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Graphical Abstract

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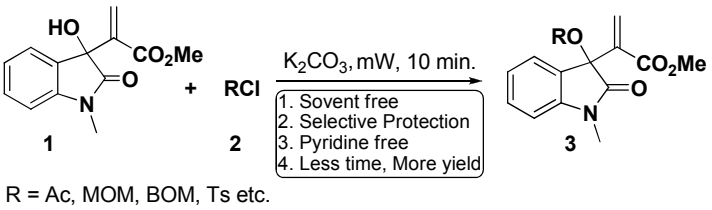
Kodirajan Selvakumar,[a]* Kandapalam Arun Prasath Lingam[a], Rama Varma Luxmi Varma[c]



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

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

Introduction

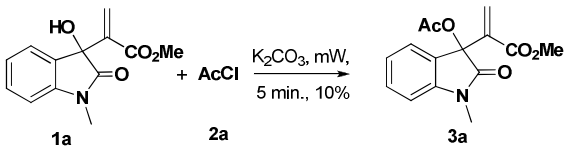
The sequence of protection-deprotection reactions of hydroxyl group are an important synthetic transformation for the selective oxidation, reduction, rearrangement, synthesis of natural products, amino acid, carbohydrate chemistry and so on.[1] With this intention, several groups have made a significant effort to develop an efficient and simple method for the protection of hydroxyl group using a variety of protecting group reagents and catalytic conditions.[2-6] Nevertheless, 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. Besides, most of the reported procedures were applicable to limited reagents and substrates scope. Thus, the paucity of general and efficient method for the protection of the hydroxyl group prompted to develop a facile and mild synthetic method.

Microwave promoted reactions have advantages over the conventional thermal reactions, practically more feasible and provided greener synthetic pathway under solvent free condition. Owing to its benefit, a number of synthetic transformations have been efficiently explored with the blend of microwave resource 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 condition.[8]However, the combined source of microwave and K_2CO_3 assisted the protection of hydroxyl group has still in infancy.[9]

During the novel synthetic transformation of Morita-Baylis-Hillman (MBH) adduct of isatin,[10] the protection of tertiary allyl alcohol of oxindole is demanded dry pyridine and solvent at low temperature. In addition, the nucleophilic substitution of allyl alcohol of oxindole prompted preferentially either isomerization or ring cleavage of lactam moiety rather than C-3 substitution.[11] This phenomenon is due to the sluggish leaving ability of free 3º-hydroxyl group and the stabilization of the isomerized product by the amide functionality of oxindole moiety. In order to achieve the selective nucleophilic substitution at 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 3º-hydroxyl group by pertinent protecting group which resulted the C-3 position of oxindole can be competent reactive centre for nucleophilic substitution than allylic position. Thus, we report herein a mild protocol for the protection and *O*-alkylation of 3º-allyl alcohol of oxindole with a number of protecting group reagents in the presence of K_2CO_3 and microwave irradiation condition.

Results and discussion

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



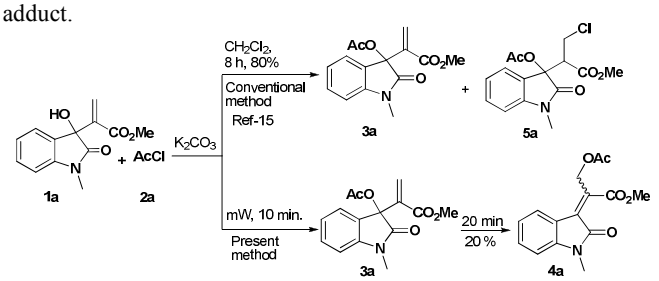
1a 2a 3a

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

The compound **3a** was unambiguously characterized by usual spectroscopic methods (IR, ^{1}H, ^{13}CNMR and mass). In 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** provoked us to optimize the reaction condition by changing parameters such as power level (PL), temperature and time interval (Table 1). The gradual upsurge of 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 was furnished

