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Development of a mild and efficient protocol for the protection and *O*-alkylation of allyl alcohols†

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An efficient, pyridine-free protocol has been developed for the protection of the 3°-allyl alcohol of oxindole using a mild base, such as potassium carbonate, under microwave irradiation conditions. The methodology has been tested with a variety of substrates and protecting group reagents, which provides a clean and good yield of the desired products within a short reaction time.

Introduction

The sequence of protection–deprotection reactions of hydroxyl groups is an important synthetic transformation for the selective oxidation, reduction, rearrangement, and synthesis of natural products, amino acids, carbohydrates, *etc.*[1] For this, several groups have made significant efforts to develop an efficient and simple method for the protection of hydroxyl groups using a variety of protecting group reagents and catalytic conditions.[2–6] However, these methodologies have certain limitations such as longer reaction time, stringent experimental conditions, usage of expensive, hazardous and flammable chemicals and/or the preparation of catalysts required special care and efforts. In addition, most of the reported procedures were applicable only to limited reagents and substrates. Thus, the paucity of a general and efficient method for the protection of the hydroxyl group prompted the development of a facile and mild synthetic method.

Microwave-promoted reactions have advantages over the conventional thermal reactions, which are practically more feasible and provide a greener synthetic pathway under solvent-free conditions. Because of this benefit, a number of synthetic transformations have been efficiently explored with the blend of microwave resources and K_2CO_3.[7] In particular, solid acids, such as PTSA, montmorillonite-K10, montmorillonite-KSF, and acid-adsorbed solid catalysts have been well documented for the protection of hydroxyl group under microwave conditions.[8] However, the combined source of microwave and K_2CO_3 assisted protection of hydroxyl group is still in its early stages.[9]

During the novel synthetic transformation of Morita–Baylis–Hillman (MBH) adduct of isatin,[10] the protection of tertiary allyl alcohol of oxindole requires dry pyridine and solvent at low temperatures. In addition, the nucleophilic substitution of allyl alcohol of oxindole preferentially prompted either the isomerization or ring cleavage of lactam moiety rather than C-3 substitution.[11] This phenomenon is due to the sluggish leaving ability of the free 3°-hydroxyl group and the stabilization of the isomerized product by the amide functionality of oxindole moiety. To achieve the selective nucleophilic substitution at the C-3 position, the protected and/or masked allyl derivatives of oxindole have been used and converted into corresponding natural product derivatives, spiro compounds and active pharmaceutical intermediates (API).[10a,b,12,13] Hence, it is necessary to enhance the leaving ability of the 3°-hydroxyl group by an appropriate protecting group, which results in the C-3 position of oxindole to be a stronger competent reactive centre for nucleophilic substitution than allylic position. Thus, herein, we report a mild protocol for the protection and *O*-alkylation of the 3°-allyl alcohol of oxindole with numerous protecting group reagents in the presence of K_2CO_3 and microwave irradiation conditions.

Results and discussion

Initially, we carried out an experiment with a well-mixed slurry prepared from the MBH adduct of isatin **1a**, acetyl chloride **2a** and K_2CO_3 (100% w/w), and subjected it to microwave irradiation (500 W, at 60 °C) for 5 min. The reaction mixture successfully provided an acetyl-protected MBH adduct **3a** with 10% yield after column chromatography (Scheme 1).

The compound **3a** was precisely characterized by general spectroscopic methods (IR, ^1H, ^{13}C NMR and mass). In

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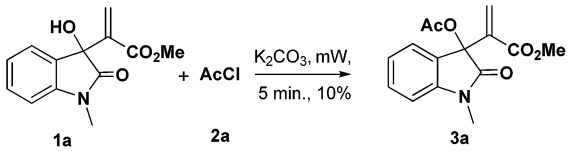


Scheme 1 Protection of 3°-allyl alcohol of MBH adduct of isatin by microwave method.

