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A simple conversion of azlactones into indenones via $H_3PW_{12}O_{40}/Al_2O_3$ catalyzed intramolecular Friedel–Crafts reaction

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ABSTRACT

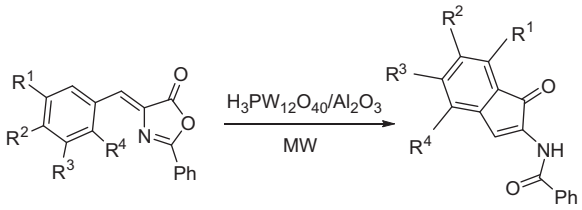
A rapid and simple procedure for the synthesis of the indenone derivatives, *N*-(1-oxo-1*H*-inden-2-yl)-benzamides, via intramolecular Friedel–Crafts (IFC) reaction of (*Z*)-4-arylidene-2-phenyl-5(4)-oxazolones (azlactones) catalyzed by $H_3PW_{12}O_{40}$ supported on neutral alumina under microwave irradiation has been developed. The reaction is straightforward and allows easy isolation of the product. The catalyst could be re-used up to four times after simple filtration.

The demand for increasingly clean and efficient chemical syntheses is important from both economic and environmental points of view. Solid-state organic reactions have gained importance in organic synthesis due to several advantages including faster reactions, selectivities different from those in solution, and greener procedures.[1] Nonetheless, the long reaction times, which are frequently required for full conversions have limited the exploitation of these reactions in high-throughput synthesis. In recent years, investigation on organic synthesis via microwave-assisted methods has gained importance.[2] Clean reactions, short reaction times, simple procedures, increased selectivities, and high yields are advantageous features of MW-assisted methods.[3]

Recently, applications of heteropoly acids (HPAs) in chemistry have increased significantly.[4] Among HPAs, $H_3PW_{12}O_{40}$, owing to its stronger acidity (Brønsted acid) and higher thermal stability compared to other examples, is usually the catalyst of choice.[5] Furthermore, modification of the activity of $H_3PW_{12}O_{40}$ has been accomplished by supporting it on a solid such as alumina.[6]

The presence of the indenone skeleton in a number of naturally occurring compounds and synthetic materials, with important biological properties, illustrates the need for the development of new methods for the preparation of these compounds. For instance, euplectin, a rare natural product with an indenone moiety, was reported to exhibit cytotoxicity against the growth of murine P-815 mastocytoma cells.[7] Some indenone derivatives are used as important starting materials for the synthesis of kinamycin antibiotics, which show excellent activity against Gram-positive bacteria.[8] On the other hand, increased effort has been directed toward the development of new indenone-based structures as ligands in organometallic chemistry.[9]

The intramolecular Friedel–Crafts (IFC) reaction is an attractive method for the formation of these types of compounds. This method was established by Awad et al. for the synthesis of 2-benzamidoindenone in the presence of $AlCl_3$ in anhydrous carbon tetrachloride.[10] Recently, this transformation was modified by Kangani et al. through IFC reaction of 2-benzylamino-3-phenylacrylic acid using cyanuric chloride, pyridine, and $AlCl_3$.[11] However, one of the challenging problems in such processes is the introduction of appropriate substituents during cyclization because, in some cases, the presence of functional groups often hinders the desired IFC reaction. Therefore, to overcome these problems, more convenient methods for the synthesis of these types of compounds are required.



Scheme 1. IFC reaction of azlactones to afford indenones.

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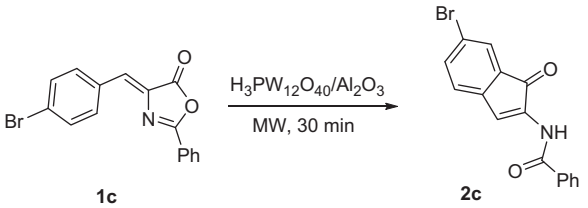
Table 1
Optimization of the IFC reaction of **1c** to give **2c**



1c **2c**

Entry	Catalyst (mg)	Solvent	Power (W)	Temperature (°C)	Yield (%)[a]
1	150	—	650	115	79
2	200	—	650	115	83
3	250	—	650	115	86
4	300	—	650	115	87
5	250	—	650	90	66
6	250	—	650	100	73
7	250	—	650	120	85
8	250	—	550	115	70
9	250	—	750	115	88
10[b]	250	—	—	115	—
11	250	CH_3CN[c]	650	80	46
12	250	EtOH[c]	650	78	42
13	250	PEG-400[c]	650	115	65

[a] Isolated yield.
[b] Under oil bath heating.
[c] Two milliliters of solvent.

