Facile One-Pot Synthesis of Inden-1-ol Derivatives

Subbiah Nagarajan, Paneerselvam Muthuvel, Thangamuthu Mohan Das*

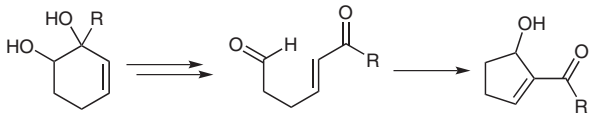
Department of Organic Chemistry, University of Madras, Guindy Campus, Chennai 600 025, India
Fax +91(44)22352494; E-mail: tmdas_72@yahoo.com

Received 26 April 2011

Abstract: A facile one-pot synthesis of a novel class of inden-1-ol/indanone derivatives has been developed and formation of ionic clusters by lithium perchlorate has been demonstrated using UV-vis studies.

Key words: methyl ketones, *o*-phthaldialdehyde, inden-1-ol derivatives, β-anomer, XRD analysis

Carbon–carbon bond formation remains an important challenge for synthetic organic chemists.[1,2] Among different C–C bond-formation reactions the Morita–Baylis–Hillman reaction (MBH)[3–5] has received growing interest since the mid 1990's as it converts simple starting materials, in the presence of a catalyst such as trialkylphosphine,[6] pipecolic acid, *N*-methylimidazole,[7] or triphenylphosphine[8] into highly functionalized compounds, which can be used for further transformations.[4] In addition, intramolecular BH ring-closing reactions offer additional opportunities in synthetic design.[9] In one instance, the substrates for cyclization were prepared by oxidative cleavage of vicinal cyclohexenediols[10] through the initially formed *Z*-isomers, which rearranged to the corresponding *E*-isomers followed by intramolecular MBH reaction with Ph_3P catalyst in *tert*-BuOH (Scheme 1). A study of Michael acceptor stereochemistry on the efficiency of intramolecular MBH reactions has been reported in the literature,[8] but involves complex procedures and results in poor yields.[11,12] Several indenones have synthesized by using a palladium-mediated [3+2]-cycloaddition process between *ortho*-halobenzaldehydes and diaryl propynones.[12f] To the best of our knowledge, this is the first report on the synthesis of inden-1-ol from readily available aryl-/alkyl-substituted methyl ketones.

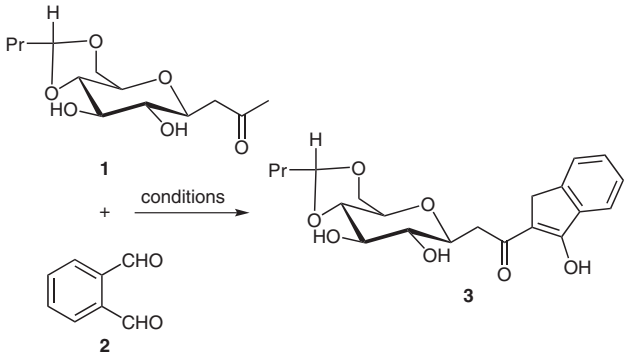


Scheme 1 Synthesis of inden-1-ol derivatives through intramolecular MBH reaction[8]

In the present study, we report a facile one-pot synthesis of inden-1-ol derivatives which exhibit keto–enol tautomerism. Sugar-substituted methyl ketones 1-(4,6-*O*-butylidene-β-D-glucopyranosyl)propan-2-one (**1a**), 1-(4,6-*O*-benzylidene-β-D-glucopyranosyl)propan-2-one (**1b**), 1-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)propan-2-one (**1c**), and 1-(2,3,4-tri-*O*-acetyl-β-D-xylopyranosyl)propan-2-one (**1d**) were synthesized following literature procedures.[13,14] For the optimization of the reaction conditions and the identification of the best catalyst and solvent, 1-(4,6-*O*-butylidene-β-D-glucopyranosyl)propan-2-one (**1a**) and *o*-phthaldialdehyde were chosen as model substrates, and the one-pot reaction provided the desired product in low but promising yields. The results are summarized in Table 1.

