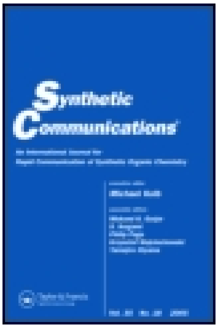

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Task-Specific Ionic Liquid as Reagent and Reaction Medium for the One-Pot Horner-Wadsworth-Emmons-Type Reaction Under Microwave Irradiation

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Task-Specific Ionic Liquid as Reagent and Reaction Medium for the One-Pot Horner–Wadsworth–Emmons–Type Reaction Under Microwave Irradiation

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Abstract: A task-specific imidazolium-based phosphinite ionic liquid (IL-$OPPh_2$) was used as the dual solvent–reagent for the synthesis of E-cinamates and coumarin derivatives via the one-pot Horner–Wadsworth–Emmons–type reaction. The ionic liquid containing its corresponding phosphinite moiety was reacted with α-chloro esters and benzaldehyde or salicylaldehyde derivatives in the presence of sodium methoxide under microwave irradiation to produce the related E-cinamates or coumarins, respectively. The satisfactory results were obtained with good yields, short reaction time, and simple experimental procedure.

Keywords: Coumarin, Horner–Wadsworth–Emmons reaction, microwave, task-specific ionic liquid

Coumarins are an important class of natural products with interesting biological and therapeutic properties.[1] Polycyclic coumarins such as calanolides,[2] isolated from the *Calophyllum* genus, and others have shown potent anti-HIV (NNRTI) activity. They have been used as anticoagulants,[3] additives in food and cosmetics,[1] and in the preparation of insecticides, optical brighteners,[4] and dispersed fluorescent and laser

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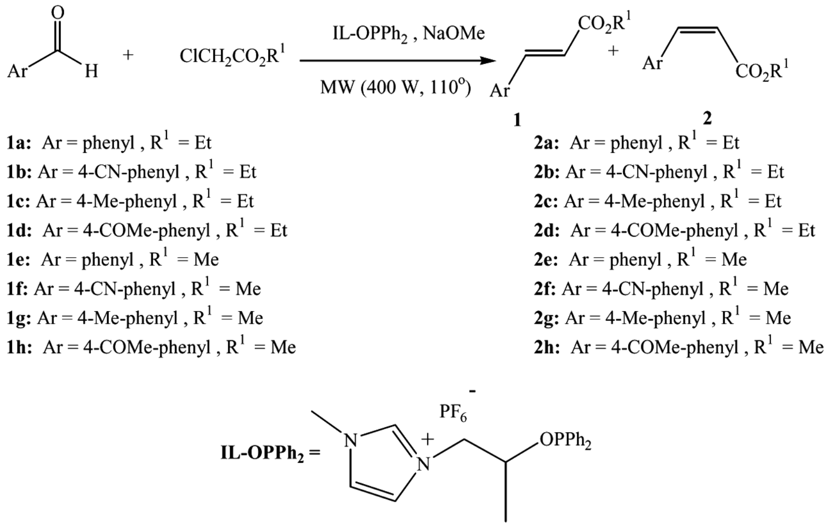
dyes.[5] Coumarins have been synthesized using several synthetic routes, such as Pechmann,[6] Perkin,[7] Knoevenagel,[8] Reformatsky,[9] and Wittig reactions.[10,11] The Wittig reaction involves the condensation of phosphorous ylides with salisylaldehydes to yield simple coumarins. We reported the synthesis of 3,4-unsubstituted coumarins via the one-pot Wittig reaction in a solventless system.[12]

Ionic liquids (ILs) have received attention as ecofriendly, reusable, and alternative reaction media in organic synthesis because of their unique properties, such as high thermal and chemical stability, negligible vapor pressure, no flammability, high loading capacity, and excellent electrical conductivity.[12,13] A number of organic reactions including hydrogenation, oxidation, and C–C bond-forming reactions have already been demonstrated in Ils.[14–20] ILs also play significant roles as catalysts[21–23] and reagents[24,25] and are easy to recycle.[25,26] A recent review[26] presents studies on applications of ILs to asymmetric syntheses, showing their ever-increasing importance. L-Proline has been reported to act as a recyclable chiral base in ILs in the chiral aldol condensations between propanone and a range of aromatic and aliphatic aldehydes.[27,28] In addition, Iranpoor and coworkers have demonstrated that in task-specific imidazolium-based phosphinite ionic liquid (IL-$OPPh_2$), the selective dehalogenation or homocoupling of aryl halides has been performed in good yields.[29]

