Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron Letters
Tetrahedron Letters 47 (2006) 6851–6855

Activation of the NC–H bond of Baylis–Hillman adducts of *N*-methylisatin with CAN/ROH

Ponnusamy Shanmugam,* Vadivel Vaithiyanathan and Baby Viswambharan

Chemical Sciences and Technology Division, Regional Research Laboratory (CSIR), Thiruvananthapuram 695 019, Kerala, India

Received 25 May 2006; revised 6 July 2006; accepted 13 July 2006
Available online 8 August 2006

Dedicated to Professor Dr. Martin F. Semmelhack, Princeton University, NJ, USA, on the occasion of his forthcoming 65th birthday

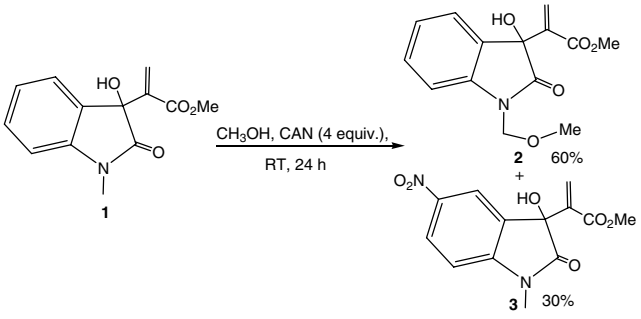
Abstract—A facile method for activation of the NC–H bond of *N*-methylisatin and Baylis–Hillman adducts of *N*-methylisatin with cerium ammonium nitrate (CAN) and saturated and unsaturated alcohols is reported. Adducts bearing an ester group at the activated alkene afford functionalized ethers, while those with a nitrile afforded ethers and nitrated aromatic products in good yield.

1. Introduction

Activation of C–H bonds by oxidative processes[1] and by organometallic reagents[2] has been of great interest to organic chemists in recent years. Cerium(IV) ammonium nitrate (CAN) has emerged as a versatile reagent for a variety of synthetic transformations, which have been well documented.[3] The synthetic versatility of isatin and its derivatives has led to the extensive use of this compound in organic synthesis.[4] Amongst the various carbon–carbon bond forming reactions, the Baylis–Hillman reaction is an important reaction giving rise to densely functionalized molecules and is considered to be atom economic.[5] In continuation of our research in the area of novel synthetic applications of Baylis–Hillman adducts,[6] we were interested to study the C–H activation of Baylis–Hillman derivatives of *N*-methylisatin with CAN as a one electron oxidant and with a number of alcohols as reagents. The details of this study are the subject matter of this letter.

2. Results and discussion

The studies were initiated using the Baylis–Hillman adduct of *N*-methylisatin **1** as a starting material. The preliminary results are outlined in Scheme 1. Thus,



Scheme 1. Optimization of the NC–H activation with CAN/MeOH.

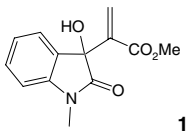
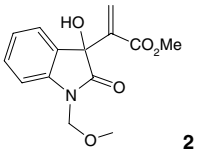
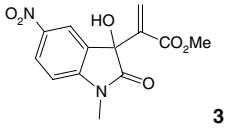
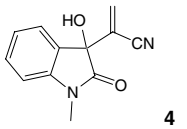
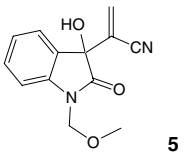
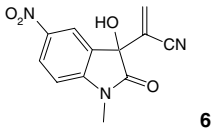
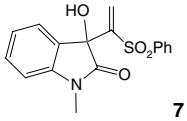
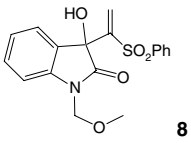
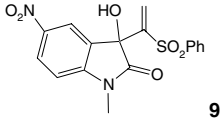
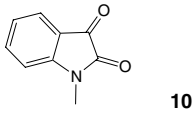
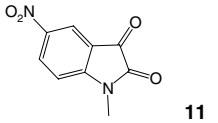
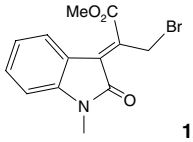
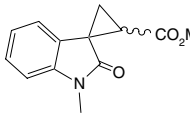
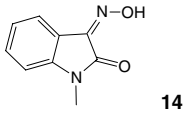
adduct **1** was treated with 4 equiv of CAN in the presence of excess methanol at room temperature to afford the NC–H oxidized ether derivative **2** in 60% yield along with the nitrated product **3** in 30% yield (Table 1, entry 1). The compounds were separated by column chromatography and characterized by spectral techniques.

