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Tetrahedron Letters 49 (2008) 2119–2123
Tetrahedron Letters

A mild and efficient CAN mediated oxidation of Morita–Baylis–Hillman adducts of 5-methyl-*N*-alkylisatin to 5-formyl-*N*-alkylisatin

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Received 21 November 2007; revised 21 January 2008; accepted 29 January 2008
Available online 1 February 2008

Abstract

A simple, mild and efficient CAN mediated oxidation of Morita–Baylis–Hillman adducts of 5-methyl-*N*-alkylisatins **1a**–**13a** to 5-formyl-*N*-alkylisatins **1b**–**13b** under ambient reaction conditions is reported. Simple and isomerized 5-methyl-*N*-alkylisatin derivatives **1**–**4** have also been tested and failed to provide the corresponding formylated products. A plausible reaction mechanism has been proposed.

Keywords: CAN; Morita–Baylis–Hillman adduct; Aryl methyl oxidation; Isatin; Aromatic aldehydes

1. Introduction

The synthesis of aromatic aldehydes and functionalization of aromatic rings with an aldehyde group is still an important synthetic challenge in organic chemistry.[1] Aryl aldehydes are important industrial materials for the manufacture of odorants, flavors, foods and beverages. They also serve as principal synthetic intermediates in the production of dyes, optical brighteners, agricultural chemicals and pharmaceuticals.[1] The oxidation of an aromatic alkyl group to aryl aldehydes and aryl ketones is well known in the literature. Methods include enzymatic oxidation,[2] the use of transition metals or non-metallic reagents and other reagents.[3] Although the reported procedures afford aryl aldehydes, many of them have disadvantages such as cost of the reagent, pollution, harsh reaction conditions, less selectivity, and low yield. Thus, the development of novel, mild, simple, economical, and high yield procedures are required. Cerium(IV) ammonium nitrate (CAN) has emerged as a versatile reagent for a variety of synthetic transformations which have been well documented.[4] Only a few methods for the oxidation of aromatic alkanes to the corresponding aldehydes and ketones mediated by CAN are known.[5] The synthetic versatility of isatin and its derivatives has led to the extensive use of this compound in organic synthesis.[6] The aromatic oxidation of 5-methylisatin derivatives is highly important in alkaloid natural product synthesis. Amongst various carbon–carbon bond forming reactions, the Morita–Baylis–Hillman (MBH) reaction is an important procedure giving rise to densely functionalized molecules and is considered to be atom economic.[7] In continuation of our research in the area of novel synthetic applications of Baylis–Hillman adducts,[8] in particular with isatin derivatives,[8a–c,e] we report herein the oxidation of MBH adducts of 5-methylisatin to 5-formylisatin using CAN as a one electron oxidant under mild reaction conditions.

The preliminary studies were initiated using the MBH adduct of 1,5-dimethylisatin **1a** as a substrate. The adduct **1a** in MeOH–CH_3CN (1:0.5) was treated with 5 equiv of CAN at room temperature to afford the aldehyde derivative **1b** in >95% yield (Table 1, entry 1) after silica gel column purification. To determine the effect of solvent,

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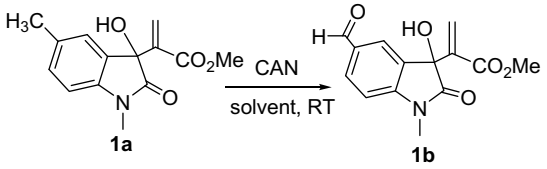
0040-4039/$ - see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2008.01.119