The Wittig and Horner–Wadsworth–Emmons reactions are among the most popular methods for C=C bond formation, in most cases giving good to excellent stereocontrol.[30] The generality and high stereoselectivity of these reactions constitute two desirable features offered by these protocols. Additionally, the double-bond geometry can generally be predicted and controlled by choosing the appropriate reagents and reaction conditions. Many novel and useful adaptations of the Wittig reaction have been described in the literature, including those employing microwaves,[31] light irradiation,[32] silica,[33] lithium salts,[34] and many more. We reported the synthesis of alkenes via the Wittig reaction in imidazolium-based IL.[35] In this communication, we demonstrate the usefulness of the task-specific IL (IL-$OPPh_2$) as a medium and reagent to prepare stabilized ylides and in situ Horner–Wadsworth–Emmons–type reaction with benzaldehyde derivatives.

Task-specific IL (IL-$OPPh_2$) was prepared according to the procedure reported in the literature.[36,37] In initial efforts to evaluate different conditions, we used methyl chloroacetate and several benzaldehyde derivatives as model substrates. The reactions were studied using methyl chloroacetate (1.5 mmol) in conjunction with benzaldehydes (1.0 mmol) in IL-$OPPh_2$ (1.5 mmol) in the presence of sodium methoxide (Scheme 1).



1a: Ar = phenyl, R^1 = Et
1b: Ar = 4-CN-phenyl, R^1 = Et
1c: Ar = 4-Me-phenyl, R^1 = Et
1d: Ar = 4-COMe-phenyl, R^1 = Et
1e: Ar = phenyl, R^1 = Me
1f: Ar = 4-CN-phenyl, R^1 = Me
1g: Ar = 4-Me-phenyl, R^1 = Me
1h: Ar = 4-COMe-phenyl, R^1 = Me

2a: Ar = phenyl, R^1 = Et
2b: Ar = 4-CN-phenyl, R^1 = Et
2c: Ar = 4-Me-phenyl, R^1 = Et
2d: Ar = 4-COMe-phenyl, R^1 = Et
2e: Ar = phenyl, R^1 = Me
2f: Ar = 4-CN-phenyl, R^1 = Me
2g: Ar = 4-Me-phenyl, R^1 = Me
2h: Ar = 4-COMe-phenyl, R^1 = Me

Scheme 1. One-pot Horner–Wadsworth–Emmons–type reaction in task-specific ionic liquid ($IL\text{-}OPPh_2$).

We investigated these procedures both by thermal heating and microwave irradiation as shown in Table 1. When the experiment was conducted by conventional heating, it took about 13 h for completion of

Table 1. One-pot Horner–Wadsworth–Emmons–type reaction in $IL\text{-}OPPh_2$ for the synthesis of E-cinamates[a]

