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ARTICLE TYPE

Hypervalent iodine mediated direct one pot transformation of aldehydes to ketones[†‡]

Prateep Singh Sagara, Rajesh Chebolu, Ashish Bahuguna, P. C. Ravikumar*

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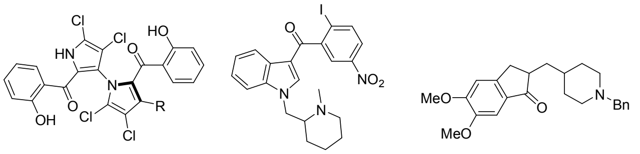
An environmentally benign, step economical synthesis of ketones directly from aldehydes has been developed using hypervalent iodine as an oxidant. The key features of this protocol are its mild conditions without the use of any heavy and toxic metals for the synthesis of a wide range of ketones.

The high abundance of ketone motifs present in many biologically active natural products/heterocycles (Figure 1) and strategic usefulness[1] of ketones for further functional group manipulation in organic synthesis is reflected in the myriad strategies for its construction. The majority of strategies involve either the alkylation of aldehyde followed by subsequent oxidation[1e-i] or by alkylation of dithianes[2] followed by unmasking the carbonyl functionality (umpolung method). But both these strategies are less direct and require two or more steps. As conversion of aldehydes to ketones is a very common chemical transformation in synthetic labs and chemical industries, use of conventional toxic transition metal (Cr, Mn & V) based oxidants causes environmental damage. Keeping in view of the environment[3] a direct conversion of aldehydes to ketones in single step using less expensive, non-toxic reagent is more attractive compared to the conventional metal-based two-step procedures. Transition metal catalysed aldehydic carbon-hydrogen (C-H) bond activation/functionalization have received much attention in recent years.[4]



(±) Marinopyrrole A
antibiotic & anticancer agent[1b]

3-acylindole
cannabinoid 2 receptor[1c]

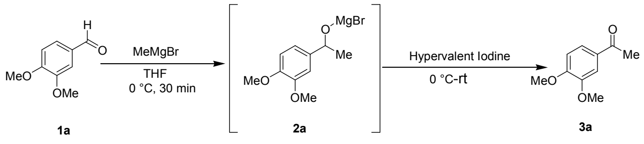
Donepezil
Alzheimer's disease treatment[1d]

Figure 1. Therapeutic and biologically active ketone motifs

The limited synthetic protocols available for direct conversion of aldehydes to ketones include the use of organovanadium reagents,[5a] magnesium-mediated addition/Oppenauer oxidation,[5b,c] boron-Wittig process,[5d] *N-tert*-butylphenylsulfinimidoyl chloride,[5e] and the transition metal-catalyzed coupling of aldehyde with the coupling partners such as aryl halides,[6a] aryl boronic acid[6b] and esters.[7] Even though existing protocols provide a wider choice for direct conversion of aldehydes to ketones, limitations such as use of expensive and toxic metal catalyst/reagent, elaborate reaction procedures, longer reaction times and limited substrate scope still needs to be addressed. Therefore, there is a need to develop a practical, economical and environmentally benign procedure for the direct oxidative alkylation of aldehydes with wide substrate scope.

In the recent decade, hypervalent iodine reagents have emerged as a useful alternative for wide array of organic transformations[8] due to its easy handling, high stability, low toxicity, and easy availability. It is widely considered as a valuable oxidant for conducting environmentally benign reactions. Recent reports on hypervalent iodine mediated amidation[9a] and organocatalytic arylation[9b] of aldehydic C-H bond prompted us to explore its use along with Grignard reagents. We presumed that aromatic aldehydes upon sequential treatment with Grignard reagent and hypervalent iodine reagents might directly lead to ketones due to oxidative and electrophillic nature of hypervalent iodine. To test our hypothesis, a model reaction was performed with 3, 4-dimethoxybenzaldehyde **1a**. Addition of methyl magnesium iodide followed by diacetoxyiodobenzene (DIB) to 3, 4-dimethoxybenzaldehyde indeed gave us expected ketone **3a** in excellent yield (table 1, entry 1).