particular, the olefinic protons appeared as two separate singlets at δ 6.50 and 6.57 ppm and the ester methyl groups appeared at 2.03 and 3.77 ppm, respectively. The observed low yield of product **3a** encouraged us to optimize the reaction conditions by changing parameters such as power level (PL), temperature and time interval (Table 1). The gradual increase in product yield was observed by the successive increments of power level, time and temperature (Table 1, entries 1–7). To our surprise, the addition of 1.5 equiv. of tetra-butyl ammonium bromide (TBAB) in the reaction mixture furnished an optimum yield of **3a** (80%) within 10 min (Table 1, entry 8). Under microwave irradiation conditions, the molten salt of TBAB probably acts as a solvent, which makes the reaction a homogeneous mixture.[14] It is worth mentioning that not even a trace of Michael-type addition product **5a** was detected under microwave-assisted protection of the allyl alcohol of the MBH adduct of isatin. However, the conventional method produced the Michael-type addition product as a major isomer along with the protected derivative (yield = 86/5%).[15] The extended microwave irradiation (20 min) yielded 20% of one-pot, acyl-isomerized compound **4a** along with protected compound **3a** (Table 1, entry 9). At high temperatures (>100 °C), the irradiation of the reaction mixture resulted in the decomposition of starting material **1a**.

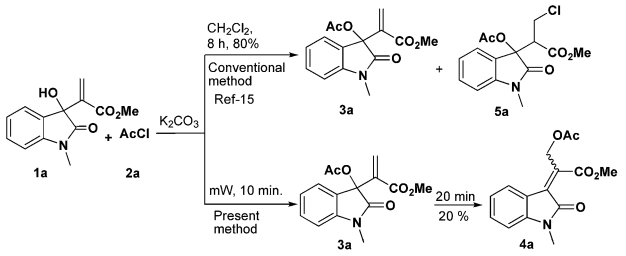
With this viable optimization, the scope and limitation of the method has been examined against various protecting group reagents with *N*-methyl MBH adducts of isatin **1a**, and the results are shown in Table 2.

The use of acetic anhydride (Ac_2O) instead of acetyl chloride has led to a better yield of the product **3a** (89%) (Table 2, entry 1). The other protecting group reagents such as Boc-anhydride and tosyl chloride reacted well and obtained the corresponding products **3b** and **3c** in 86% and 89% yields, respectively (Table 2, entries 2 and 3). The ^{1}H NMR spectrum of compound **3c** showed that it is an isomeric mixture of protected and tosyl-isomerized product in 1 : 0.5 ratio. Similarly, the other protection group reagents, such as MOM-Cl and BOM-Cl, provided the desired products **3d** and **3e** in moderate to good yields (Table 2, entries 4 and 5). Microwave-assisted *O*-alkylation of alcohols with alkyl halides in the presence of solid-supported catalysts was well established.[16] Hence, we envisaged to investigate the feasibility of *O*-alkylation of 3°-allyl alcohol of MBH adduct of isatin under the optimized condition, which can be a viable synthon for further synthetic manipulation. The alkyl halides, such as propargyl bromide, allyl chloride and ethyl 2-bromoacetate, treated with MBH adducts of isatin furnished the corresponding highly functionalized *O*-alkylated products in good yield (Table 2, entries 6–8).[17] It should be noted that the *O*-alkylated derivatives are a new entry in the family of MBH adduct of isatin derivatives. Surprisingly, the bulky silyl halides, such as TBDMS-Cl and TES-Cl, did not furnish any characteristic product under the optimized condition.

This viable synthetic strategy prompted us to explore the substrate scope of the reaction. Thus, we selected various types of the hydroxyl group of primary- secondary- and tertiary-alcohol, carboxylic acid, α,β-unsaturated acid, cinnamyl alcohol, oxime and phenol in this study. All the substrates furnished desired products in good to excellent yields, and the results are summarized in Table 3.

To examine this strategy with secondary allylic alcohol, the MBH adduct of benzaldehyde and ferrocene carboxaldehyde were chosen as representative substrates. Among them, the MBH adduct of benzaldehyde with $(Ac)_2O$ and propargyl bromide exclusively provided the corresponding acylated MBH and *O*-alkylated derivatives (Table 3, entries 1 and 2).[18] However, the acetyl *E*-isomerized derivative **6c** was obtained from the MBH adduct of ferrocene carboxaldehyde (Table 3, entry 3).[19] It may be because of the migratory nature of the acyl group and the stability of the product **6c** together triggering the isomerization.[20] It should be noted that the introduction of an acetyl group on the MBH adduct of ferrocene moiety still remains a challenging task.[21] Furthermore, the MBH adduct of ninhydrine provided the desired product in good yield (Table 3, entry 4). If the isatin N–H is unprotected, the isatin hydroxime derivative provided *O*-alkylation, along with the *N*-alkylated product (Table 3, entries 5

Table 1 Microwave-assisted protection of the 3°-allyl alcohol of MBH adduct



Entry	Time (min)	Temp (°C)	Power (W)	Yield[a] (%)
1	5	60	500	10
2	5	70	500	15
3	5	75	700	24
4	10	75	800	40
5	10	75	1000	47
6	10	85	1000	55
7	10	100	1000	65
8	***10***	***100***	***1000***	***80***[b]
9	20	100	1000	55[c]

[a] Isolated yield. [b] Addition of TBAB (1.5 equiv.). [c] Combined yield of isomerized and protected compounds.