For aryl-/sugar-substituted methyl ketones, moderate yields (53–85%) were obtained using $CHCl_3$ as solvent with a catalytic amount of pyrrolidine at room tempera-

Table 1 Optimization of Reaction Conditions[a]



Entry	Organocatalyst	Solvent	Yield (%)
1	pyrrolidine	CH_2Cl_2	52
2	pyridine	CH_2Cl_2	21
3	NaOH	CH_2Cl_2	–[b]
4	KO*t*-Bu	THF	–[c]
5	pyrrolidine	MeOH	–[b]
6	pyrrolidine	MeCN	15
7	pyrrolidine	$CHCl_3$	72
8	pyrrolidine	THF	43
9	pyrrolidine	$CHCl_3$ + MeOH (3:1)	24

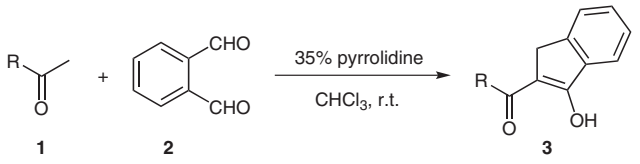
[a] (4,6-*O*-butylidene-β-D-glucopyranosyl)propan-2-one (**1a**), *o*-phthaldialdehyde, pyrrolidine (35%), r.t., 12 h.
[b] No reaction.
[c] KO*t*-Bu was used as base and dry THF as a solvent for aliphatic substrates, such as acetone and 4-methylpentan-2-one.

SYNLETT 2011, No. 15, pp 2163–2166
Advanced online publication: 24.08.2011
DOI: 10.1055/s-0030-1261196; Art ID: D12911ST
© Georg Thieme Verlag Stuttgart · New York

This document was downloaded for personal use only. Unauthorized distribution is strictly prohibited.

ture; whereas, in case of aliphatic ketones (acetone and 4-methylpentan-2-one), improved yields (27% and 15%) were obtained by using dry THF as solvent and KO*t*-Bu as base. Different substituted inden-1-ol derivatives **3a–k** were synthesized directly from the reaction of aryl-/alkyl-substituted methyl ketones with *o*-phthaldialdehyde in the presence of 35% pyrrolidine as an organocatalyst (Table 2).

Table 2 Synthesis of Aryl-/Alkyl-/Sugar-Substituted Inden-1-ol Derivatives **3a–k**



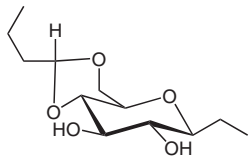
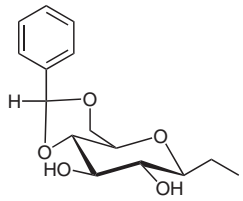
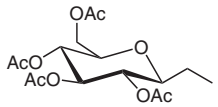
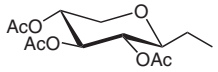
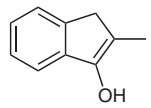
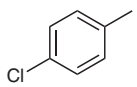
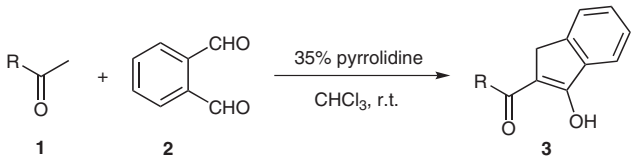
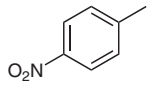
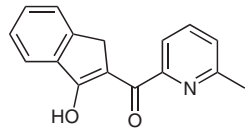
Entry	**3a–k** R	**1a–k** (mg/mL)	Reaction time (h)	Yield in mg (%)
1	 **3a**	548	12	280 (72)
2	 **3b**	616	24	360 (85)
3	 **3c**	776	18	328 (65)
4	 **3d**	632	18	310 (72)
5	 **3e**	0.25	24	117 (27)[a]
6	 **3f**	0.15	48	087 (15)[a,b]
7	 **3g**	240	24	130 (55)
8	 **3h**	310	8	180 (66)

Table 2 Synthesis of Aryl-/Alkyl-/Sugar-Substituted Inden-1-ol Derivatives **3a–k** (continued)



Entry	**3a–k** R	**1a–k** (mg/mL)	Reaction time (h)	Yield in mg (%)
9	 **3i**	330	12	150 (53)
10	 **3j**	163	36	154 (39)[c]
11	 **3k**	0.22	36	203 (42)

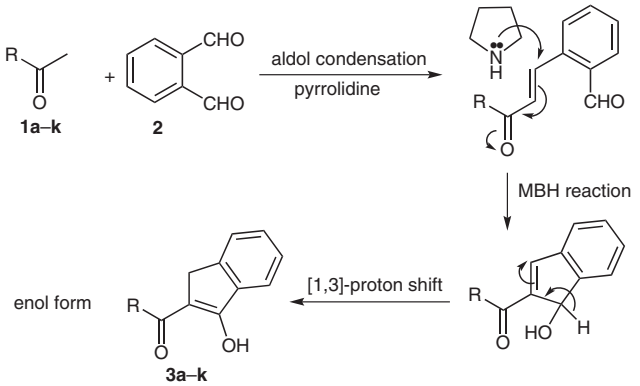
[a] KO*t*-Bu was used as base and dry THF as a solvent.
[b] Compound **3f** was derived from acetone (**1f**).
[c] Compound **3j** was derived from 2,6-diacetylpyridine (**1j**).

