The First One-Pot Synthesis of Morita–Baylis–Hillman Adducts Starting Directly from Alcohols

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Abstract: The first example of one-pot oxidative carbon–carbon bond formation via the Morita–Baylis–Hillman reaction using alcohols is reported. The protocol involves silica gel–DABCO catalyzed oxidation of alcohols to aldehydes with chloramine-T followed by their Morita–Baylis–Hillman reaction with acrylonitrile or methyl acrylate to give 70–87% overall yields of the corresponding Morita–Baylis–Hillman adducts. The present work opens up a new and efficient synthetic route to Morita–Baylis–Hillman adducts directly from alcohols in a one-pot operation.

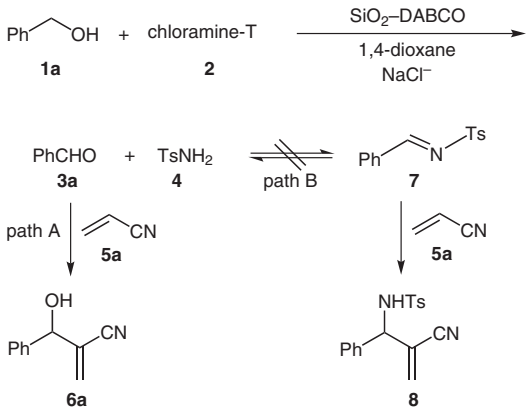
Key words: oxidation, C–C bond formation, alcohols, chloramine-T, silica gel–DABCO, Morita–Baylis–Hillman adducts

The Morita–Baylis–Hillman (MBH) reaction is an efficient carbon–carbon bond-forming reaction between Michael acceptors and carbonyl or imine compounds under mild conditions. The reaction yields densely functionalized molecules,[1] which can be utilized for the construction of complex molecular frameworks.[2] Therefore, the MBH reaction has been drawing much attention from synthetic organic chemists during the past decade.[2,3] The major problem associated with this reaction is its slow reaction rate. In view of this situation numerous methods, including chemical as well as physical attempts, have been made to accelerate the reaction with some good results.[4]

In general, the MBH reaction utilizes an aldehyde as one of the starting materials. However, some of the aldehydes are volatile, toxic, or unstable, especially because of aerial oxidation. On the other hand, alcohols are usually more stable, less volatile, and less toxic than the corresponding aldehydes, meanwhile, oxidation of alcohols is an important method for forming aldehydes. Moreover, one-pot sequential multistep reactions are of increasing academic, economical, and ecological interest because they address fundamental principles of synthetic efficiency and reaction design. Thus, hitherto unexplored one-pot synthesis of MBH adducts starting directly from alcohols is an interesting target of investigation.

A number of procedures employing various reagents have been developed for oxidative carbon–carbon bond formation.[5] It is noteworthy that only few reports are available in the literature on oxidative C–C bond formation via MBH reaction, but in all these cases the oxidation product (an aldehyde) of starting alcohol has to be isolated and then subjected to the MBH reaction in a separate step.[6] Oxidation of primary alcohols using different oxidants has been carried out by many workers.[7] However, some of the more historically prominent methods have significant drawbacks. Cr(VI) reagents[8] (Jones,[9] Ollins/Sarrett,[10] PCC[11]) are toxic and their use often involves a difficult workup. Swern[12] oxidation requires low temperature, solvent that can be difficult to remove, and generates stench. TEMPO[13] oxidant lacks tolerance for many functionl groups. The *o*-iodoxybenzoic acid (IBX)[14,15] is a mild and selective reagent for this transformation, but its solubility in common solvents remains a problem for which new solutions are still to be sought.[16] Furthermore, most of the above reagents leave acidic byproducts, which would hamper the catalytic activity of the catalyst used for the subsequent MBH reaction undergoing in the same vessel. Advantageously, chloramine-T acts as an oxidizing agent in both acidic and alkaline solutions,[17] and leaves $TsNH_2$ and NaCl as byproducts, whose presence would not adversely affect the ensuing MBH reaction, hence it is a well-suited oxidant for the present study.