In continuation of our recent studies on azlactone chemistry,[12] and as a part of our ongoing research program to develop new methodologies for the synthesis of fine chemicals,[13] herein we describe the successful use of $H_3PW_{12}O_{40}$ supported on neutral alumina[14] as an active catalyst for the synthesis of *N*-(1-oxo-1*H*-inden-2-yl)benzamides via IFC reaction of azlactones under microwave irradiation (Scheme 1).[15]

In order to optimize the reaction conditions, the IFC reaction of (*Z*)-4-(4-bromobenzylidene)-2-phenyloxazol-5(4*H*)-one (**1c**, 1 mmol) in the presence of $H_3PW_{12}O_{40}/Al_2O_3$ (250 mg) was selected as a model reaction (Table 1). We investigated the reaction under microwave irradiation with a temperature controlled program. During irradiation, the temperature was monitored by an IR sensor which controlled the MW power levels.

Optimization by screening the reaction conditions including the amount of the catalyst, temperature and output power of the microwave irradiation was investigated. The results indicated that lower amounts of catalyst gave lower yields (Table 1, entries 1 and 2). The reactions were carried out at temperatures ranging from 90 to 120 °C. It was found that a higher reaction temperature (120 °C) led to no improvement in the yield, but using a lower temperature (100 °C), sharply decreased the conversion to 73%. The procedure was carried out at different microwave irradiation output power (Table 1, entries 3, 8, and 9). It was found that the yield reached a plateau at 650 W (Table 1, entry 3).

To demonstrate the positive effect of MW irradiation, the synthesis of **2c** was investigated with and without microwave irradiation. When the reaction was carried out in the absence of

Table 2
Synthesis of *N*-(1-oxo-1*H*-inden-2-yl)benzamides via IFC-reaction of azlactones catalyzed by $H_3PW_{12}O_{40}/Al_2O_3$ (see Scheme 1)

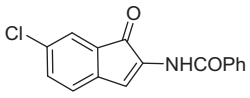
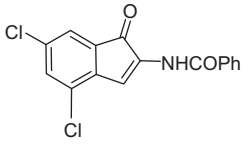
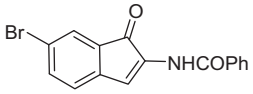
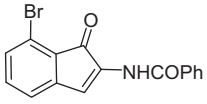
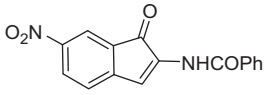
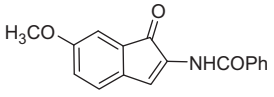
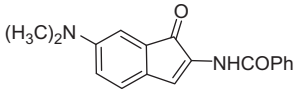
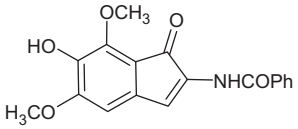
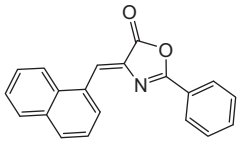
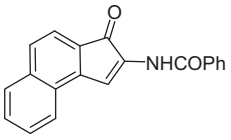
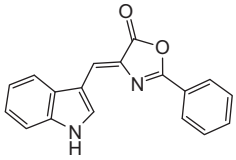
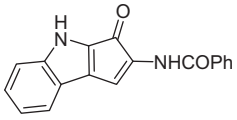
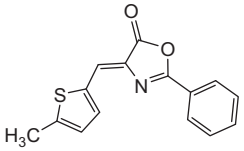
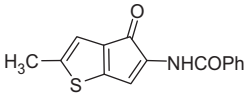
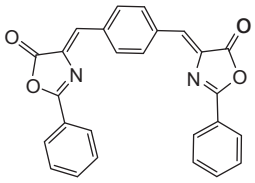
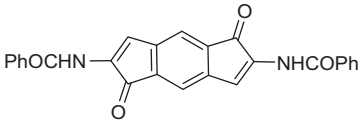
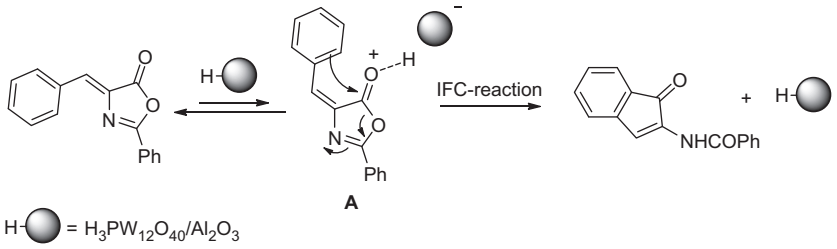
Entry	R^1	R^2	R^3	R^4	Product		Time (min)	Yield (%)[a]
1	H	Cl	H	H		**2a**	40	86[16]
2	H	Cl	H	Cl		**2b**	45	81
3	H	Br	H	H		**2c**	40	87
4	Br	H	H	H		**2d**	40	85
5	H	NO_2	H	H		**2e**	42	83
6	H	CH_3O	H	H		**2f**	35	88
7	H	$(CH_3)_2N$	H	H		**2g**	35	80
8	CH_3O	HO	CH_3O	H		**2h**	40	81