Table 1
Optimization of the oxidation of adduct **1a**–**1b** with CAN



Entry	Solvent (ratio)	CAN (equiv)	Time (min)	Yield (%)
1	MeOH–CH_3CN(1:0.5)	5	5	>95
2	CH_3CN	5	10	>95
3	MeOH	5	10	>95
4	CH_2Cl_2/H_2O (1:0.1)	5	10	85
5	MeOH–CH_3CN (1:0.5)	1	120	25
6	MeOH–CH_3CN (1:0.5)	2	120	50
7	MeOH–CH_3CN (1:0.5)	3	120	75
8	MeOH–CH_3CN (1:0.5)	4	5	>95

acetonitrile, methanol, and dichloromethane were tested. The yields and reaction times were found to vary (Table 1, entries 2–4). Hence, the methanol–acetonitrile (1:0.5) solvent system was found to be the best for this reaction. To determine the optimum amount of oxidizing reagent, reactions with different equivalents (1–4) of CAN were tested. Increasing the equivalents of CAN increased the yields gradually (Table 1, entries 5–7) and the optimum amount was found to be 4 equiv of CAN (Table 1, entry 8). The preliminary results are shown in Table 1.

In order to screen various substrates, selectivity and the effect of substitution in the CAN mediated oxidation, a number of 5-methylisatin derivatives **1**–**4**, **1a** and **2a** were investigated under optimized conditions (Fig. 1). Interestingly, only the MBH adducts of isatin **1a/2a** afforded the corresponding aldehydes **1b/2b** in >95% yield. All the other substrates did not react with CAN under optimized conditions. Hence, the present oxidation is feasible only for the MBH adducts of 5-methylisatin.

Encouraged by the preliminary results and to demonstrate the generality of the reaction, a number of MBH adducts of 5-methyl-*N*-alkylisatins **1a**–**13a** were investigated. All the substrates underwent oxidation smoothly

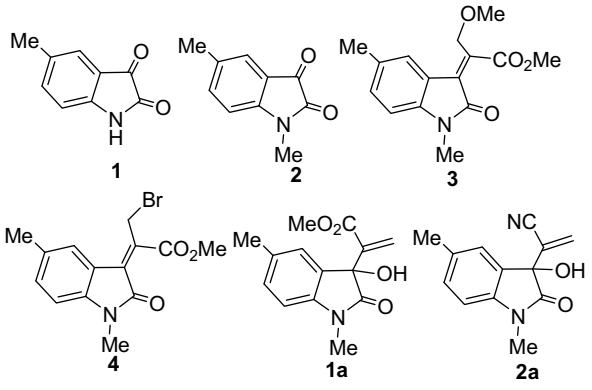
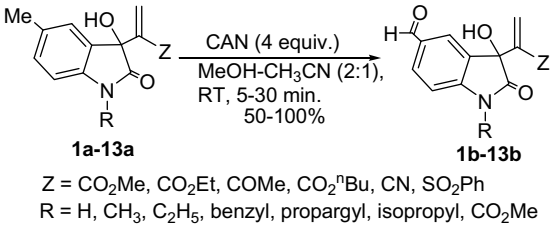


Fig. 1. Screening of substrates for CAN mediated oxidation of 5-methylisatin derivatives.



Scheme 1. CAN mediated oxidation of adducts **1a**–**13a** to **1b**–**13b**.

and provided the corresponding aldehydes **1b**–**13b** in excellent yield (Scheme 1).

Accordingly, the oxidation of MBH adducts **3a**–**6a** derived from 1,5-dimethylisatin under optimized conditions was complete in 5 min at room temperature to afford aldehydes **3b**–**6b** in excellent yields (Table 2, entries 1–5). The MBH adduct **7a** synthesized from 5-methylisatin also underwent oxidation to afford adduct **7b** in very good yield (Table 2, entry 6). Reactions with the MBH adducts of

Table 2
Generality of the CAN mediated methyl to aldehyde oxidation of adducts **2a**–**13a**

