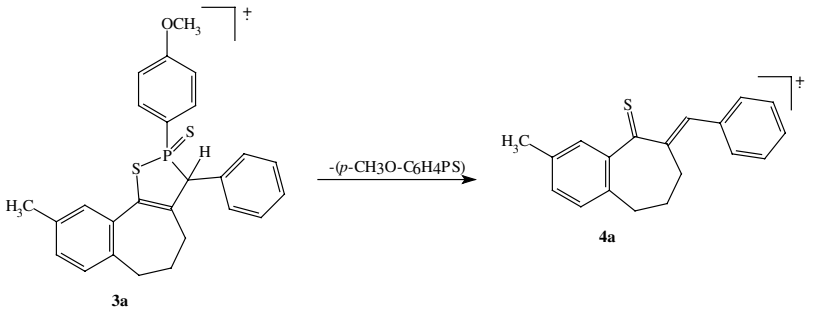
3-methylbenzocyclohepten-5-one **1** with appropriate aldehydes.[16] In the enones **2a–h**, the olefinic proton =CH–Ar appeared at δ 7.75–7.80 in the ^{1}H NMR spectra. The 6-arylmethylene derivatives **2a–h** reacted with Lawesson's reagent in xylene at reflux for 30–45 min, to give 9-methyl-2-(4-methoxyphenyl)-3-phenyl-benzocyclohepta-1,2-thiaphospholene-2-sulfides **3a–h** as the sole products in moderate yields. The mass spectral fragmentation pattern and the ^{1}H NMR spectral data gave strong substantiation for the structures **3a–h**. The mass spectrum of **3a** (taken as a representative example), had the molecular ion $C_{26}H_{25}OPS_2$ at m/z 448, consistent with the molecular formula, and fragment ion **4a**, which would be formed by the cleavage of **3a**.



The ^{1}H NMR spectrum showed the singlet of one methine proton at δ 4.90 and a singlet at 3.80 ppm (OCH_3). Further, the spectrum had signals for three methylene groups between 2.00 and 2.90 ppm. Besides these signals, the aromatic protons appeared as a multiplet at δ 6.60–7.70. The IR spectrum also showed the disappearance of the C=O absorption band. This suggests the formation of a ring. Similarly, the structures of **3b–h** were confirmed on the basis of their spectral properties. In all these cases the reaction of 6-arylmethylene derivatives **2** with Lawesson's reagent in refluxing xylene did not afford any identifiable dimeric product (see Scheme 2) as observed earlier.[8]

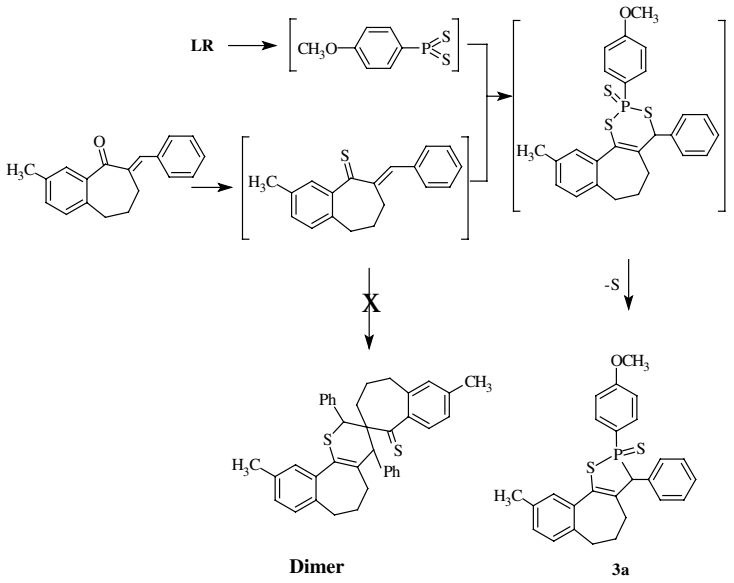
1. Biological evaluation

1.1. Antimicrobial activity

All the compounds **3a–h** were screened for their antimicrobial activity at a concentration of 40 μg/well in agar media[17] using Doxycyclin in antibacterial and nalidixic in antifungal activity studies as reference compounds. Compound **3b** showed the best activity (20 mm) as compared with Doxycyclin (25 mm) against gram positive *Staphylococcus aureus*, while all the compounds were resistant towards gram negative *E. coli*. All the compounds were ineffective against the fungus *Trichoderma species*.

1.2. Analgesic and anti-inflammatory activity

The analgesic and anti-inflammatory activities of the compounds were determined by the Turner[18] writhing test[19] and rat-paw edema test.[20] The inhibition of edema was recorded on a plethysmometer (UGO BASILE) and expressed as % inhibition. All the compounds **3a–h** showed maximum inhibition (28–32%) in rats while aspirin and phenyl butazone at the same dose (100 mg/kg, per oral) produced 17% and 39% inhibition of 1% Carrageenan-induced inflammation, respectively. However, they were found to possess weak analgesic action with reference to aspirin.



Scheme 2.

In conclusion we have shown that 2,4-bis-(*p*-methoxyphenyl)-1,3,2,4-dithiadiphosphetane-2,4-disulfide LR can be utilized for the conversion of α,β-unsaturated ketones into new phosphorus containing compounds.

General procedure for the synthesis of compounds 3a–h: A mixture of **2a** (0.6 g, 2.29 mmol) and LR (1.10 g, 2.74 mmol) in xylene (10 mL) was refluxed for 30–45 min. The progress of the reaction was monitored by TLC. After cooling, the reaction mixture was filtered and the filtrate was evaporated under reduced pressure to give a gummy product, which was purified by column chromatography on silica gel using 3% ethyl acetate in petroleum ether as eluent. It was further purified by preparative TLC using 10% ethyl acetate in petroleum ether. Of the multiple spots obtained in the TLC, compound **3a** was isolated as the major products in 40% yield. Mp 118–120 °C, ^{1}H NMR ($CDCl_3$, 200 MHz): δ 2.00–2.20 (4H, m, 4 and 5-CH_2), 2.40 (3H, s, 9-CH_3), 2.70–2.90 (2H, t, $J = 4.5$ Hz, 6-CH_2), 3.80 (3H, s, OCH_3), 4.90 (1H, d, $J = 16$ Hz, 3-CH) and 6.60–7.70 (12H, m, aromatic); MS: 448 (M^+).

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