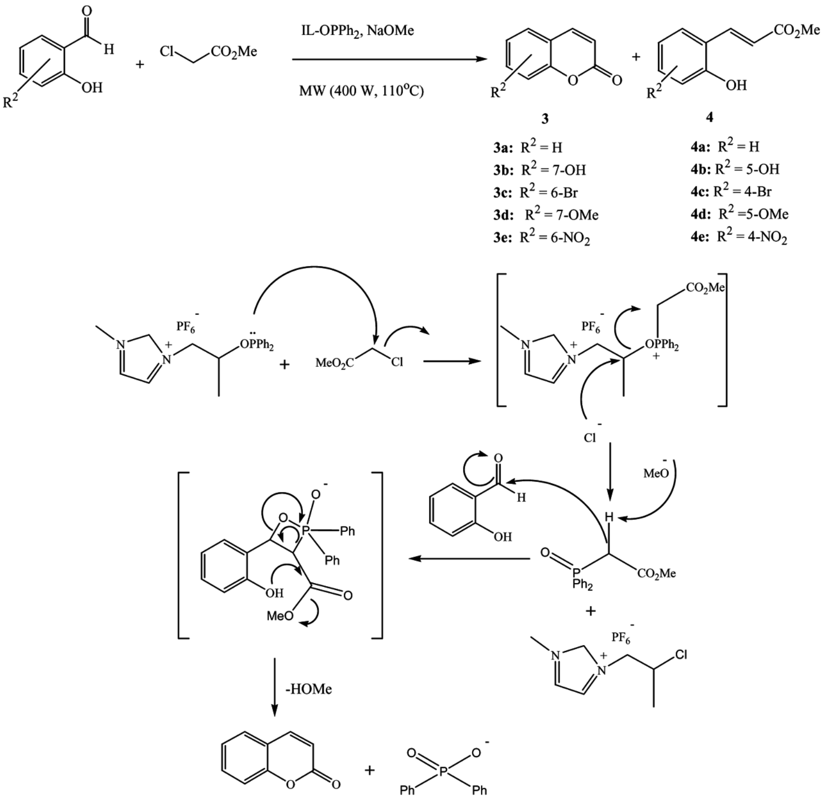
			Heating method			Microwave		
Entry	Ar	R^1	Time (h)	Yield[b] (%)	E/Z	Time (min)	Yield[b] (%)	E/Z
1	Phenyl	Et	12	74	76/24	12	82	78/22
2	4-CN-phenyl	Et	10	78	73/27	11	80	81/19
3	4-Me-phenyl	Et	13	75	79/21	11	80	85/15
4	4-COMe-phenyl	Et	10	79	76/24	10	84	84/16
5	Phenyl	Me	12	77	75/25	11	82	83/17
6	4-CN-phenyl	Me	13	74	78/22	12	79	81/19
7	4-Me-phenyl	Me	10	79	80/20	8	84	86/14
8	4-COMe-phenyl	Me	11	80	81/19	9	87	88/12

[a] All the products have been characterized by ^1H NMR, ^{13}C NMR (300 MHz, $CDCl_3$), and IR spectral analysis (spectroscopic data of well-known products are not reported here).

[b] Isolated yields.

the reaction. The optimization of the process by varying temperature and time was done to get products in good yields and purity. ^{1}H NMR and ^{13}C NMR analysis of the reactions revealed that the alkenes were isolated with good improvement of the E/Z ratio. At lower temperature, lower chemical yields were observed with less improvement of E/Z ratio.

The use of microwave (MW) irradiation for carrying out reactions in the laboratory provides advantages for the synthesis of numerous types of compounds. When the technique is applied successfully, the most evident improvements are reduced time of reaction and cleaner reactions as a result of fewer side reactions. Thus, MW-assisted synthesis can be considered to be more economical. The reaction was examined at different MW powers (100–600 W) with controlled temperature (max. 120°C). The best results were observed at 110°C and 400 W. As can be seen from Table 1, the yields of the products obtained by MW irradiation verses



Scheme 2. A plausible mechanism for the synthesis of coumarins in task-specific ionic liquid (IL-OPPh$_2$).

Table 2. One-pot Horner–Wadsworth–Emmons–type reaction in IL-$OPPh_2$ for the synthesis of coumarins[a]

		Heating method			Microwave		
Entry	R^2	Time (h)	Yield[b] (%)	**3/4**	Time (min)	Yield[b] (%)	**3/4**
1	H	14	68	76/24	12	80	80/20
2	4-OH	13	66	82/18	11	79	84/16
3	4-OMe	15	65	80/20	11	81	86/14
4	5-Br	13	68	78/22	10	81	81/19
5	5-NO_2	16	69	77/23	11	83	79/21

[a] All the coumarins have been characterized by ^1H NMR, ^{13}C NMR (300 MHz, $CDCl_3$), and IR spectral analysis. [39]

[b] Isolated yields.

thermal heating are greater with remarkable reduction in reaction time because of homogeneous heating (as a result of strong agitation of reactant molecules) throughout the reaction media by microwave irradiation as compared to convection currents in thermal heating. Evidently, the MW irradiation increased the reaction rate and selectivity. To establish the generality and applicability of this method, some substituted benzaldehydes were used in this procedure. The results are listed in Table 1. A variety of salicylaldehyde derivatives were also used in this procedure, and coumarin derivatives were synthesized in good yields (Scheme 2). The results are shown in Table 2. A plausible mechanism for the formation of the selected product is outlined in Scheme 2.