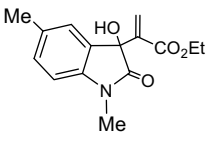
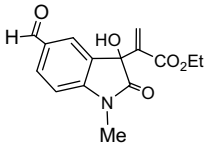
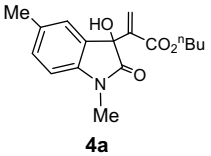
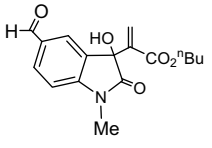
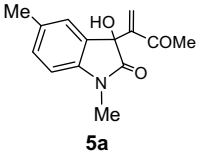
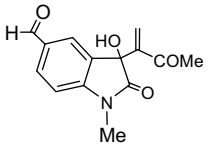
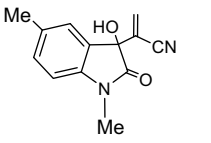
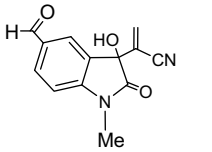
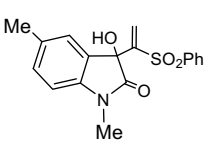
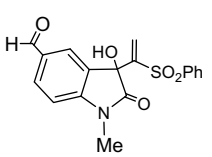
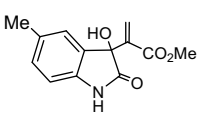
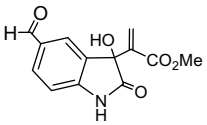
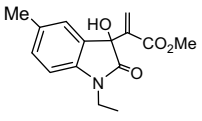
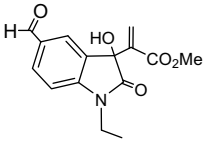
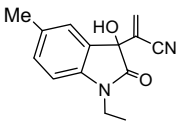
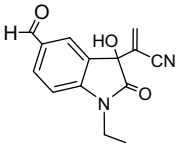
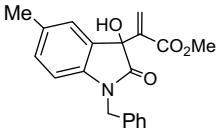
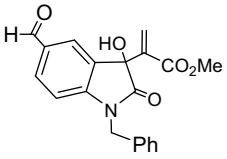
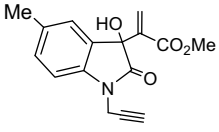
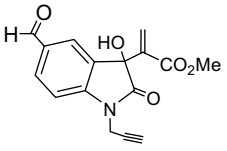
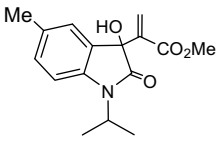
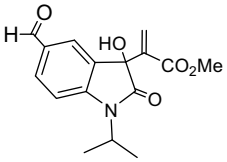
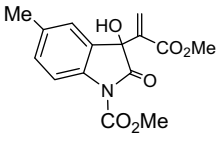
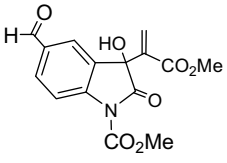
Entry	Substrate	Product (reaction time in min)	Yield (%)
1	 **3a**	 **3b** (5)	>95
2	 **4a**	 **4b** (5)	>95
3	 **5a**	 **5b** (5)	>95
4	 **2a**	 **2b** (5)	>95
5	 **6a**	 **6b** (5)	>95

Table 2 (*continued*)

Entry	Substrate	Product (reaction time in min)	Yield (%)
6	 **7a**	 **7b** (5)	87
7	 **8a**	 **8b** (10)	>95
8	 **9a**	 **9b** (10)	>95
9	 **10a**	 **10b** (10)	>95
10	 **11a**	 **11b** (10)	67
11	 **12a**	 **12b** (5)	>95
12	 **13a**	 **13b** (30)	50[a]

[a] Product **13c** was isolated in 49% yield.

1-ethyl-5-methylisatin **8a/9a** afforded the corresponding aldehydes **8b/9b** in excellent yields (Table 2, entries 7 and 8). Similarly, reactions with *N*-benzyl, *N*-propargyl, *N*-isopropyl, *N*-methyl carboxylate derived 5-methyl adducts **10a–13a** of isatin afforded the respective aldehydes **10b–13b** in good (entries 10 and 12) to excellent yields (Table 2, entries 9 and 11). All the new compounds were characterised from spectroscopic (IR, ^{1}H and ^{13}C NMR) and FAB mass data (see Sections 2 and 3).