Silica gel without modification is generally used for separation of organic compounds in normal-phase chromatography. Alternatively, silica should be an efficient aqueous organic reaction media[18] because the organic substrate is adsorbed to the silica by hydrophobic interaction between the surface of the silica and the organic molecule.[19] A significant advantage of the silica medium is that the workup procedure is extremely simple.[20]



Scheme 1 One-pot synthesis of MBH adduct **6a** from benzyl alcohol

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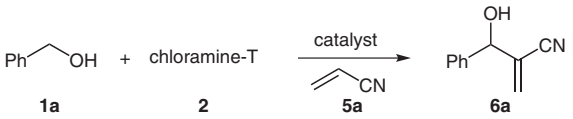
The above points and our continued work on MBH chemistry[3i,j,21] intrigued us to develop a one-pot synthesis of MBH adducts starting directly from alcohols employing chloramine-T as the oxidant. Initially, we investigated the possibility of the formation of aza-MBH adduct **8** via oxidative imine formation as depicted in Scheme 1, path B. Thus, an equimolar mixture of alcohol **1a** and chloramine-T (**2**) in 1,4-dioxane using silica gel–DABCO catalyst and MS 4 Å, stirred at room temperature for 8 hours followed by addition of 3 equivalents of acrylonitrile **5a** and stirring at room temperature for 17 hours, the reaction proceeded very slowly to afford only benzaldehyde (**3a**) and MBH adduct **6a** (Scheme 1, path A). There was no formation of any appreciable amount of imine **7** or aza-MBH adduct **8** under the present reaction conditions (Scheme 1, path B). This urged us to develop a one-pot sequential oxidation–MBH reaction to prepare MBH adducts instead of aza-MBH adducts. The key to effect a one-pot procedure is to explore appropriate reaction conditions.

Thus, we turned our attention to optimize the conditions for one-pot oxidative C–C bond formation between benzyl alcohol and the Michael acceptor acrylonitrile via the MBH reaction (Scheme 1, path A). It was noted that on addition of water as a co-solvent the reaction was significantly accelerated and that the binary medium consisting of 1:1 ratio of 1,4-dioxane and water was found to be the best solvent system (Table 1, entries 2–5). This is in conformity with the earlier observations that aqueous media are suitable for oxidation with chloramine-T, and the MBH reaction is accelerated in the presence of water.[4j,n,q] Optimization of the catalyst revealed that among the catalysts tested, silica gel–DABCO gave the best result (Table 1, entries 5 and 7). It is worth noting that the catalyst used exhibited distinguishing effects as manifested by yields (Table 1, entries 5 and 10–12). We also attempted the protic ionic liquid 1-methylimidazolium hydrogen sulfate [Hmim]HSO_4 with DABCO under the same conditions but the reaction proceeded very slowly and afforded only 20% yield of **6a** (Table 1, entry 1). This is probably because the catalytic activity of DABCO for the MBH reaction is inhibited by its protonation with [Hmim]HSO_4. The optimum catalyst loading was 200 mg silica gel with 5 mmol of DABCO, which furnished 87% yield of adduct **6a** (Table 1, entry 5).

The present optimized one-pot procedure for oxidative carbon–carbon bond formation via the MBH reaction involves stirring of an equimolar mixture of an alcohol **1** and chloramine-T (**2**) in 1,4-dioxane–H_2O (1:1) using silica gel–DABCO catalyst system at room temperature for 6–24 hours followed by addition of 3 equivalents of acrylonitrile-methyl acrylate **5** and further stirring at room temperature for 5–45 hours to afford MBH adduct **6** in 70–87% yields (Table 2).[22] The reaction proceeded through sequential oxidation of alcohol **1** to aldehyde **3** and MBH reaction with acrylonitrile-methyl acrylate. *p*-Toluenesulfonamide formed as the oxidation byproduct was easily recovered after the reaction, converted into

Table 1 Optimization of Reaction Conditions[a]