In the case of sugar-based inden-1-ol derivatives **3a–d**, the sugar moiety is in β-anomeric form, confirmed by ^{1}H NMR spectroscopic analysis.[15] Notably compound **3c** exhibited a large coupling constant ($J_{H\text{-}1,H\text{-}2}$ = 8.6 Hz) indicating a *trans* diaxial orientation of H-1 and H-2. A plausible mechanism involves aldol condensation followed by MBH reaction, which results in the formation of aryl-/sugar-substituted inden-1-ol derivatives via [1,3]-proton shift. Amongst the two aldehyde groups present in the *o*-phthaldialdehyde (**2**), only one aldehydic group is involved in the aldol condensation with the methyl ketone. The lack of involvement of the second aldehydic functionality may be due to the steric hindrance.

In order to understand the reaction pathway, the reaction between **1d** and **2** was quenched with ice water after 1 hour, extracted with CH_2Cl_2 and the crude product was subjected to NMR analysis. The existence of the *E*-isomer of the intermediate α,β-unsaturated ketone [**3d**: δ = 6.63 ppm (d, *J* = 16.2 Hz)] was determined from coupling-constant values and a singlet observed at δ = 10.24 ppm showed the presence of a free aldehydic group (see ESI). Thus the free availability and close proximity of the aldehydic group in the intermediate favors the intramolecular MBH reaction, giving rise to the inden-1-ol derivatives (Scheme 2).

Formation of sugar based inden-1-ol **3a** and also the existence of extended π-conjugation was confirmed from single-crystal XRD studies; the ORTEP representation of **3a** is shown in Figure 1. The torsion angle [H(10)–C(9)–C(10)–H(10) = 176.58°] shows that the 4,6-*O*-butylidene-D-glucopyranosyl moiety is in the β-anomeric form and

This document was downloaded for personal use only. Unauthorized distribution is strictly prohibited.



Scheme 2 Mechanism for the formation of substituted inden-1-ol derivatives

the inden-1-ol coupled with the sugar is planar within the limits of standard deviation. The crystal forms a two-dimensional hydrogen bonded (O–H···O) network (Table 3), which is parallel to the (001) plane [see ESI for H-bonding interaction of **3a**], and the enol form is stabilized through an intramolecular hydrogen bond.

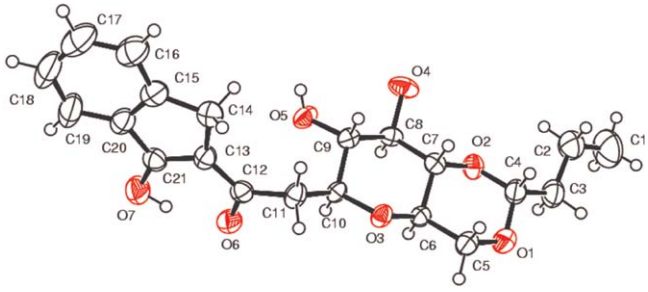


Figure 1 ORTEP view of compound **3a**

Table 3 Hydrogen Bonds for Compound **3a**[a]

D–H···A	d(D–H)	d(H···A)	d(D···A)	<(DHA)
O(7)–H(7A)···O(6)	0.88(4)	1.73(4)	2.563(2)	156 (3)
O(4)–H(4A)···O(3)#1	0.82	2.11	2.777(2)	137.9
O(5)–H(5)···O(6)#2	0.81(4)	1.99(4)	2.801(2)	179 (3)

[a] Symmetry transformations used to generate equivalent atoms: #1 x – 1, y + 1, z; #2 x, y + 1, z.

Modulation of tautomeric equilibrium of **3a** by Li^+ ions was determined by UV-vis spectral studies. The shift in absorbance from 324 to 334 nm over the increase in concentration of $LiClO_4$ is mainly due to the formation of ionic clusters with enolate of **3a**, which aggregates in solution (Figure 2).

In conclusion, we have developed a new methodology for the synthesis of inden-1-ol derivatives from different sugar-/aromatic-/heteroaromatic-/alkyl-substituted methyl ketones. The existence and modulation of tautomeric equilibrium was demonstrated by UV-vis studies. Some indanone- and indenol-based natural products[12f,16] are reported to have tubulin polymerization properties and have also been used for the treatment of Alzheimer's disease, and investigations in this direction are in progress.