optimum yield of **3a** (80%) within 10 min (Table 1, entry 8).Under microwave irradiation condition, the molten salt of TBAB probably acts as a solvent which makes the reaction as a homogeneous mixture.[14] It is noteworthy to mention that not even a trace of Michael type addition product **5a** was detected under microwave assisted protection of allyl alcohol MBH adduct of isatin. However, the conventional method afforded the Michael type addition product as a major isomer along with protected derivative (yield= 86/5%).[15] The extended microwave irradiation (20 min) yielded one-pot acyl isomerized compound **4a** in 20% along with protected compound **3a** (Table 1, entry 9). At high temperature (>100 ^{O}C), irradiation of the reaction mixture resulted decomposition of starting material **1a**.

Table 1. Microwave assisted protection of 3^{o}-allyl alcohol of MBH adduct.

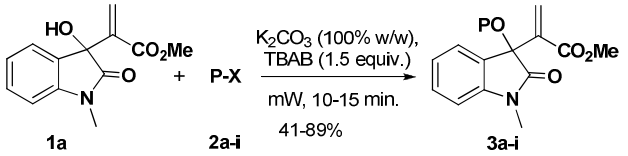


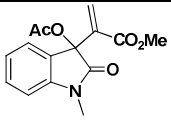
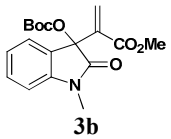
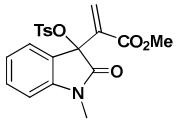
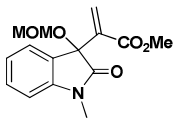
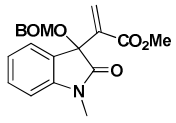
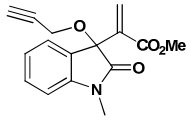
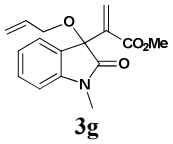
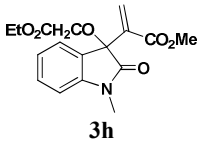
Entry	Time (min)	Temp (^{o}C)	Power (W)	Yield (%)[a]
1	5	60	500	10
2	5	70	500	15
3	5	75	700	24
4	10	75	800	40
5	10	75	1000	47
6	10	85	1000	55
7	10	100	1000	65
8	***10***	***100***	***1000***	***80^{b}***
9	20	100	1000	55^{c}

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

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.

Table 2. Protection and *O*-alkylation of 3^{o}-allyl alcohol of MBH adduct of isatin **1a** with various protecting group reagents.



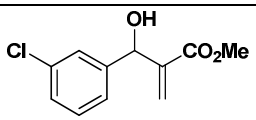
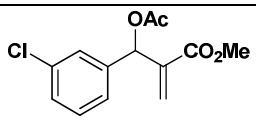
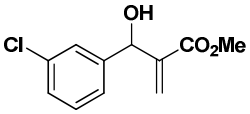
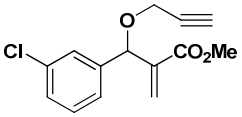
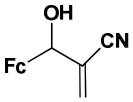
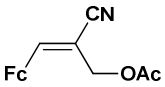
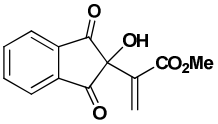
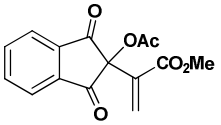
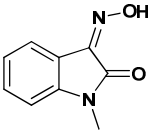
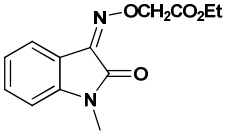
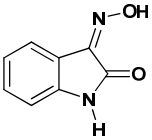
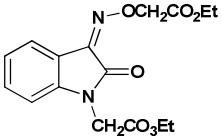
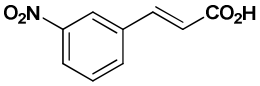
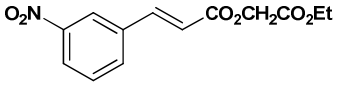
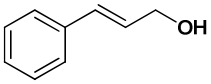
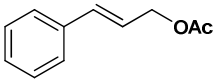
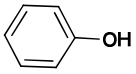
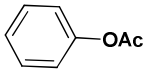
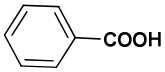
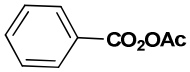
Entry	P-X **2a-i**	Time(min), Temp (^{o}C)	Product **3a-h**	Yield (%)[a]
1	$(Ac)_2O$ **2b**	10, 100	 **3a**	89
2	$(BOC)_2O$ **2c**	10, 100	 **3b**	86
3	TsCl **2d**	10, 80	 **3c**	89
4	MOM-Cl **2e**	15, 100	 **3d**	45
5	BOM-Cl **2f**	15, 100	 **3e**	78
6	Propargyl bromide **2g**	15, 100	 **3f**	71
7	Allyl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