Table 1. Screening of various hypervalentiodines for oxidative alkylation of 1[a]



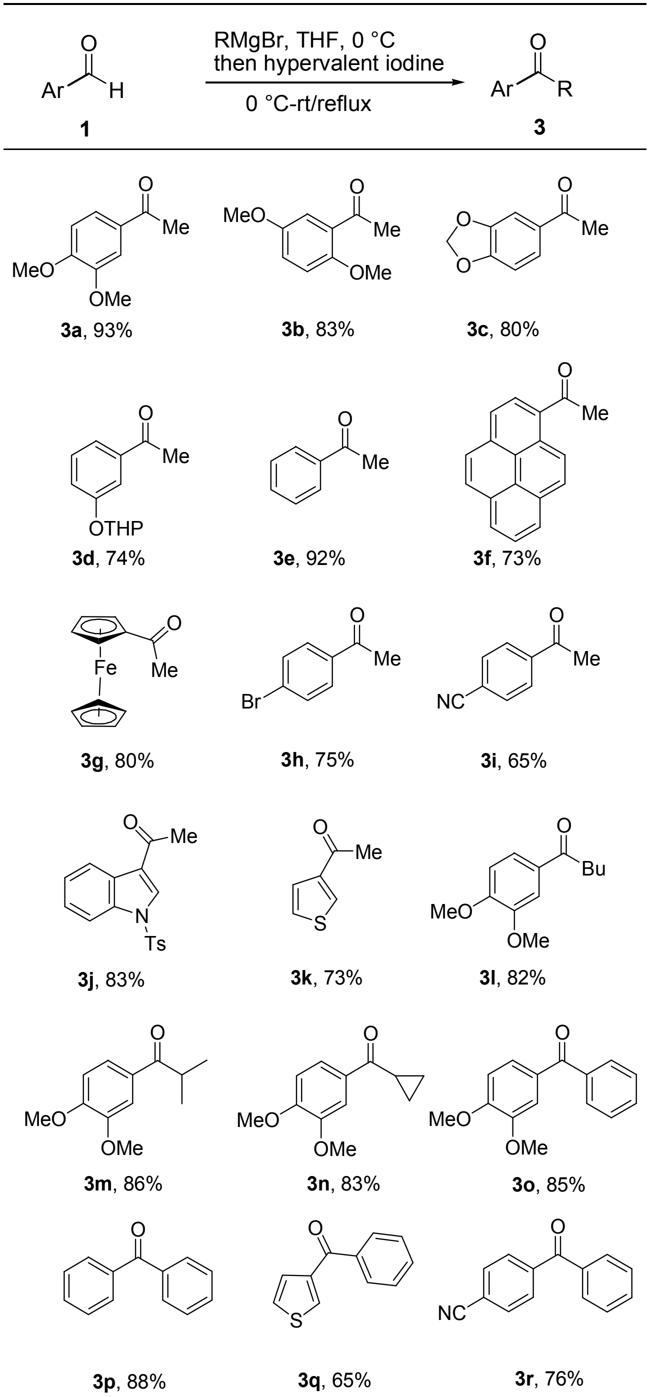
Entry	oxidant	time (h)	yield (%)[b]
1	$PhI(OAc)_2$	1	93
2	$PhI(OCOCF_3)_2$	1	90
3	PhI(OH)(OTs)	1	89
4	Dess Martin periodinane	1	87
5	IBX	12	57

[a] Reaction conditions: benzaldehyde (0.5 mmole), Griganard reagent (1.5 equiv.) in THF (1 mL) at 0 °C, then oxidant (2 equiv.) at 0 °C to rt.
[b] Isolated yield of purified products.