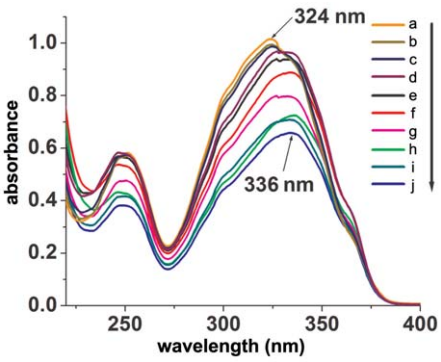


Figure 2 UV absorbance spectra of **3a** (1×10^{-6} M) in different ratios of $LiClO_4$ (1×10^{-6} M) in MeOH: (a) 1:10; (b) 2:10; (c) 3:10; (d) 4:10; (e) 5:10; (f) 6:10; (g) 7:10; (h) 8:10; (i) 9:10; (j) 1:1.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

Acknowledgment

The authors acknowledge DST New Delhi, India for financial support. T.M. thanks DST, New Delhi for access to the NMR facility, Department of Organic Chemistry, University of Madras, Chennai, India. S.N. thanks CSIR, New Delhi for a Senior Research Fellowship.

References

(1) (a) Trost, B. M. *Science* **1991**, *254*, 1471. (b) Roy, D.; Patel, C.; Sunoj, R. B. *J. Org. Chem.* **2009**, *74*, 6936. (c) Renodo, M. C.; Ribagorda, M.; Carreno, M. C. *Org. Lett.* **2010**, *12*, 568. (d) Shi, M.; Liu, X.-G. *Org. Lett.* **2008**, *10*, 1043.
(2) (a) Trost, B. M. *Acc. Chem. Res.* **2002**, *35*, 695. (b) Sirasani, G.; Paul, T.; Dougherty, W. Jr.; Kassel, S.; Andrade, R. B. *J. Org. Chem.* **2010**, *75*, 3529. (c) Clive, D. L. J.; Li, Z.; Yu, M. *J. Org. Chem.* **2007**, *72*, 5608.
(3) Morita, K.-I.; Suzuki, Z.; Hirose, H. *Bull. Chem. Soc. Jpn.* **1968**, *41*, 2815.
(4) (a) Baylis, A. B.; Hillman, M. E. D. *Chem. Abstr.* **1972**, *77*, 34174q. (b) Baylis, A. B.; Hillman, M. E. D. Ger. Offen. 2,155,113, **1972**. (c) Drewes, S. E.; Roos, G. H. P. *Tetrahedron* **1988**, *44*, 4653. (d) Basavaiah, D.; Rao, P. D.; Hyma, R. S. *Tetrahedron* **1996**, *52*, 8001. (e) Ciganek, E. *Org. React.* **1997**, *51*, 201. (f) Langer, P. *Angew. Chem. Int. Ed.* **2000**, *39*, 3049. (g) Kim, J. M.; Lee, K. Y. *Curr. Org. Chem.* **2002**, *6*, 627. (h) Basavaiah, D.; Rao, A. J.; Satyanarayana, T. *Chem. Rev.* **2003**, *103*, 811.
(5) (a) Declerck, V.; Martinez, J.; Lamaty, F. *Chem. Rev.* **2009**, *109*, 1. (b) Singh, V.; Batra, S. *Tetrahedron* **2008**, *64*, 4511.
(6) Krafft, M. E.; Wright, J. A. *Chem. Commun.* **2006**, 2977.
(7) Aroyan, C. E.; Vasbinder, M. M.; Miller, S. J. *Org. Lett.* **2005**, *7*, 3849.
(8) Teng, W.-D.; Huang, R.; Kwong, C. K.-W.; Shi, M.; Toy, P. H. *J. Org. Chem.* **2006**, *71*, 368.
(9) Basavaiah, D.; Rao, K. V.; Reddy, R. J. *Chem. Soc. Rev.* **2007**, *36*, 1581.

This document was downloaded for personal use only. Unauthorized distribution is strictly prohibited.