To check the selectivity and effect of the substituents, various Baylis–Hillman adducts were investigated. Nitrile bearing adduct **4** afforded the corresponding ether **5** and the nitrated compound **6** in 50% and 30% yields, respectively (Table 1, entry 2). The sulfone bearing adduct **7** afforded compounds **8** and **9** in only trace amounts (Table 1, entry 3). Interestingly, the simple *N*-methylisatin **10**, under optimized conditions, yielded only the nitrated product **11** in 15% yield. Other *N*-methylisatin derivatives such as the bromo compound

Keywords: CAN; Baylis–Hillman adduct; CH-activation; Isatin; Functionalized ethers.
* Corresponding author. Tel.: +91 471 2515275; fax: +91 471 2491712; e-mail: shanmu196@rediffmail.com

0040-4039/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2006.07.070

Table 1. Optimization of CH-activation reactions of isatin derivatives[a]

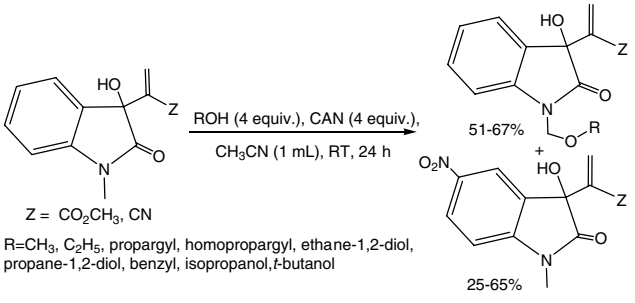
Entry	Substrate	Products		Yield (%)	
		C–H activated (A)	Nitrate (B)	(A)	(B)
1	 **1**	 **2**	 **3**	60	30
2	 **4**	 **5**	 **6**	50	30
3	 **7**	 **8**	 **9**	Trace	Trace
4	 **10**	—	 **11**	—	15
5	 **12**	—	—	—	—
6	 **13**	—	—	—	—
7	 **14**	—	—	—	—

[a] Reagents and conditions; CAN (4 equiv), MeOH, rt, 24 h.

12, *N*-methyl-3-spirocyclopropyl-2-indolone **13** and oxime derivative **14** did not yield any NC–H activated ether product or nitrated product.