It is noteworthy that the *N*-methyl carboxylate derived MBH adduct **13a** upon oxidation afforded a 1:1 mixture of 5-methyl oxidized aldehyde **13b** and nitrated product **13c** in excellent combined yield (99%) as evidenced from spectroscopic and analytical data. The reaction is shown in Scheme 2.

In order to show the efficiency and superiority of the CAN catalyst in this reaction, a number of other oxidants known for similar synthetic transformations such as manganese(III) acetate,[9a] selenium dioxide,[9b–d] potassium permanganate,[9e] and DDQ[9f,g] were tested. None of them was found to be as efficient as CAN and the results are collected in Table 3.

A plausible mechanism for the formation of the aldehyde is shown in Scheme 3. Single electron oxidation of MBH adduct **A** by CAN generates a resonance-stabilized radical cation **B**.[10] Further one electron oxidation of **B** with CAN followed by the liberation of H^+ would provide a cation intermediate **C** which is trapped by the nitrate oxygen of CAN to afford intermediate **D**. Further oxidation of intermediate **D** with CAN followed by the elimination of a proton affords the observed products.

In conclusion, we have demonstrated a simple, novel, and efficient oxidation of Morita–Baylis–Hillman adducts of 5-methyl-*N*-alkylisatins to 5-formyl-*N*-alkylisatins using CAN as a single electron oxidizing reagent. It is noteworthy that the compounds obtained here are highly functionalized and the methodology can be applied in alkaloid natural product synthesis. Further work using this reagent for novel methodology is in progress.

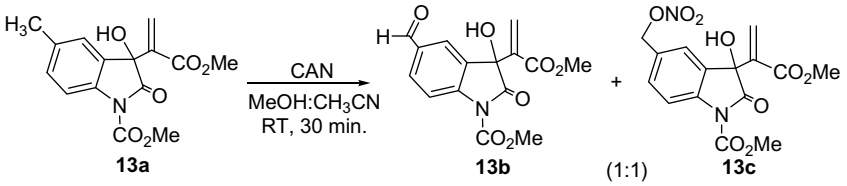
2. General experimental procedure

A mixture of Morita–Baylis–Hillman adduct (1 mmol), 4 equiv of cerium ammonium nitrate (4 mmol) in MeOH–CH_3CN (1:0.5; 3 mL) was allowed to stir at rt for 5–30 min. The progress of the reaction was monitored by TLC. After the completion of the reaction, the solvent was removed under reduced pressure. The crude reaction mixture was extracted with dichloromethane and washed with water and brine. The organic layer was separated and dried (Na_2SO_4) and concentrated in vacuo to afford pure functionalized aldehyde product after passing through a silica gel column chromatography.

3. Spectral data for selected compounds

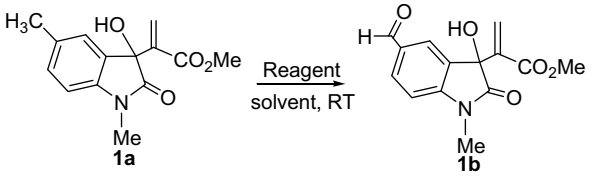
3.1. Methyl 2-(5-formyl-3-hydroxy-1-methyl-2-oxoindolin-3-yl) acrylate **1b**

IR (CH_2Cl_2): 3372, 1716, 1607 cm^{-1}; ^{1}H NMR ($CDCl_3$/TMS, 300.1 MHz): δ 3.26 (s, 3H), 3.59 (s, 3H), 4.53 (br s, OH), 6.55 (s, 1H), 6.60 (s, 1H), 6.96 (d, $J = 8.0$ Hz, 1H),



Scheme 2. CAN mediated oxidation of MBH adduct **13a**.