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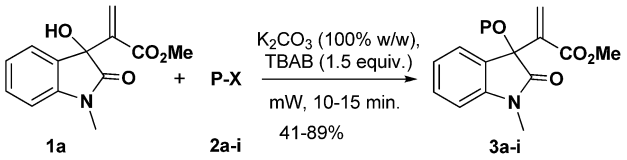
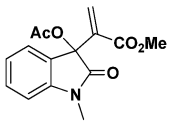
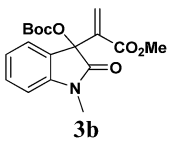
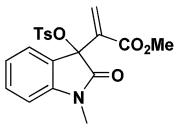
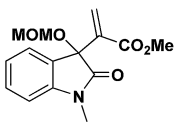
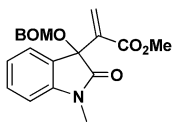
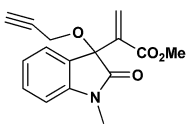
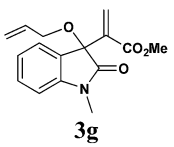
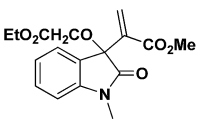
Table 2 Protection and *O*-alkylation of the 3°-allyl alcohol of MBH adduct of isatin **1a** with various protecting group reagents



1a 2a-i 3a-i

Entry	P-X **2a–i**	Time (min), temp (°C)	Product **3a–h**	Yield[a] (%)
1	$(Ac)_2O$ **2b**	10, 100	 **3a**	89
2	$(BOC)_2O$ **2c**	10, 100	 **3b**	86
3	TsCl **2d**	10, 80	 **3c**	89
4	MOM-Cl **2e**	15, 100	 **3d**	45
5	BOM-Cl **2f**	15, 100	 **3e**	78
6	Propargyl bromide **2g**	15, 100	 **3f**	71
7	Allyl bromide **2h**	15, 100	 **3g**	61
8	$BrCH_2CO_2Et$ **2i**	10, 100	 **3h**	85

[a] Isolated yield. Yields are not optimized, microwave oven of Start-S (Milestone-Italy).

and 6). Remarkably, the α,β-unsaturated acid and cinnamyl alcohol have also been proven to be excellent substrates for protection and *O*-alkylation reactions (Table 3, entries 7 and 8). The non-allyl functionalities such as phenol and benzoic acid can also be good substrates for protection under microwave reaction conditions (Table 3, entries 9 and 10).

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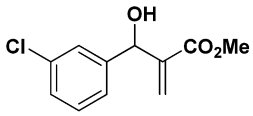
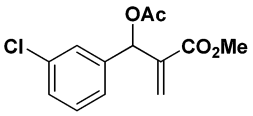
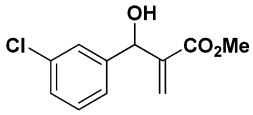
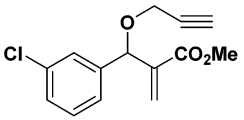
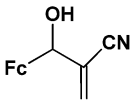
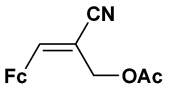
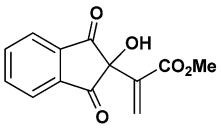
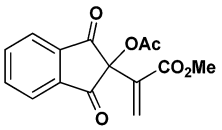
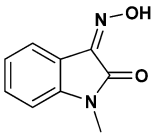
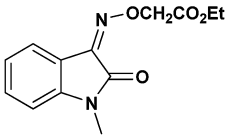
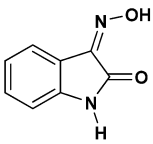
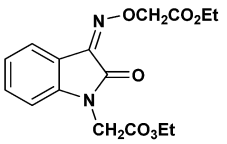
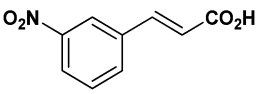
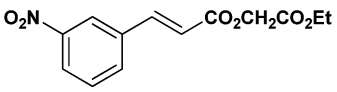
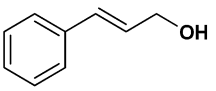
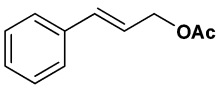
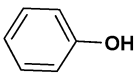
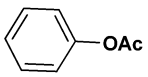
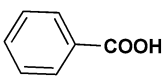
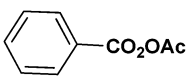
Table 3 Protection and *O*-alkylation of various hydroxyl groups by microwave irradiation