In order to test the influence of hypervalent iodine oxidant, various electron rich and electron deficient hypervalent iodine reagents such as $PhI(OCOCF_3)_2$, PhI(OH)(OTs), Dess Martin periodinane and 2-Iodoxybenzoic acid (IBX) were screened.

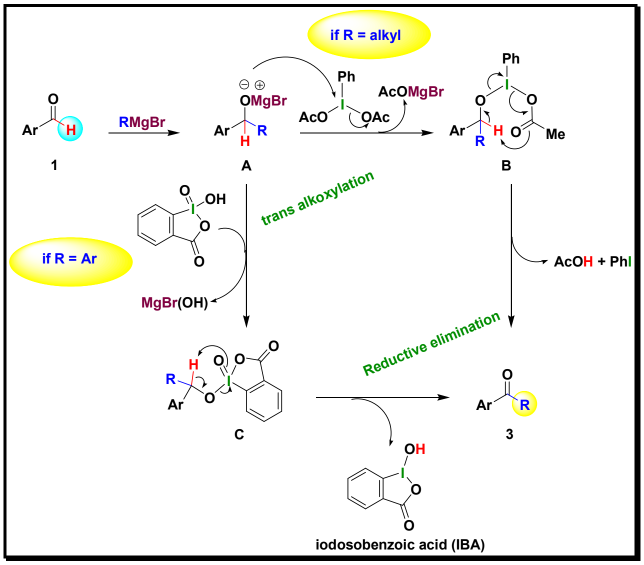
Comparable results were observed with almost all hypervalent iodine oxidants (table 1, entries 1-4) except with IBX (table 1, entry 5). The best result was found with DIB, affording the 1-(3,4-dimethoxyphenyl)ethanone **3a** in 93% yield, at rt for 1 h (table 1, entry 1). We therefore decided to continue our further studies with DIB as oxidant.

Table 2. One pot oxidative alkylation/arylation of aldehyde [a, b]



[a] Isolated yield of purified products. [b] Reaction conditions for entries **3a-n**: aldehyde (0.5 mmole), Grignard reagent (1.5 equiv.) in THF (1 mL) at 0 °C, then DIB (2 equiv.) at 0 °C to rt. For entries **3o-r**: IBX (3 equiv.) is used as oxidant instead of DIB under refluxing conditions.

To ascertain the wide application of this procedure, diverse electron rich and electron deficient aromatic, hetero-aromatic and organometallic aldehydes (table 2) were examined with methyl magnesium iodide and DIB under the optimized reaction condition. To our delight, the desired ketones (table 2, entries **3a-k**) were obtained in good to excellent yields (table 2). Apparently, electron donating/withdrawing (table 2, entries **3a-n**) nature and the position of substitution on the aromatic ring did not make much difference to reactivity, even the reaction with sensitive aldehydes i.e. piperonal & *O*-tetrahydropyran (THP) protected *m*-hydroxybenzaldehyde and ferrocene carboxaldehyde, proceeded smoothly and produced good yields (table 2, entries **3c**, **3d** & **3i**). Reaction of benzaldehyde **1a** with Grignard reagents such as butyl, isopropyl, cyclopropyl magnesium bromides also produced corresponding ketones (table 2, entries **3l-n**) in good yields. For the synthesis of biaryl ketones DIB as internal oxidant produced low yields along with some side products. After screening several hypervalent iodine reagents, the best result was observed with IBX under refluxing THF condition. The optimized condition was screened with various aldehydes (table 2, entries **3o-r**) and obtained good results. The generality of this reaction is further confirmed, when treatment acetaldehyde with phenylmagnesium bromide and DIB produced the acetophenone **3e** in 94% yield, which is comparable to the 92% yield (table-1) obtained using benzaldehyde as starting material.