Table 3
A comparison of the oxidation of adduct **1a**–**1b** with CAN and other oxidants



Entry	Reagent	% Yield after 5 min	% Yield after 12 h
1	**CAN**	**>95**	**>95**
2	$Mn(OAc)_3.2H_2O$	0	Trace
3	SeO_2	0	0
4	$KMnO_4$	0	0
5	DDQ	0	Decomposed

Solvent: MeOH–CH_3CN (2:1).

7.66 (d, $J = 1.4$ Hz, 1H), 7.84 (dd, $J = 8.0$ Hz, 1.4 Hz, 1H), 9.80 (s, 1H); ^{13}C NMR ($CDCl_3$/TMS, 75.3 MHz): δ 26.83, 51.11, 75.27, 108.75, 123.38, 124.65, 128.37, 130.73, 131.85, 138.72, 149.98, 164.58, 176.85, 190.54; FAB mass: Calcd for $C_{14}H_{13}NO_5$: 275.26. Found 276.26 (M^+).

3.2. 2-(5-Formyl-3-hydroxy-1-methyl-2-oxoindolin-3-yl) acrylonitrile **2b**

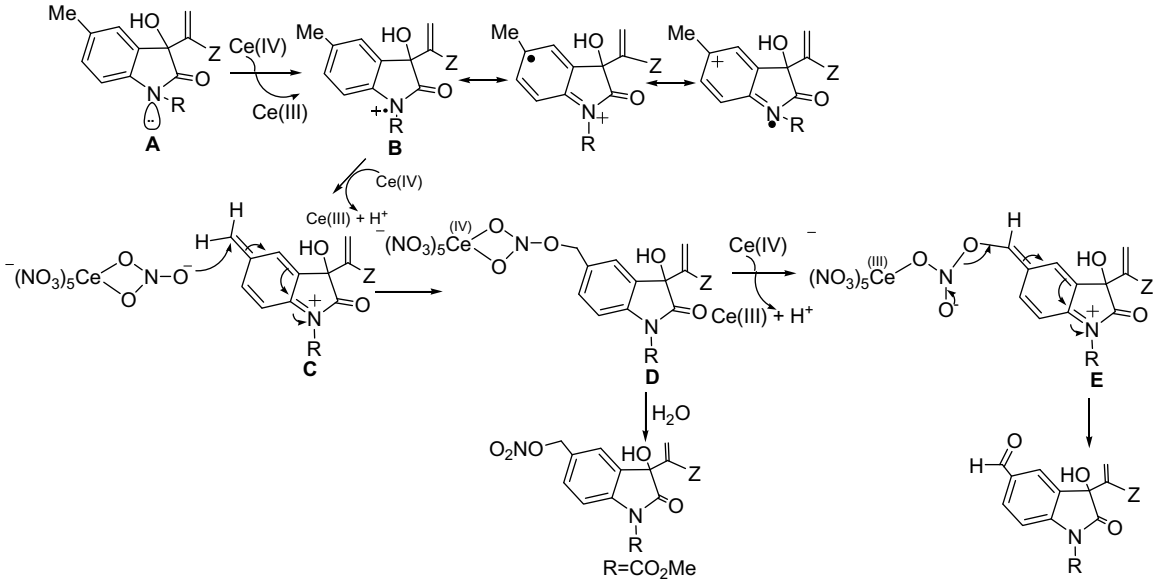
IR (CH_2Cl_2): 3391, 1726, 1611 cm^{-1}; ^{1}H NMR ($CDCl_3$/TMS, 300.1 MHz): δ 3.29 (s, 3H), 4.55 (br s, OH), 6.26 (s, 1H), 6.46 (s, 1H), 7.07 (d, $J = 8.1$ Hz, 1H), 7.92 (d, $J = 1.5$ Hz, 1H), 7.97 (dd, $J = 8.1$ Hz, 1.5 Hz, 1H), 9.93 (s, 1H); ^{13}C NMR ($CDCl_3$/TMS, 75.3 MHz): δ 27.06, 76.01, 109.42, 115.16, 122.14, 125.30, 127.99, 132.11, 132.72, 134.77, 148.69, 174.52, 190.40; FAB mass: Calcd for $C_{13}H_{10}N_2O_3$: 242.23. Found 243.48 (M^+).