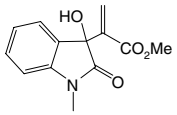
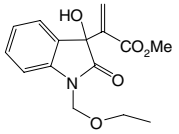
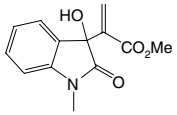
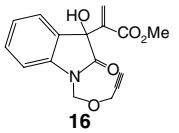
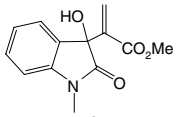
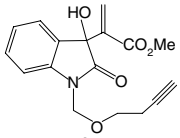
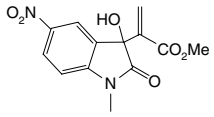
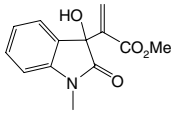
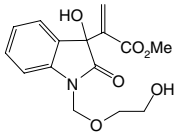
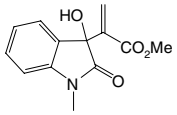
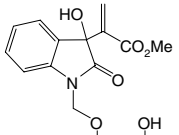
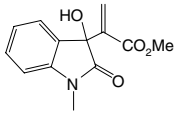
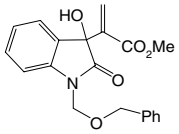
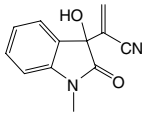
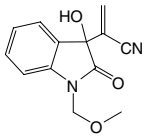
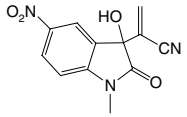
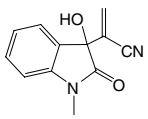
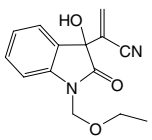
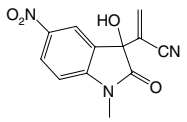
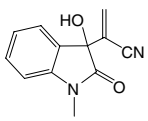
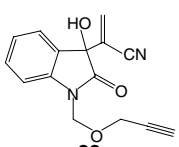
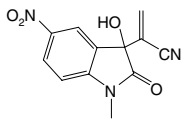
When acetonitrile was used as a solvent, with 4 equivs of alcohol and 4 equiv of CAN, higher yields were obtained than when methanol was used in excess as reagent and solvent. Hence, we chose acetonitrile as the solvent in the rest of our studies. Thus, according to preliminary experiments, only Baylis–Hillman adducts bearing nitrile and ester groups underwent the desired NC–H activation reaction under the optimized reaction conditions. All the new compounds were characterized by spectroscopic (IR, ^{1}H and ^{13}C NMR) and HRMS data.

Encouraged by these results, we were interested to demonstrate the generality of the reaction of Baylis–Hillman adducts of *N*-methylisatin **1** with various alcohols (Scheme 2). Thus, the reaction of the Baylis–Hillman adduct **1** with ethanol (Table 2, entry 1) afforded NC–H activated ether **15** in moderate yield. In order to functionalize the *N*-methyl group with unsaturated systems, the reaction of adduct **1** with propargyl alcohol and homopropargyl alcohol afforded highly functionalized NC–H activated ethers **16** and **17** in good yields (Table 2, entries 2 and 3). The reaction of



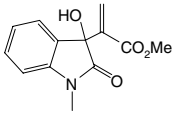
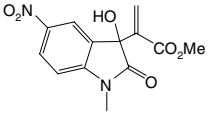
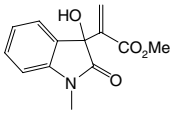
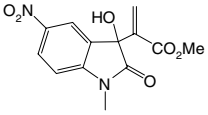
Scheme 2. Generality of the NC–H activation with various alcohols.

Table 2. Generality of the C–H activation with various alcohols[a]

Entry	Substrate	Alcohol[b]	Products		Yield (%)	
			Ether (A)	Nitrate (B)	A	B
1	 **1**	EtOH	 **15**	—	52	—
2	 **1**	Propargyl alcohol	 **16**	—	51	—
3	 **1**	Homopropargyl alcohol	 **17**	 **3**	58	25
4	 **1**	Ethane-1,2-diol	 **18**	—	55	—
5	 **1**	Propane-1,3-diol	 **19**	—	67	—
6	 **1**	Benzyl alcohol	 **20**	—	59	—
7	 **4**	MeOH	 **5**	 **6**	50	30
8	 **4**	EtOH	 **21**	 **6**	53	27
9	 **4**	Propargyl alcohol	 **22**	 **6**	57	35

(*continued on next page*)

Table 2 (*continued*)

Entry	Substrate	Alcohol[b]	Products		Yield (%)	
			Ether (A)	Nitrate (B)	A	B
10	 **1**	*iso*-Propanol	—	 **3**	—	54
11	 **1**	*t*-Butanol	—	 **3**	—	65