Scheme 1. Plausible mechanism for the direct one pot synthesis of the ketone

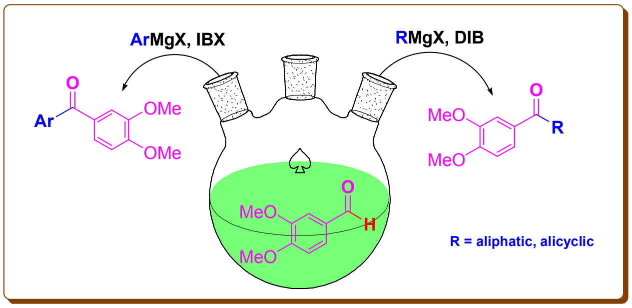
A plausible reaction mechanism for the hypervalent iodine mediated direct oxidative alkylation/arylation of aldehydes to ketones is depicted in Scheme 1. Both the reaction follows similar pattern in functionalizing the aldehydes. The two key steps are trans alkoxylation of Grignard adduct **A** with the hypervalent iodine (i.e. DIB or IBX) to produce the corresponding intermediates **B** or **C** and reductive elimination of the intermediates **B** or **C** to produce the desired ketones along with the corresponding reduced hypervalent iodine i.e. iodobenzene in case of DIB or iodoso benzoic acid in case of IBX.

In order to ascertain the mechanism of this reaction a test reaction was performed by concomitant addition of Grignard reagent and DIB to 3,4-dimethoxybenzaldehyde, this apparently did not produce the desired ketone in good yield, suggesting a possible side reaction between Grignard reagent and DIB, it also justifies the involvement of stepwise mechanism (Scheme-1) and the need for deferred addition of the hypervalent iodine reagent. During purification of crude reaction mixtures, we have often isolated a less polar spot, which was found to be iodobenzene, this evidence again reinforces our proposed mechanism.

Conclusions

In conclusion, an operationally simple, and environmentally benign one pot synthesis of variety of ketones directly from aldehydes, using Grignard and hypervalent iodine reagents were described. Reduction of one step of intermediate hydroxyl purification, generation of non-toxic by-products, atom economy, and shorter reaction time periods,[3] attributes this strategy as a environmentally benign protocol for the synthesis of ketones from aldehydes. Further studies with various other Grignard and organometallic reagents are in progress.

Inserting Graphics.



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Notes and references

School of Basic Sciences, Indian Institute of Technology Mandi, Kamand Campus, H.P.,175005 India. E-mail: ravi@iitmandi.ac.in

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

‡ Dedicated to the memory of Prof. A. Srikrishna.

1 (a) F. Epifano, S. Genovese, *Chemistry and Pharmacology of Naturally Occurring Bioactive Compounds,* CRC Press publishing, USA, 2013; (b) C. Cheng, L. Pan, Y. Chen, H. Song, Y. Qin, R. Li,. *J. Comb. Chem.*, 2010, **12**, 541; (c) J. Frost, M. Dart, J. M, K. R. Tietje, T. R. Garrison, G. K.. Grayson, A. V. Daza, O. F. El-Kouhen, B. B. Yao, G. C. Hsieh, M. Pai, C. Z. Zhu, P. Chandran, M. D. Meyer, *J. Med. Chem.*, 2010, **53**, 295; (d) D. B. Ramachary, M. Kishor, Y. V. Reddy, *Eur. J. Org. Chem.*, 2008, 975; (e) J. Otera, *Modern Carbonyl Chemistry;* John Wiley & Sons publishing, 2001; (f) K.. Lafleur, D. Huang, T. Zhou, A. Caflisch, C. Nevado, *J. Med. Chem.*, 2009, **52**, 6433; (g) J. I. Kawakami, K. Kimura, M. Yamaoka, *Org. Process Res. Dev.*, 2007, **11**, 206; (h) S. Roy, A. Sharma, B. Dhotare, P. Vichare, A. Chattopadhyay, S. Chattopadhyay, *Synthesis*, 2007, 1082; (i) Z. Li, V. Gevorgyan, *Angew. Chem. Int. Ed.*, 2011, **50**, 2808.