The use of acetic anhydride (Ac_2O) instead of acetyl chloride has led better yield of the product **3a** (89%) (Table 2, entry 1). The other protecting group reagents such as Boc-anhydride and tosyl chloride proceeded well and fetching the corresponding products of **3b** and **3c** in 86% and 89% yields, respectively (Table 2, entries 2 and 3). The ^{1}H NMR spectrum of compound **3c** has implied 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 yield (Table 2, entries 4-5). Microwave assisted *O*-alkylation of alcohols with alkyl halides in the presence of solid supported catalysts was well established.[16] Hence, we envisaged to check the feasibility of *O*-alkylation of 3^{o}-allyl alcohol of MBH adduct of isatin under the optimized condition which can be a viable synthons for further synthetic strategy. The alkyl halides such as propargyl bromide, allyl chloride and ethyl 2-bromoacetate treated with MBH adducts of isatin and 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 new entry in the family of MBH adduct of isatin derivatives. To our dismay, 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 different types of the hydroxyl group of primary, secondary, tertiary alcohol, carboxylic acid, α, β-unsaturated acid, cinnamyl alcohol, oxime and phenol in this study. All the substrates furnished the desired products in good to excellent yield and the results are summarized in Table 3.

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, Micro wave oven of Start S (milestone-Italy)

To examine this strategy with secondary allylic alcohol, the MBH adduct of benzaldehyde and ferrocene carboxaldehyde were chosen as a representative substrates. Among them, the MBH adduct of benzaldehyde with $(Ac)_2O$ and propargyl bromide provided the corresponding acylated MBH and *O*-alkylated derivatives exclusively (Table 3, entries1 and 2).[18] However, the acetyl *E*-isomerized derivative **6c** was obtained from the MBH adduct of ferrocene carboxaldehyde (Table 3, entry 3). It may be due to the migratory aptitude of acyl group and stability of the product **6c** both together trigger the isomerization.[20] It should be mentioned that the introduction of acetyl group on MBH adduct of ferrocene moiety is still remains a challenging task.[21] Furthermore, the MBH adduct of ninhydrine gave the desired product in good yield (Table 3, entry 4). If the isatin *N-H* is insecure, the isatin hydroxime derivative provided *O*-alkylation along with *N*-alkylated product (Table 3, entries 5 and 6). Remarkably, the α,β-unsaturated acid and cinnamyl alcohol have also been proven as excellent substrates for protection and *O*-alkylation reactions (Table 3, entries 7 and 8). The non-allyl functionality such as phenol and benzoic acid can also be a good substrate for the protection under microwave reaction condition (Table 3, entries 9 and 10).

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 clean and pyridine free condition in 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 underway in our laboratory.

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Notes and References

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†Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/b000000x/

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 a slurry and subjected to 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 minutes. After cooling the reaction mixture to room temperature, the crude mixture was dissolved in EtOAc and filtered through celite pad then purified by a silica gel column chromatography and afforded the corresponding products in good to moderate yield (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* = 7Hz, 1H), 7.20(s, 1H), 7.60(s, 1H), 7.79(d, *J* = 7Hz, 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* = 7.5Hz, 1H), 7.04-7.06(t, *J* = 7.0Hz, 1H), 7.12-7.14(d, *J* = 7.5Hz, 1H), 7.34-7.34(t, *J* = 7.0Hz, 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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