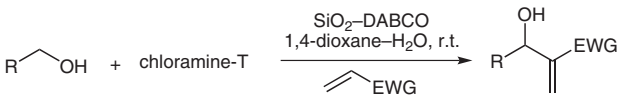
1a **2** **5a** **6a**

Entry	Solvent	Catalyst	Yield (%)[b]
1	[Hmim]HSO_4–H_2O (1:1)	DABCO (5 mmol)	20
2	DMF–H_2O (1:1)	SiO_2 (200 mg)–DABCO (5 mmol)	30
3	THF–H_2O (1:1)	SiO_2 (200 mg)–DABCO (5 mmol)	46
4	1,4-dioxane–H_2O (2:1)	SiO_2 (200 mg)–DABCO (5 mmol)	57
5	1,4-dioxane–H_2O (1:1)	SiO_2 (200 mg)–DABCO (5 mmol)	87
6	1,4-dioxane–H_2O (1:1)	SiO_2 (200 mg)–DABCO (2 mmol)	60
7	1,4-dioxane–H_2O (1:1)	SiO_2 (200 mg)–DABCO (10 mmol)	87
8	DMF–H_2O (1:1)	SiO_2 (200 mg)–DBU (5 mmol)	49
9	THF–H_2O (1:1)	SiO_2 (200 mg)–DBU (5 mmol)	25
10	1,4-dioxane–H_2O (1:1)	SiO_2 (200 mg)–DBU (5 mmol)	42
11	1,4-dioxane–H_2O (1:1)	DABCO (5 mmol)	53
12	1,4-dioxane–H_2O (1:1)	DBU (5 mmol)	35

[a] Reaction conditions: **1a** (5 mmol), chloramine-T (5 mmol), acrylonitrile (15 mmol), solvent (3 mL), time (25 h). For experimental procedure, see ref. 22.

[b] Yield of isolated and purified product **6a**.

Table 2 One-Pot Synthesis of MBH Adducts **6** Starting Directly from Alcohols **1**



1 2 5 6

Entry	R	EWG	Time (h)[a]	Yield (%)[b,c]
1	Ph	CN	25	87
2	4-BrC_6H_4	CN	60	77
3	4-$MeOC_6H_4$	CN	35	70
4	3-$O_2NC_6H_4$	CN	49	78
5	4-ClC_6H_4	CN	30	75
6	$PhCH_2CH_2$	CN	32	85
7	2-furyl	CN	33	75
8	Et	CN	31	83
9	Ph	COOMe	25	86
10	4-BrC_6H_4	COOMe	55	79
11	4-$MeOC_6H_4$	COOMe	33	73
12	3-$O_2NC_6H_4$	COOMe	48	80
13	4-ClC_6H_4	COOMe	49	78
14	Et	COOMe	28	82
15	*n*-C_5H_{11}	COOMe	27	80
16	2-furyl	COOMe	30	76

[a] Total time required for the conversion of alcohols **1** into MBH adducts **6**, see ref. 22 for general procedure.
[b] Yield of isolated and purified products.
[c] All compounds are known[4j,n,o,q,23] and were characterized by comparison of their mp or bp, TLC, IR, and NMR data with those of authentic samples prepared by literature methods.

chloramine-T on treatment with aqueous sodium hypochlorite, and used in subsequent runs.

In summary, we have developed a one-pot process for C–C bond formation via sequential oxidation of alcohols to aldehydes and their Morita–Baylis–Hillman reaction with acrylonitrile-methyl acrylate. This simple protocol involves chloramine-T as oxidizing reagent and silica gel–DABCO as the catalyst system. The present work opens up a new, efficient, and one-pot synthetic route to Morita–Baylis–Hillman adducts starting directly from alcohols.

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References and Notes

(1) (a) Morita, K.; Suzuki, Z.; Hirose, H. *Bull. Chem. Soc. Jpn.* **1968**, *41*, 2815. (b) Baylis, A. B.; Hillman, M. E. D. Offenlegungsschrift 2155113, 1972; US 3,743,669, **1972**; *Chem. Abstr.* **1972**, *77*, 34174. (c) Ciganek, E. In *Organic Reactions*, Vol. 51; Wiley: New York, **1997**, 201. (d) Ghosh, A. K.; Bilcer, G.; Schiltz, G. *Synthesis* **2001**, 2203.

(2) (a) Basavaiah, D.; Rao, A. J.; Satyanarayana, T. *Chem. Rev.* **2003**, *103*, 811. (b) Basavaiah, D.; Rao, K. V.; Reddy, R. J. *Chem. Soc. Rev.* **2007**, *36*, 1581. (c) Singh, V.; Batra, S. *Tetrahedron* **2008**, *64*, 4511.