2 (a) V. Bertini, F. Lucchesini, M. Pocci, A. D. Munno, *Tetrahedron Lett.*, 1998, **39**, 9263; (b) D. J. Callis, N. F. Thomas, D. P. J. Pearson, B. V. L. Potter, *J. Org. Chem.*, 1996, **61**, 4634; (c) V. Bertini, F. Lucchesini, M. Pocci, A. D. Munno, *J. Org. Chem.*, 2000, **65**, 4839; (d), S. G. Ghorai, A. Bhattacharjya, *Org. Lett.*, 2006, **8,** 313; (e) S. Perreault, C. Spino, *Org. Lett.*, 2006, **8**, 4385

3 (a) P. T. Anastas, J. Warner, *Green Chemistry Theory and Practice*, Oxford University Press, Oxford, 1998; (b) P. A. Clarke, S. Santos and W. H. C. Martin, *Green Chem.*, 2007, **9**, 438; (c) M. Poliakoff, J. M. Fitzpatrick, T. R. Farren, P. T. Anastas, *Science*, 2002, **297**, 807; (d) S. L. Y. Tang, R. L. Smith, M. Poliakoff, *Green Chem.*, 2005, **7**, 761.

4 (a) M. C. Willis, *Chem. Rev.*, 2010, **110**, 725; (b) K. Ekoue-Kovi, C. Wolf, *Chem. Eur. J.*, 2008, **14**, 6302.

5 (a) T. Hirao, D. Misu, T. Agawa, *J. Am. Chem. Soc.*, 1985, **107**, 7179; (b) R. J. Kloetzing, A. Krasovskiy, P. Knochel, *Chem. Eur. J.*, 2007, **13**, 215; (c) B. Byrne, M. Karras, *Tetrahedron Lett.* 1987, **28**, 769; (d) A. Pelter, K. Smith, S. Elgendy, M. Rowlands, *Tetrahedron Lett.*,1989, **30**, 5643; (e) J. J. Crawford, K. W. Henderson, W. J. Kerr, *Org. Lett.*, 2006, **8**, 5073.

6 (a) Y. C. Huang, K. K. Majumdar, C. H. Cheng, *J. Org. Chem.*, 2002**, 67**, 1682; (b) M. Pucheault, S. Darses, J. P. Genet, *J. Am. Chem. Soc.*, 2004, **126**, 15356; (c) C.H. Jun, H. Lee, J. B. Hong, *J. Org. Chem.*, 1997, **62**, 1200; (d) Y. J. Park, J. W. Park, C. H. Jun, *Acc. Chem. Res.*, 2008, **41**, 222.

7 (a) J. Karthikeyan, K. Parthasarathy, C. H. Cheng, *Chem. Commun.*, 2011, **47**, 10461; (b) L. Yang, T. Zeng, Q. Shuai, X. Guo, C.-J. Li, *Chem. Commun.*, 2011, **47**, 2161; (b) G. Mora, S. Darses, J. P. Genet, *Adv. Synth. Catal.*, 2007, **349**, 1180; (c) O. Chuzel, A. Roesch, J. P. Genet, S. Darses, *J. Org. Chem.*, 2008, **73**, 7800

8 (a) V. V. Zhdankin, P. J. Stang, *Chem. Rev.*, 2008, **108**, 5299; (b) E. A. Merritt, B. Olofsson, *Angew. Chem. Int. Ed.*, 2009, **48**, 9052; (c) V. V. Zhdankin, *J. Org. Chem.* 2011, **76**, 1185; (d) A. Duschek, S. F. Kirsch, *Angew. Chem. Int. Ed.*, 2011, **50**, 1524; (e) E. A. Merritt, B. Olofsson, *Synthesis,* **2011**, 517.

9 (a) V. Prasad, R. R. Kale, B. B. Mishra, D. Kumar, V. K. Tiwari, *Org. Lett.*, 2012, **14**, 2936; (b) Q. Y. Toh, A. McNally, S. Vera, N. Erdmann, M. J. Gaunt, *J. Am. Chem. Soc.*, 2013, **135**, 3772.