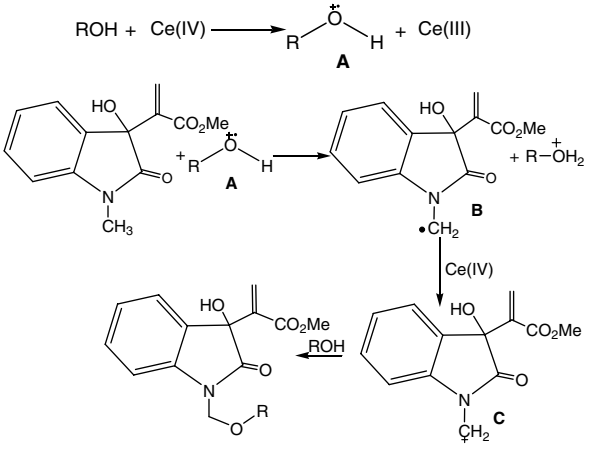
[a] Reagents and conditions; CAN (4 equiv), ROH, rt, 24 h.
[b] 4 equiv.

ethane-1,2-diol and propane-1,3-diol afforded alcoholic ethers **18** and **19** in good yields (Table 2, entries 4 and 5).

Benzyl alcohol also reacted with *N*-methylisatin adduct **1** under these conditions and afforded a good yield of the desired product **20** (Table 2, entry 6).

Repeating the experiments with nitrile bearing Baylis–Hillman adduct **4** with methanol, ethanol and propargyl alcohol afforded functionalized ethers **5**, **21** and **22** along with the corresponding nitrated product **6** in excellent combined yields (Table 2, entries 7–9). To our surprise, the reaction of 2° and 3°-alcohols (*iso*-propanol and *t*-butanol) with Baylis–Hillman adduct **1** did not yield any NC–H activated product, only the nitrated product was obtained in good yields (Table 2, entries 10 and 11). All new compounds were characterized by spectral (IR, ^{1}H and ^{13}C NMR) and HRMS data. The results are summarized in Table 2.

A plausible mechanism for the formation of the ether products is shown in Scheme 3. The cation radical[7] **A** of the alcohol, believed to be generated by oxidation with CAN, oxidizes *N*-methylisatin to the *N*-methyl radical **B**. Further one electron oxidation of **B** with CAN generates the methyl cation **C**, which upon trapping with the alcohol provides the observed products. The aromatic nitration mechanism with CAN is well known in the literature.[8]



Scheme 3. A plausible mechanism for ether formation.

3. Conclusion

In conclusion, we have demonstrated a novel NC–H activation of Baylis–Hillman adducts of *N*-methylisatin with various alcohols using CAN as a single electron oxidizing agent. It is noteworthy that the compounds obtained here are highly functionalized and can be used for further modification. Further work using these compounds for the synthesis of natural products is under progress in our laboratory.

4. General experimental procedure

A mixture of Baylis–Hillman adduct (1 mmol), 4 equiv of cerium ammonium nitrate (4 mmol) and 4 equiv of ROH (4 mmol) in CH_3CN (1 mL) was allowed to stir at rt for 24 h. The progress of the reaction was monitored by TLC. After 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. The crude mixture was purified by silica gel column chromatography using gradient elution with hexane and EtOAc to afford pure functionalized ethers and aromatic nitrated products.

4.1. Spectral data for selected compounds

4.1.1. Methyl 2-(1-(ethoxymethyl)-3-hydroxy-2-oxoindolin-3-yl) acrylate 15. IR (CH_2Cl_2): 3382, 1716, 1089, 1053 cm^{-1}; ^{1}H NMR ($CDCl_3$/TMS, 300.1 MHz): δ 1.20 (t, $J = 6.9$ Hz, 3H), 2.67 (br s, 1H), 3.65 (m, 5H), 5.17 (d, $J = 11.1$ Hz, 1H), 5.22 (d, $J = 11.1$ Hz, 1H), 6.43 (s, 1H), 6.58 (s, 1H), 7.05–7.13 (m, 2H), 7.20 (d, $J = 7.2$ Hz, 1H), 7.35 (t, $J = 7.2$ Hz, 1H); ^{13}C NMR ($CDCl_3$/TMS, 75.3 MHz): δ 15.10, 52.26, 64.58, 70.56, 76.66, 110.43, 123.60, 124.09, 128.04, 128.98, 130.63,

139.24, 143.27, 165.24, 176.97.; HRMS: calcd for $C_{15}H_{17}NO_5$: 291.1107. Found: 291.1088.