(3) (a) Kim, J. N.; Lee, K. Y. *Curr. Org. Chem.* **2002**, 627. (b) Wasnaire, P.; de Merode, T.; Marko, I. E. *Chem. Commun.* **2007**, 4755. (c) Kim, H. S.; Kim, H. S.; Kim, J. N. *Bull. Korean Chem. Soc.* **2007**, *28*, 1841. (d) Cabrera, S.; Aleman, J.; Bolze, P.; Bertelsen, S.; Jorgensen, K. A. *Angew. Chem. Int. Ed.* **2008**, *47*, 121. (e) Ye, L.-W.; Han, X.; Sun, X.-L.; Tang, Y. *Tetrahedron* **2008**, *64*, 1487. (f) Grange, R. L.; Ziogas, J.; North, A. J.; Angus, J. A.; Schiesser, C. H. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 1241. (g) Cha, M. J.; Song, Y. S.; Han, E.-G.; Lee, K.-J. *J. Heterocycl. Chem.* **2008**, 235. (h) Sa, M. M.; Fernandes, L.; Ferreira, M.; Bortoluzzi, A. J. *Tetrahedron Lett.* **2008**, *49*, 1228. (i) Yadav, L. D. S.; Srivastava, V. P.; Patel, R. *Tetrahedron Lett.* **2009**, *50*, 1423. (j) Yadav, L. D. S.; Patel, R.; Srivastava, V. P. *Tetrahedron Lett.* **2009**, *50*, 1335. (k) Reddy, C. R.; Kiranmai, N.; Johny, K.; Pendke, M.; Naresh, P. *Synthesis* **2009**, 399. (l) Nayak, M.; Batra, S. *Eur. J. Org. Chem.* **2009**, 3505.

(4) (a) Isaacs, N. S. *Tetrahedron* **1991**, *47*, 8463. (b) Rozendaal, E. L. M.; Voss, B. M. W.; Scheeren, H. W. *Tetrahedron* **1993**, *49*, 6931. (c) Roos, G. H. P.; Rampersadh, P. *Synth. Commun.* **1993**, *23*, 1261. (d) Bode, M. L.; Kaye, P. T. *J. Chem. Soc., Perkin Trans. 1* **1993**, 1809. (e) Kundu, M. K.; Mukherjee, S. B.; Balu, N.; Padmakumar, R.; Bhat, S. V. *Synlett* **1994**, 444. (f) Brzezinski, L. J.; Rafel, S.; Leahy, J. W. *Tetrahedron* **1997**, *53*, 16423. (g) Brzezinski, L. J.; Rafel, S.; Leahy, J. W. *J. Am. Chem. Soc.* **1997**, *119*, 4317. (h) Almeida, W. P.; Coelho, F. *Tetrahedron Lett.* **1998**, *39*, 8609.. (i) Masunari, A.; Ishida, E.; Trazzi, G.; Almeida, W. P.; Coelho, F. *Synth. Commun.* **2001**, *31*, 2127. (j) Yu, C.; Liu, B.; Hu, L. *J. Org. Chem.* **2001**, *66*, 5413. (k) Balan, D.; Adolfsson, H. *J. Org. Chem.* **2001**, *66*, 6498. (l) Balan, D.; Adolfsson, H. *J. Org. Chem.* **2002**, *67*, 2329. (m) Aggarwal, V. K.; Dean, D. K.; Mereu, A.; Williams, R. *J. Org. Chem.* **2002**, *67*, 510. (n) Cai, J.; Zhou, Z.; Zhao, G.; Tang, C. *Org. Lett.* **2002**, *4*, 4723. (o) Chandraekhar, S.; Narsihmulu, Ch.; Saritha, B.; Sultana, S. S. *Tetrahedron Lett.* **2004**, *45*, 5865. (p) Mi, X.; Luo, S.; Cheng, J.-P. *J. Org. Chem.* **2005**, *70*, 2338. (q) de Souza, R. O. M. A.; Pereira, V. L. P.; Esteves, P. M.; Vasconcellos, M. L. A. A. *Tetrahedron Lett.* **2008**, *49*, 5902. (r) Bugarin, A.; Connell, B. T. *J. Org. Chem.* **2009**, *74*, 4638.

