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Microwave-Assisted Synthesis and Diels–Alder Reactions of 1,3-Azaphospholo[5,1-*a*]isoquinolines

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ABSTRACT: *The application of microwave technique has been extended successfully for the first time to the synthesis of a representative class of azaphospholes, viz. 1,3-bis(alkoxycarbonyl)-1,3-azaphospholo[5,1-*a*]-isoquinolines (**2**), which occurs rapidly giving higher yields. Stereoselectivity is observed in the reaction with 2,3-dimethyl-1,3-butadiene, and isoprene reacts regioselectively as well. 1-Methyl-3-ethoxycarbonyl-1,3-azaphospholo[1,5-*a*]pyridine (**4**) remains inert toward [2+4] cycloaddition. The nonoccurrence of the Diels–Alder reaction in the latter case has been supported by semiempirical PM3 calculations.*

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INTRODUCTION

Mainly four methods, namely [4+1] condensation [1–6], and [3+2] cyclocondensation [1,7,8], [3+2] cycloaddition [1,9–15], and 1,5-electrocyclization [16,17], have been developed for the anellated azaphospholes [18] during the last few years. These methods are in fact extension of the methods employed for the non-phosphorus analogues [19]. All these methods being based on the conventional synthesis require the use of the appropriate solvents and in some cases they occur quite slowly.

We have recently reported one-pot synthesis of 1,3-bis(alkoxycarbonyl)-1,3-azaphospholo[5,1-*a*]isoquinolines via 1,5-electrocyclization [17] and also [2+4] cycloaddition reactions of these compounds and 1,3-azaphospholo-[1,5-*a*]pyridine [20].

Microwave technology has attracted the attention of the synthetic chemists because of two reasons: shortening of the reaction time and the possibility of dispensing with the hazardous solvents [21–24]. In spite of its now wide application in the synthesis of classical heterocyclic compounds, this technique has not been employed so far for the synthesis of the azaphospholes. As a part of our program [25–28] to use microwave irradiation for economic and facile synthesis of heterocycles, we herein report our results of the synthesis of some anellated azaphospholes and their Diels–Alder (DA) reactions, using inorganic solid support to develop solvent-free methodology. Furthermore, in order to make comparative studies, reactions have also been carried out using solvents as energy transfer media.

RESULTS AND DISCUSSION

Synthesis of 1,3-Azaphospholes

A mixture of *N*-alkylisoquinolinium bromide **1**, phosphorus trichloride (1/2 equiv.), and triethylamine (2 equiv.) adsorbed on montmorillonite KSF on irradiation in slightly modified domestic microwave oven afforded **2** (Method A). For a comparative study, a synthesis in minimum amount of acetonitrile under microwave irradiation was also carried out (Method B) (Scheme 1).

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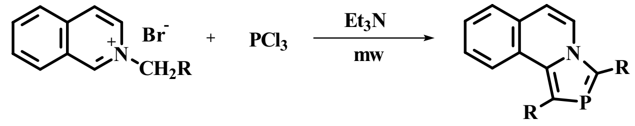


1a: R = CO_2Me
1b: R = CO_2Et

2a: R = CO_2Me
2b: R = CO_2Et

SCHEME 1

TABLE 1 Synthesis and DA Reactions of **2** Under Microwave Irradiation (Method A and B) and Conventional [20]

	Method	*Solvent*	*Power (W)*	*Reaction Time*	*Yield (%)*
2a	A	–	630	2.0 min	48
	B	CH_3CN	480	1.5 min	45
	[20]	CH_2Cl_2	–	∼8–9 h	28
2b	A	–	630	2.0 min	53
	B	CH_3CN	480	1.5 min	53
	[20]	CH_2Cl_2	–	∼8–9 h	29
3a	A	–	630	16 min	96
	B	C_6H_5Cl	480	10 min	94
	[20]	$CHCl_3$	–	12 days	90
3b	A	–	630	22 min	94
	B	C_6H_5Cl	480	15 min	93
	[20]	$CHCl_3$	–	28 days	90

[2+4] Cycloadditions

1,3-Bis(alkoxycarbonyl)-1,3-azaphospholo[5,1-*a*]-isoquinolines **2**, 2,3-dimethyl-1,3-butadiene or isoprene (4 equiv.), and sulfur (1/8 equiv.) adsorbed on montmorillonite KSF on microwave irradiation afforded the cycloadducts **3** (Method A). In Method B, chlorobenzene was used as energy transfer medium when the cycloadducts **3** were obtained in comparable yields (Scheme 2).

The reaction with isoprene is regiospecific and only one regioisomer is formed in each case. The reaction of 1-methyl-3-ethoxycarbonyl-1,3-azaphospholo[1,5-*a*]pyridine [4] **4** with 2,3-dimethyl-1,3-butadiene and sulfur under similar conditions (Methods A and B) however does not take place even after irradiating the reactants for 30 min at the maximum power. These results are similar to those observed for this substrate under thermal conditions [20].

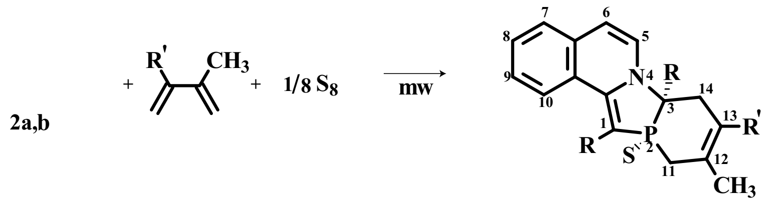
The products **2a,b** and **3a,b** were identified on the basis of physical and spectral data reported earlier [17,20]. The yields of the products and reaction times under conventional and microwave conditions are shown in Table 1.