Table 2 (*continued*)

Entry	R^1	R^2	R^3	R^4	Product		Time (min)	Yield (%)[a]
9						**2i**	39	85
10						**2j**	40	84[16]
11						**2k**	38	86[16]
12						**2l**	42	80[16]

[a] Yield refers to isolated pure product characterized by FTIR, ^{1}H NMR,^{13}C NMR and mass spectroscopy.



Scheme 2. Proposed mechanism.

microwave irradiation with stirring at 115 °C, **2c** was not produced at all (Table 1, entry 10), while at the same temperature under microwave irradiation, a high yield of the corresponding product was obtained (86%, Table 1, entry 3). The effect of solvent on this transformation was also investigated. As shown in Table 1, the desired product was obtained in unsatisfactory conversion in acetonitrile, ethanol, and PEG-400 (46%, 42%, and 65%, respectively). Thus the optimum conditions required solvent-free microwave irradiation at 115 °C and 650 Watt power for the IFC reaction of azlactones to give the corresponding indenones in the presence of $H_3PW_{12}O_{40}/Al_2O_3$.

After successful generation of **2c**, we next introduced greater diversity to the *N*-(1-oxo-1*H*-inden-2-yl)benzamide scaffold (Table 2).

As shown in Table 2, it is clear that using the optimized reaction conditions, this procedure was quite general. In most cases, the reaction proceeded with high efficiency and with broad functional group tolerance. To expand the scope of the azlactone substrates, various mono and disubstituted azlactones containing both electron-withdrawing and electron-donating substituents were used, and these displayed good reactivity and afforded the desired products in high yields. In addition, polycyclic or heterocyclic azlactones, such as (*Z*)-4-(naphthalen-1-ylmethylene)-2-phenyloxazol-5(4*H*)-one (**1i**), (*Z*)-4-[(1*H*-indol-3-yl)methylene]-2-phenyloxazol-5(4*H*)-one (**1j**), or (*Z*)-4-[(5-methylthien-2-yl)methylene]-2-phenyloxazol-5(4*H*)-one (**1k**),[12d] were reactive substrates and provided the desired products in satisfactory yields. A particularly noteworthy feature of the present protocol is the successful synthesis of **2l** from (4*Z*,4′*Z*)-4,4′-[1,4-phenylenebis(methan-1-yl-1-ylidene)]bis(2-phenyloxazol-5(4*H*)-one[12d] (**1l**). The wide potential of this method makes it an attractive strategy for the synthesis of *N*-(1-oxo-1*H*-inden-2-yl)benzamides.

Another advantage of this method is the recyclability of the catalyst. $H_3PW_{12}O_{40}/Al_2O_3$ can be separated by simple filtration, washing with ethanol, and drying at 80 °C under reduced pressure and reused for at least four runs without any loss of activity.

A plausible mechanism for the formation of *N*-(1-oxo-1*H*-inden-2-yl)benzamides is shown in Scheme 2. Initially, tautomerism of the (*Z*)-azlactone into (*E*)-isomer **A** is catalyzed by $H_3PW_{12}O_{40}/Al_2O_3$. Subsequently, **A** undergoes the intramolecular Friedel–Crafts reaction followed by rearrangement into amide.

In conclusion, we have demonstrated a simple and facile synthesis of *N*-(1-oxo-1*H*-inden-2-yl)benzamides from azlactones in the presence of $H_3PW_{12}O_{40}/Al_2O_3$ under microwave irradiation. The process is simple and has been shown to generate a diverse range of indenones in high yields. The experimental simplicity,

ease of product isolation, reusability of the catalyst and ready availability of the catalyst could make this process very useful for the synthesis of *N*-(1-oxo-1*H*-inden-2-yl)benzamides.