(5) (a) Baran, P. S.; Ambhaikar, N. B.; G uerrero, C. A.; Hafensteiner, B. D.; Lin, D. W.; Richter, J. M. *ARKIVOC* **2006**, *(vii)*, 310. (b) Lei, M.; Hu, R.-J.; Wang, Y.-G. *Tetrahedron* **2006**, *62*, 8928. (c) Matsuo, J.-I.; Kawai, H.; Ishibashi, H. *Tetrahedron Lett.* **2007**, *48*, 3155. (d) Huertu, R.; Flores-Figueroa, A.; Ugalde-Saldivar, V. M.; Castillo, I. *Inorg. Chem.* **2007**, *46*, 9510. (e) Clift, M. D.; Taylor, C. N.; Tomson, R. J. *Org. Lett.* **2007**, *9*, 4667. (f) Konkol, L. C.; Jones, B. T.; Thomson, R. J. *Org. Lett.* **2009**, *11*, 5550.

(6) (a) Yeo, J. E.; Yang, X.; Kim, H. J.; Koo, S. *Chem. Commun.* **2004**, 236. (b) Krishna, P. R.; Kannan, V.; Sharma, G. V. M. *J. Org. Chem.* **2004**, *69*, 6467.

(7) (a) Tandon, M.; Krishna, P. K. Z. *Phys. Chem.* **1985**, *266*, 1153. (b) Mantzavinos, D.; Hellenbrand, R.; Livingston, A. G.; Metcalfs, I. S. *Appl. Catal., B* **1996**, *11*, 99. (c) Singh, R. A.; Singh, R. S. *Oxid. Commun.* **1997**, *20*, 248. (d) Konyukhov, V. Y.; Chernaa, I. V.; Naumov, V. A. *Kinet. Catal.* **1997**, *38*, 811. (e) Navarro, M.; De Giovani, W. F.; Romero, J. R. *J. Mol. Catal. A: Chem.* **1998**, *135*, 249. (f) Hirano, M.; Kojima, K.; Yakabe, S.; Morimoto, T. *J. Chem. Res. Synop.* **2001**, 274. (g) Svetlakov, N. V.; Nikitin, V. G.; Orekhova, A. O. *Russian J. Org. Chem.* **2002**, *38*, 753. (h) Joseph, J. K.; Jain, S. L.; Sain, B. *Eur. J. Org. Chem.* **2006**, 590. (i) Kguchi, S.; Kitazume, T. *Tetrahedron Lett.* **2006**, *47*, 2797. (j) Jiang, N.; Ragauskas, A. J. *Tetrahedron Lett.* **2007**, *48*, 273.

(8) Cainelli, G.; Cardillo, G. *Chromium Oxidations in Organic Chemistry*; Springer: Berlin, **1984**.

(9) Harding, K. E.; May, L. M.; Dick, K. F. *J. Org. Chem.* **1975**, *40*, 1664.

(10) Collins, J. C.; Hess, W. W.; Frank, F. J. *Tetrahedron Lett.* **1968**, *9*, 3363.

(11) Corey, E. J.; Suggs, J. W. *Tetrahedron* **1975**, *31*, 2647.

(12) Omura, K.; Swern, D. *Tetrahedron* **1978**, *34*, 1651.

(13) Annelli, P. L.; Montanari, F.; Quici, S. *Org. Synth.* **1990**, *69*, 212.

(14) (a) Frigerio, M.; Santagostino, M. *Tetrahedron Lett.* **1994**, *35*, 8019. (b) Frigerio, M.; Santagostino, M.; Sputore, S.; Palmisano, G. *J. Org. Chem.* **1995**, *60*, 7272. (c) De Munari, S.; Frigerio, M.; Santagostino, M. *J. Org. Chem.* **1996**, *61*, 9272. (d) Frigerio, M.; Santagostino, M.; Sputore, S. *J. Org. Chem.* **1999**, *64*, 4537.

(15) (a) Zhdankin, V. V.; Stang, P. J. *Chem. Rev.* **2002**, *102*, 2523. (b) Wirth, T. *Angew. Chem. Int. Ed.* **2005**, *44*, 3656. (c) Ladziata, U.; Zhdankin, V. V. *ARKIVOC* **2006**, *(ix)*, 26. (d) Zhdankin, V. V.; Stang, P. J. *Chem. Rev.* **2008**, *108*, 5299.