4.1.2. Methyl 2-(1-[(but-3-ynyloxy)methyl]-3-hydroxy-2-oxoindolin-3-yl) acrylate 17. IR (CH_2Cl_2): 3406, 1716, 1614, 1089, 1050 cm^{-1}; ^1H NMR ($CDCl_3$/TMS, 300.1 MHz): δ 1.80 (br s, OH, 1H), 1.95 (t, $J = 2.4$ Hz, 1H), 2.46 (td, $J = 6.6$, 2.4 Hz, 2H), 3.63 (s, 3H), 3.66 (t, $J = 6.6$ Hz, 2H), 5.20 (d, $J = 11.1$ Hz, 1H), 5.28 (d, $J = 11.1$ Hz, 1H), 6.46 (s, 1H), 6.59 (s, 1H), 7.05–7.20 (m, 3H), 7.35 (t, $J = 7.8$ Hz, 1H); ^{13}C NMR ($CDCl_3$/TMS, 75.3 MHz): δ 19.84, 30.38, 52.31, 66.90, 69.55, 70.64, 81.34, 110.51, 123.73, 124.12, 126.24, 127.89, 130.71, 139.19, 143.10, 165.22, 176.95. HRMS: calcd for $C_{17}H_{17}NO_5$: 315.1107. Found: 315.1101.

4.1.3. Methyl 2-(1-[(3-hydroxypropoxy)methyl]-3-hydroxy-2-oxoindolin-3-yl) acrylate 19. IR (CH_2Cl_2): 3418, 1716, 1613, 1086, 1055 cm^{-1}; ^1H NMR ($CDCl_3$/TMS, 300.1 MHz): δ 1.73 (quintet, $J = 7.2$ Hz, 2H), 3.11 (br s, 2OH), 3.48–3.80 (m, 7H), 5.14 (d, $J = 11.4$ Hz, 1H), 5.21 (d, $J = 11.4$ Hz, 1H), 6.55 (s, 1H), 6.60 (s, 1H), 7.03–7.16 (m, 3H), 7.33 (t, $J = 7.5$ Hz, 1H); ^{13}C NMR ($CDCl_3$/TMS, 75.3 MHz): δ 32.61, 52.41, 59.81, 66.21, 70.49, 76.35, 110.14, 123.66, 123.98, 128.37, 129.41, 130.53, 139.01, 143.11, 165.44, 177.23. HRMS: calcd for $C_{16}H_{19}NO_6$: 321.1212. Found: 321.1205.

4.1.4. 2-(3-Hydroxy-2-oxo-1-[(prop-2-yloxy)methyl]indolin-3-yl)acrylonitrile 22. IR (CH_2Cl_2): 3390, 2305, 1733, 1614, 1073 cm^{-1}; ^1H NMR ($CDCl_3$/TMS, 300.1 MHz): δ 1.80 (br s, OH, 1H), 2.48 (t, $J = 2.4$ Hz, 1H), 4.21 (d, $J = 2.4$ Hz, 2H), 5.24 (d, $J = 11.1$ Hz, 1H), 5.36 (d, $J = 11.1$ Hz, 1H), 6.21 (s, 1H), 6.37 (s, 1H), 7.10–7.29 (m, 2H), 7.42 (d, $J = 7.5$ Hz, 2H); ^{13}C NMR ($CDCl_3$/TMS, 75.3 MHz): δ 30.60, 56.39, 69.52, 75.79, 78.66, 110.91, 115.66, 123.05, 125.00, 126.99, 128.84, 131.61, 132.62, 141.89, 174.89; HRMS: calcd for $C_{15}H_{12}N_2O_3$: 268.0848. Found: 268.0840.