Entry	Substrate	Time (min), temp (%)	Product **6a–j**	Yield[a] (%)
1		10, 100		94
2		15, 100		88
3		10, 100		98[b]
4		10, 100		91
5		10, 100		93
6		10, 100		87
7		15, 100		98
8		15, 100		88
9		10, 100		86
10		10, 100		87

[a] Isolated yield. [b] Fc = Ferrocene. Yields are not optimized, microwave oven of Start S (Milestone-Italy).

Conclusions

In conclusion, we have developed a mild and efficient strategy for the protection and *O*-alkylation of various protecting group reagents with hydroxyl groups using K_2CO_3 under microwave irradiation. The microwave-assisted protection has been demonstrated as a clean and pyridine-free condition in a shorter reaction time than the conventional reaction. The synthesized *O*-alkylated isatin derivatives and acyl-isomerized ferrocene derivative are new entries in the family of MBH adducts. Further synthetic transformations of these compounds are undergoing in our laboratory.

Experimental procedure

The MBH adduct **1a** (100 mg, 0.404 mmol), potassium carbonate (100% w/w) and protecting reagents or alkylation reagents (1.5 equiv.) with tetra-butyl ammonium bromide (1.5 equiv.) were made into a slurry and inserted in a microwave oven of Start S (Milestone-Italy), which is equipped with a magnetic stirrer, a noncontact, infrared, continuous feedback temperature system under atmospheric pressure for a period of 10–15 min. After cooling the reaction mixture to room temperature, the crude mixture was dissolved in EtOAc and filtered through a celite pad, and then purified by silica-gel column

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chromatography, which afforded the corresponding products in good to moderate yields (45–98%).

Spectroscopic data for selected compounds 3a

IR (CH_2Cl_2) γ_{max}: 1130, 1361, 1476, 1492, 1619, 1721, 1732, 2126, 2931, 3218 cm^{-1}; ^1H NMR ($CDCl_3$/TMS, 500.1 MHz): δ 2.03 (s, 3H), 3.27 (s, 3H), 3.77 (s, 3H), 6.50 (s, 1H), 6.57 (s, 1H), 6.91 (d, $J = 7$ Hz, 1H), 7.20 (s, 1H), 7.60 (s, 1H), 7.79 (d, $J = 7$ Hz, 1H); ^{13}C NMR ($CDCl_3$/TMS, 75.3 MHz): δ 20.52, 26.99, 54.87, 78.29, 108.29, 115.52, 122.80, 127.61, 129.06, 131.61, 135.47, 135.87, 165.68, 169.87, 173.01; FAB mass: calcd for $C_{15}H_{15}NO_5$ is 289.10; found: 290.47 (M + 1).

Compound 3f

IR (CH_2Cl_2) γ_{max}: 1134, 1233, 1354, 1475, 1470, 1613, 1724, 1735, 2122, 2928, 3210 cm^{-1}; ^1H NMR ($CDCl_3$/TMS, 500.1 MHz): δ 2.35 (s, 1H), 3.27 (s, 3H), 3.57 (s, 3H), 3.88–4.03 (m, 2H), 6.62 (s, 2H), 6.85–6.87 (d, $J = 7.5$ Hz, 1H), 7.04–7.06 (t, $J = 7.0$ Hz, 1H), 7.12–7.14 (d, $J = 7.5$ Hz, 1H), 7.34–7.34 (t, $J = 7.0$ Hz, 1H); ^{13}C NMR($CDCl_3$/TMS, 75.3 MHz): δ 26.46, 51.95, 52.91, 74.62, 79.10, 80.41, 108.47, 122.89, 124.55, 125.96, 128.51, 130.75, 137.42, 145.34, 164.57, 173.43; FAB mass: calcd for $C_{16}H_{15}NO_4$ is 285.12; found: 286.32 (M + 1).

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Notes and references

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