(16) (a) Richardson, R. D.; Zayed, J. M.; Altermann, S.; Smith, D.; Wirth, T. *Angew. Chem. Int. Ed.* **2007**, *46*, 6529. (b) More, J. D.; Finney, N. S. *Org. Lett.* **2002**, *4*, 3001.

(17) (a) Banergi, K. K. *Bull. Chem. Soc. Jpn.* **1977**, *50*, 1616. (b) Kitagawa, H.; Mkaiyama, T. *Chem. Pharm. Bull.* **2002**, *50*, 1276. (c) Vinod, K. N.; Puttaswamy; Gowda, K. N. N. *Inorg. Chim. Acta* **2009**, *362*, 2044.

(18) (a) Minakata, S.; Kano, D.; Oderaotoshi, Y.; Komatsu, M. *Angew. Chem. Int. Ed.* **2004**, *43*, 79. (b) Minakata, S.; Hotta, T.; Oderaotoshi, Y.; Komatsu, M. *J. Org. Chem.* **2006**, *71*, 7471.

(19) (a) Ando, T.; Kano, D.; Minakat, S.; Ryu, I.; Komatsu, M. *Tetrahedron* **1998**, *54*, 13485. (b) Le Questel, J. Y.; Berthelot, M.; Laurence, C. *J. Phys. Org. Chem.* **2000**, *13*, 347. (c) D'hooghe, M.; Rottiers, M.; Kerkaert, I.; De Kimpe, N. *Tetrahedron* **2005**, *61*, 8746. (d) Minakata, S.; Hotta, T.; Oderaostoshi, Y.; Komatsu, M. *J. Org. Chem.* **2006**, *71*, 7471. (e) Jung, Y.; Marcus, R. A. *J. Am. Chem. Soc.* **2007**, *129*, 5492. (f) Minakata, S.; Komatsu, M. *Chem. Rev.* **2009**, *109*, 711.

(20) Witula, T.; Holmberg, K. *Langmuir* **2005**, *21*, 3782.

(21) (a) Yadav, L. D. S.; Srivastava, V. P.; Patel, R. *Tetrahedron Lett.* **2008**, *49*, 3142. (b) Yadav, L. D. S.; Srivastava, V. P.; Patel, R. *Tetrahedron Lett.* **2008**, *49*, 5652. (c) Yadav, L. D. S.; Patel, R.; Srivastava, V. P. *Synlett* **2008**, 1789. (d) Yadav, L. D. S.; Awasthi, C. *Tetrahedron Lett.* **2009**, *50*, 3801. (e) Yadav, L. D. S.; Rai, V. K. *Tetrahedron Lett.* **2009**, *50*, 2414. (f) Yadav, L. D. S.; Rai, V. K.; Singh, S. *Synlett* **2009**, 1423.

(22) **General Procedure for the Synthesis of MBH Adducts 6**
A mixture of alcohol **1** (5 mmol), chloramine-T (**2**, 5 mmol), DABCO (5 mmol), and SiO_2 (200 mg) in 1,4-dioxane–H_2O (3 mL, 1:1) was stirred at r.t. until the chloramine-T was consumed (6–24 h), then acrylonitrile or methyl acrylate (15 mmol) was added and the mixture was stirred at r.t. for 5–45 h (Table 2).The reaction progress was monitored by TLC. Upon completion, the reaction mixture was evaporated under reduced pressure and extracted with EtOAc (3 × 5 mL). The combined organic phase was dried over $MgSO_4$, filtered, and evaporated under reduced pressure. The resulting crude product was purified by silica gel column chromatography using hexane–EtOAc as eluent to give pure products **6**. The structure of the products was confirmed by comparison of their mp or bp, TLC, IR, and NMR data with authentic samples prepared by literature methods.[4j,n,o,q,23]

(23) Gong, H.; Cai, C.-Q.; Yang, N.-F.; Yang, L.-W.; Ahang, J.; Fan, Q.-H. *J. Mol. Catal. A: Chem.* **2006**, *249*, 236.