In conclusion, the Horner–Wadsworth–Emmons–type reaction between benzaldehyde and salicylaldehyde derivatives with methyl and ethyl chloroacetates can be effectively performed in IL-$OPPh_2$ under microwave irradiation. Imidazolium-based phosphinite IL (IL-$OPPh_2$) was used as both the reaction media and the reagent for the efficient synthesis of a variety of E-cinamate and coumarin derivatives via the Horner–Wadsworth–Emmons–type reaction. This new method has the advantage of good yield, high selectivity, short reaction time, ease of product isolation, and green synthesis.

EXPERIMENTAL

All reactions were carried out in a Microsynth from Milestone with maximum power output of 1000 W. All reactions were carried out in a thick-walled, 10-mL reaction vessel with Teflon-lined caps in a highly efficient fume hood. All chemicals were purchased from Merck and used as received. ^{1}H NMR spectra (400 MHz) and ^{13}C NMR spectra (75 MHz) were recorded on a Bruker Avance spectrometer using tetramethylsilane (TMS) as internal standard. Infrared (IR) spectra were recorded in KBr and were determined on a Perkin-Elmer Fourier transform (FT)–IR spectrometer.

Typical Experimental Procedure

Arylaldehyde derivative (1 mmol), chlotromethylacetate (1.5 mmol), and NaOMe (1.2 mmol) were added to 2 ml freshly prepared IL-$OPPh_2$ and mixed thoroughly in a 10-ml Teflon microwave vessel. The vessel was capped properly, and thereafter the mixture was heated under MW irradiation conditions at 110°C and 400 W for the appropriate reaction time (monitored by thin-layer chromatography, TLC). In conventional heating, the mixture was heated and stirred for the appropriate reaction time (TLC). After cooling to room temperature, the reaction mixtures were extracted with ether (5 ml × 3). The ether layers were collected and concentrated in vacuum. Then the crude mixture was purified by flash chromatography on silica gel to afford corresponding products (Tables 1 and 2).

Spectral Data for Coumarins

Compound **3a**

IR ν_{max}/cm^{-1}: 3020, 1710, 1415; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.70 (d, $J = 8.87$, 1H), 7.35–7.55 (m, 4H), 7.85 (d, $J = 8.87$, 1H).^{13}C NMR (75 MHz, $CDCl_3$) δ 108, 111.1, 113.3, 126, 127.2, 146.8, 148.8, 157.1, 160.9.

Compound **3b**

IR ν_{max}/cm^{-1}: 3313, 3025, 1719, 1435; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.59 (d, $J = 8.78$, 1H), 7.00 (d, $J = 7.18$, 1H), 7.85 (d, $J = 8.78$, 1H), 7.05 (dd, $J = 1.30$ Hz, $J = 7.18$ 1H), 7.12 (d, 1.30 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 108, 111.1, 113.3, 126, 127.2, 146.8, 148.8, 157.1, 160.9.

Compound **3c**

IR ν_{max}/cm^{-1}: 3035, 1726, 1385; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.49 (d, $J = 8.95$, 1H), 7.15 (d, $J = 7.24$, 1H), 7.75 (d, $J = 8.95$, 1H), 7.75 (d,

$J = 1.36$ Hz, 1H), 7.82 (dd, $J = 7.24$ and 1.36 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 111, 115.1, 118.3, 129, 130.2, 149.8, 151.8, 160.1, 163.9.

Compound **3d**

IR ν_{max}/cm^{-1}: 3035, 1726, 1445; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.39 (d, $J = 8.98$, 1H), 7.01 (d, $J = 7.28$, 1H), 7.95 (d, $J = 8.98$, 1H), 7.15 (dd, $J = 1.31$ Hz, $J = 7.28$ 1H), 7.32 (d, 1.31 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 108, 111.1, 113.3, 126, 127.2, 146.8, 148.8, 157.1, 160.9.

Compound **3e**

IR ν_{max}/cm^{-1}: 3035, 1726, 1349, 1545; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.40 (d, $J = 9.15$, 1H), 7.25 (d, $J = 7.34$, 1H), 7.78 (d, $J = 9.15$, 1H), 7.90 (d, $J = 1.35$ Hz, 1H), 8.04 (dd, $J = 7.34$ and 1.35 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 111.5, 112.1, 113.3, 129.1, 129.2, 148.6, 150.5, 159.1, 163.3.

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