(10) Yeo, E.; Yang, X.; Kim, H. J.; Koo, S. *Chem. Commun.* **2004**, 236.
(11) (a) Krafft, M. E.; Song, E.-H.; Davoile, R. J. *Tetrahedron Lett.* **2005**, *46*, 6359. (b) Duarte, F. J. S.; Cabrita, E. J.; Frenking, G.; Santos, A. G. *Chem. Eur. J.* **2009**, *15*, 1734. (c) Petrignet, J.; Roisnel, T.; Gree, R. *Chem. Eur. J.* **2007**, *13*, 7374. (d) Shintani, R.; Takatsu, K.; Hayashi, T. *Angew. Chem. Int. Ed.* **2007**, *119*, 3809. (e) Shintani, R.; Takatsu, K.; Katoh, T.; Nishimura, T.; Hayashi, T. *Angew. Chem. Int. Ed.* **2008**, *120*, 1469. (f) Liu, C.-C.; Korivi, R. P.; Cheng, C.-H. *Chem. Eur. J.* **2008**, *14*, 9503.
(12) (a) Roth, F.; Gygax, P.; Fráter, G. *Tetrahedron Lett.* **1992**, *33*, 1045. (b) Drewes, S. E.; Njamela, O. L.; Emslie, N. D.; Ramesar, N.; Field, J. S. *Synth. Commun.* **1993**, *23*, 2807. (c) Black, G. P.; Dinon, F.; Fratucello, S.; Murphy, P. J.; Nielsen, M.; Williams, H. L.; Walshe, N. D. A. *Tetrahedron Lett.* **1997**, *38*, 8561. (d) Dinon, F.; Richards, E.; Murphy, P. J.; Hibbs, D. E.; Hursthouse, M. B.; Malik, K. M. A. *Tetrahedron Lett.* **1999**, *40*, 3279. (e) Keck, G. E.; Welch, D. S. *Org. Lett.* **2002**, *4*, 3687. (f) Kerr, D. J.; Hamel, E.; Jung, M. K.; Flynn, B. L. *Bioorg. Med. Chem.* **2007**, *15*, 3290.
(13) (a) Mellis, R. L.; Mehltretter, C. L.; Rist, C. E. *J. Am. Chem. Soc.* **1951**, *73*, 294. (b) Bonner, T. G.; Bourne, E. J.; Lewis, D. *J. Chem. Soc.* **1965**, 7453.
(14) (a) Nagarajan, S.; Mohan Das, T. *Carbohydr. Res.* **2009**, *334*, 1028. (b) Nagarajan, S.; Mohan Das, T.; Arjun, P.; Raaman, N. *J. Mater. Chem.* **2009**, *19*, 4587. (c) Nagarajan, S.; Mohan Das, T. *New J. Chem.* **2009**, *33*, 2391. (d) Bragnier, N.; Scherrmann, M. C. *Synthesis* **2005**, 814. (e) Rodrigues, F.; Canac, Y.; Lubineau, A. *Chem. Commun.* **2000**, 2049. (f) Riemann, I.; Papadopoulos, M. A.; Knorst, M.; Fessner, W. D. *Aust. J. Chem.* **2002**, *55*, 147. (g) Nagarajan, S.; Arjun, P.; Raaman, N.; Mohan Das, T. *Carbohydr. Res.* **2010**, *345*, 1988. (h) Nagarajan, S.; Shanmugam, M. J.; Mohan Das, T. *Carbohydr. Res.* **2011**, *346*, 722.
(15) (a) Nagarajan, S.; Ravinder, P.; Subramanian, V.; Mohan Das, T. *New J. Chem.* **2010**, *34*, 123. (b) Nagarajan, S.; Anupa, K.; Babu, V.; Mohan Das, T. *Carbohydr. Res.* **2010**, *345*, 1077. (c) Karthik Kumar, K.; Elango, M.; Subramanian, V.; Mohan Das, T. *New J. Chem.* **2009**, *33*, 1570.
(16) (a) Harrowven, D. C.; Newman, N. A.; Knight, C. A. *Tetrahedron Lett.* **1998**, *39*, 6757. (b) Wessig, P.; Teubner, J. *Synlett* **2006**, 1543; and references therein. (c) Nagle, D. G.; Zhou, Y.-D.; Park, P. U.; Paul, V. J.; Rajbhandari, I.; Duncan, C. J. G.; Pasco, D. S. *J. Nat. Prod.* **2000**, *63*, 1431. (d) Sugimoto, H.; Iimura, Y.; Yamanishi, Y.; Yamatsu, K. *J. Med. Chem.* **1995**, *38*, 4821.

This document was downloaded for personal use only. Unauthorized distribution is strictly prohibited.

Copyright of Synlett is the property of Georg Thieme Verlag Stuttgart and its content may not be copied or emailed to multiple sites or posted to a listserv without the copyright holder's express written permission. However, users may print, download, or email articles for individual use.