Acknowledgements

The authors thank Professor Dr. T. K. Chandrashekar, Director, for providing infrastructure facilities. P.S. thanks Dr. Vijay Nair, CSIR-Emeritus Scientist, and the reviewer of this manuscript for suggesting the mechanism. Financial support (SR/S1/OC-38/2005) from the DST (New Delhi) is gratefully acknowledged. V.V. and B.V. thank CSIR (New Delhi) for the award of a SRF and a JRF, respectively. Thanks are due to Mrs. Viji for providing HRMS data.

References and notes

1. For reviews see: (a) Shilov, A. E.; Shul'pin, G. B. *Chem. Rev.* **1997**, *97*, 2879; (b) Sen, A. *Acc. Chem. Res.* **1998**, *31*, 550; (c) Barluinga, J.; Bobes, F. G.; Gonzales, J. M. *Angew. Chem.* **2002**, *11*, 2668; *Angew. Chem., Int. Ed.* **2002**, *41*, 2556; (d) Sakaguchi, S.; Nishiwaki, Y.; Kitamura, T.; Ishii, Y. *Angew. Chem.* **2001**, *13*, 228; *Angew. Chem., Int. Ed.* **2001**, *40*, 222; (e) Lee, S.; Fuchs, P. L. *Org. Lett.* **2004**, *6*, 1437; (f) Yu, X. Q.; Huang, J. S.; Zhou, X. G.; Che, C. M. *Org. Lett.* **2000**, *2*, 2233.
2. Periana, R. A.; Bhalla, G.; Tenn, W. J.; Young, K. J. H., III; Liu, X. Y.; Mironov, O.; Jones, C. J.; Ziatdinov, V. R. *J. Mol. Catal. A: Chem.* **2004**, *220*, 7.
3. Nair, V.; Balagopal, L.; Rajan, R.; Mathew, J. *Acc. Chem. Res.* **2004**, *37*, 21–30, and references cited therein.
4. da Silva, J. F. M.; Garden, S. J.; Pinto, A. C. *J. Braz. Chem. Soc.* **2001**, *12*, 273–324.
5. (a) Basavaiah, D.; Rao, A. J.; Satyanarayana, T. *Chem. Rev.* **2003**, *103*, 811–891; (b) Derewes, S. E.; Roos, G. H. P. *Tetrahedron* **1988**, *44*, 4653–5670; (c) Lee, K. Y.; Gowrisankar, S.; Kim, J. N. *Bull. Korean Chem. Soc.* **2005**, *26*, 1481–1490.
6. (a) Shanmugam, P.; Rajasingh, P. *Synlett* **2001**, 1314–1316; (b) Shanmugam, P.; Rajasingh, P. *Chem. Lett.* **2002**, 1212–1213; (c) Shanmugam, P.; Rajasingh, P. *Tetrahedron* **2004**, *60*, 9283–9295; (d) Shanmugam, P.; Rajasingh, P. *Synlett* **2005**, 939–942; (e) Shanmugam, P.; Rajasingh, P. *Tetrahedron Lett.* **2005**, *46*, 3369–3372; (f) Shanmugam, P.; Rajasingh, P. *Chem. Lett.* **2005**, 1494–1495; (g) Shanmugam, P.; Vaithiyanathan, V.; Baby, V. *Tetrahedron* **2006**, *62*, 4342–4347.
7. (a) Dallaeort, A. D.; Barbera, A. L.; Mandolini, L. *J. Chem. Res. (S)* **1983**, 44; (b) Chang, M.-Y.; Lin, C.-Y.; Pai, C.-L. *Tetrahedron Lett.* **2006**, *47*, 2565–2568.
8. Yang, X.; Xi, C.; Jiang, Y. *Tetrahedron Lett.* **2005**, *46*, 8781–8783.