3.3. Methyl 2-(1-ethyl-5-formyl-3-hydroxy-2-oxoindolin-3-yl) acrylate **8b**

IR (CH_2Cl_2): 3382, 1710, 1607 cm^{-1}; ^{1}H NMR ($CDCl_3$/TMS, 300.1 MHz): δ 1.32 (t, $J = 6.4$ Hz, 3H), 3.60 (s, 3H), 3.82 (q, $J = 6.4$ Hz, 2H), 4.36 (br s, OH), 6.57 (s, 1H), 6.63 (s, 1H), 7.00 (d, $J = 8.0$ Hz, 1H), 7.69 (s, 1H), 7.85 (d, $J = 8.0$ Hz, 1H), 9.83 (s, 1H); ^{13}C NMR ($CDCl_3$/TMS, 75.3 MHz): δ 11.51, 35.75, 52.07, 75.28, 108.82, 123.60, 124.84, 128.44, 130.74, 131.66, 138.58, 149.26, 164.67, 176.38, 190.63; FAB mass: Calcd for $C_{15}H_{15}NO_5$: 289.28. Found 290.59 (M^++1).

3.4. 2-(1-Ethyl-5-formyl-3-hydroxy-2-oxoindolin-3-yl) acrylonitrile **9b**

IR (CH_2Cl_2): 3375, 1722, 1617 cm^{-1}; ^{1}H NMR ($CDCl_3$/TMS, 300.1 MHz): δ 1.31 (t, $J = 7.2$ Hz, 3H), 3.82 (q, $J = 7.2$ Hz, 2H), 4.45 (br s, OH), 6.24 (s, 1H), 6.48 (s, 1H), 7.07 (d, $J = 8.1$ Hz, 1H), 7.90–7.96 (m, 2H), 9.88 (s,



Scheme 3. A plausible mechanism for the reaction.

1H); ^{13}C NMR ($CDCl_3$/TMS, 75.3 MHz): δ 12.28, 35.71, 76.04, 109.40, 115.16, 122.12, 124.85, 128.40, 131.94, 132.44, 134.40, 147.87, 174.32, 190.49; FAB mass: Calcd for $C_{14}H_{12}N_2O_3$: 256.25. Found 257.27 (M^++1).

3.5. Compound **13c**

IR (CH_2Cl_2): 3377, 1726, 1609 cm^{-1}; ^{1}H NMR ($CDCl_3$/TMS, 300.1 MHz): δ 3.63 (s, 3H), 4.02 (s, 3H), 4.45 (br s, OH), 5.36 (s, 2H), 6.52 (s, 1H), 6.60 (s, 1H), 7.19 (d, $J = 1.4$ Hz, 1H), 7.41 (dd, $J = 8.3$, 1.4 Hz, 1H), 7.98 (d, $J = 8.3$ Hz, 1H);^{13}C NMR ($CDCl_3$/TMS, 75.3 MHz): δ 51.12, 52.13, 55.78, 76.03, 109.68, 123.38, 124.65, 128.84, 133.33, 131.85, 139.04, 151.16, 164.58, 173.91, 174.11; FAB mass: Calcd for $C_{15}H_{14}N_2O_9$: 366.27. Found 367.29 (M^++1).

Acknowledgements

The authors thank Professor Dr. T. K. Chandrashekar, Director, for providing infrastructure facilities. Financial support (SR/S1/OC-38/2005) from the DST (New Delhi) is gratefully acknowledged. V.V. and K.S. thank CSIR and UGC (New Delhi) for the award of a SRF and a JRF, respectively. P.S. thanks the reviewer of this manuscript for constructive suggestions. Thanks are due to Mrs. Viji and Mrs. Soumini Mathew for providing mass and NMR data, respectively.

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