It can be seen that the reaction time in the microwave method is much shorter as compared to that required under conventional method. Furthermore, the yields of the products are higher. The use of solid support discards the solvent without affecting the yields; the reaction time also remains almost unchanged. Besides, it has an added advantage of easy work-up, and solid support can be recycled making the technique cost-effective.

The different reactivities of **2b** and **4** toward DA reaction can be explained on the basis of the energies of their frontier orbitals that have been determined by semiempirical PM3 calculations (Fig. 1). In each case, the reaction is $HOMO_{diene}$–$LUMO_{dienophile}$ controlled and thus falls in the *Sustmann Type I* category [29,30]. Futhermore, it is found that the LUMO is centered on the >C=P– moiety. It can be seen that in the case of **2b**, the energy gap, $HOMO_{diene}$–$LUMO_{dienophile}$ is 7.92 eV, which explains the successful occurrence of the DA reaction. But on the other hand, the energy $\Delta E = HOMO_{diene}–LUMO_{dienophile}$ for **4** exceeds 8.0 eV, making the cycloaddition difficult even under microwave irradiation.

EXPERIMENTAL

A domestic microwave oven BPL 700T was perforated at the top to accommodate a two-neck tube fitted with reflux condenser that was attached to a paraffin seal to release the generated pressure during irradiation. The rotating plate was replaced by a magnetic stirrer and the reaction mixture was stirred



3a: R = CO_2Et, R' = CH_3
3b: R = CO_2Et, R' = H

SCHEME 2

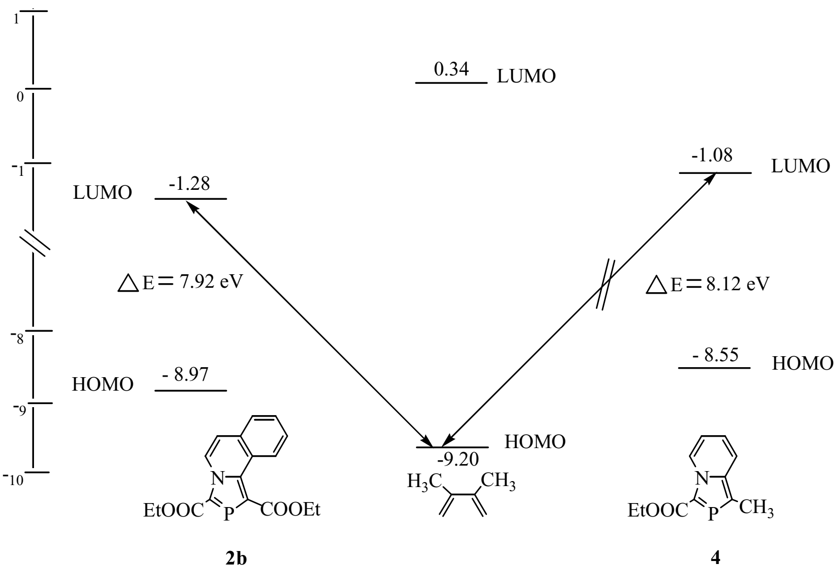


FIGURE 1 Frontier molecular orbitals of **2b** and **4**.

using a Teflon-coated magnetic needle. The reaction conditions were optimized with respect to the microwave as power level and time to give maximum yield of each product.

All the manipulations were carried out under dry nitrogen using the Schlenck technique. Solvents were freshly dried and distilled. Commercially available dienes were used without further purification and montmorillonite KSF was purchased from Aldrich and dried in vacuum for half an hour before use. Eigenvalues of the frontier molecular orbitals were calculated by PM3 procedure using MOPAC# 6.0 package [31].

*1,3-Bis(alkoxycarbonyl)-1,3-azaphospholo[5,1-a]isoquinolines (**2**)*

Method A. A solution of **1** (1.42 mmol) dissolved in minimum amount of acetonitrile was adsorbed on montmorillonite KSF (20% by weight of the reactant) taken in an Erlenmeyer flask and mixed thoroughly. The excess of solvent was removed in vacuum to obtain free-flowing powder. Phosphorus trichloride (0.09 g, 0.06 ml, 0.71 mmol) and triethylamine (0.28 g, 0.39 ml, 2.84 mmol) were added to the powder, which was then irradiated in the microwave oven at 630 W for an appropriate time. The product was extracted with diethyl ether (3 × 20 ml) and filtered. The ether extract was concentrated and left in the refrigerator when yellow to brown crystalline solid deposited, which was then separated and dried.

Method B. A slurry of **1** (1.42 mmol), phosphorus trichloride (0.09 g, 0.06 ml, 0.71 mmol), and triethylamine (0.28 g, 0.39 ml, 2.84 mmol) in acetonitrile was taken in an Erlenmeyer flask and irradiated in microwave oven at 480 W for an appropriate time. The residue was extracted with diethyl ether and worked up in the similar manner.

Diels–Alder Reaction of 1,3-Azaphospholo[5,1-a]isoquinoline

Method A. A solution of **2b** (0.16 g, 0.47 mmol) dissolved in minimum amount of chloroform was adsorbed on montmorillonite KSF (0.03 g, 20% by weight of the reactant) by swirling, and excess of solvent was removed in vacuum. To this were added 2,3-dimethyl-1,3-butadiene (0.13 g, 0.19 ml, 1.88 mmol) and sulfur (0.02 g, 0.47 mmol), followed by irradiation at 630 W for an appropriate time. The product was obtained in the manner described above.

Method B. The reaction was carried out in chlorobenzene for the time and power shown in Table 1.

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