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15. *Typical procedure for the synthesis of N-(6-chloro-1-oxo-1H-inden-2-yl)benzamide* (**2a**): In a high pressure Teflon reactor equipped with a magnetic stir bar and an IR sensor (for controlling the reaction temperature), (*Z*)-4-(4-chlorobenzylidene)-2-phenyloxazol-5(4*H*)-one (0.283 g, 1 mmol) and $H_3PW_{12}O_{40}/Al_2O_3$ (0.250 g, 5.2 mol %) were submitted to microwave irradiation at 115 °C (650 W) using a micro-SYNTH lab station reactor for 40 min. During this time, the power was modulated automatically to hold the reaction temperature at 115 °C. After the reaction was complete (monitored by TLC), the mixture was cooled to room temperature, filtered, washed with a hot mixture of EtOAc–EtOH (10:1, 2 × 10 ml), and concentrated in vacuo to give a crude residue, which was purified as appropriate by recrystallisation from EtOH.
16. Selected spectral data for **2a**, **2j**, **2k** and **2l**: *N-(6-chloro-1-oxo-1H-inden-2-yl)benzamide* (**2a**): FTIR (KBr, solid): 3235, 1698, 1644, 1470, 1423, 1311, 1277, 1088, 910, 699, 524. ^{1}H NMR (500 MHz, DMSO-d_6): δ = 9.54 (s, 1H), 7.88–7.89 (d, *J* = 7.55 Hz, 2H), 7.54–7.56 (t, *J* = 7.8 Hz, 1H), 7.47–7.50 (t, *J* = 7.8 Hz, 2H), 7.34–7.35 (d, *J* = 8.1 Hz, 1H), 7.28–7.29 (d, *J* = 8.1 Hz, 2H), 7.16 (s, 1H). ^{13}C NMR (125 MHz, DMSO-d_6): δ = 167.6, 163.5, 149.5, 137.1, 135.8, 134.7, 131.4, 130.9, 130.4, 128.4, 127.6, 127.3, 124.2, 122.9. MS (EI): *m*/*z* 285.32 [M+2], 283.74 [M]$^+$, 149.94, 104.87, 76.86, 50.9. *N-(3,4-Dihydro-3-oxocyclopenta[b]indol-2-yl)benzamide* (**2j**): FTIR (KBr, solid): 3364, 3343, 1698, 1644, 1539, 1079, 962, 889, 792, 437. ^{1}H NMR (300 MHz, DMSO-d_6): δ = 10.31 (s, 1H), 9.98 (s, 1H), 7.83–7.85 (d, *J* = 5.58 Hz, 2H), 7.65 (br s, 3H), 7.48–7.49 (d, *J* = 4.4 Hz, 2H), 7.40–7.43 (t, *J* = 4.7 Hz, 2H), 7.3 (s, 1H). ^{13}C NMR (125 MHz, DMSO-d_6): δ = 166.15, 163.73, 149.35, 137.98, 133.48, 133.18, 131.76, 131.47, 131.46, 130.97, 130.84, 128.41, 128.22, 127.63, 122.29, 117.99. MS (EI): *m*/*z* 167.07 [M-120], 149, 71, 57. *N-(2-methyl-4-oxo-4H-cyclopenta[b]thiophen-5-yl)benzamide* (**2k**): FTIR (KBr, solid): 3395, 1695, 1610, 1539, 1448, 1028, 670, 469. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.3 (s, 1H), 7.99 (s, 2H), 7.33–7.68 (m, 3H), 7.01 (s, 1H), 6.71 (s, 1H), 2.35 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d_6): δ = 166.09, 163.80, 149.89, 144.12, 141.57, 135.82, 130.91, 130.4, 128.46, 127.65, 127.32, 121.99, 17.21. MS (EI): *m*/*z* 148.96 [M−120], 104.94, 76.95, 57.04. *N,N′-(1,5-Dioxo-1,5-dihydros-indacene-2,6-diyl)dibenzamide* (**2l**): FTIR (KBr, solid): 3374, 1703, 1610, 1569, 1437, 1266, 1026, 675, 589. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.7 (s, 2H), 7.94–7.95 (d, *J* = 7.1 Hz, 2H), 7.84–7.85 (d, *J* = 7.1 Hz, 2H), 7.66 (br s, 2H), 7.49–7.51 (t, *J* = 8.4 Hz, 4H), 7.41–7.44 (t, *J* = 8.35 Hz, 4H). ^{13}C NMR (125 MHz, DMSO-d_6): δ = 167.01, 165.93, 152.17, 142.38, 133.22, 131.76, 131.48, 128.41, 127.63, 126.40, 121.48. MS (EI): *m*/*z* 420.19 [M]$^+$, 105.01, 77.02, 55.04.