ORGANIC
LETTERS

2005
Vol. 7, No. 17
3769−3771

One-Step Assembly of Functionalized γ-Butyrolactones from Benzoins or Benzaldehydes via an N-Heterocyclic Carbene-Mediated Tandem Reaction

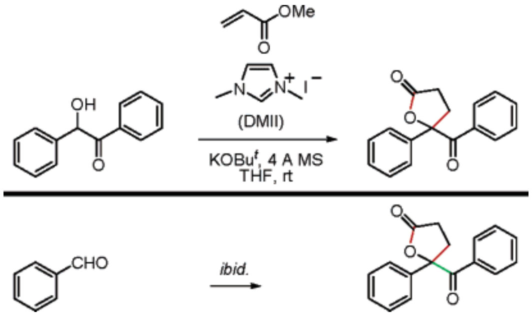
Wei Ye,[†,‡] Guanliang Cai,[‡] Zeyang Zhuang,[†,§] Xueshun Jia,[§] and Hongbin Zhai*,[†]

Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, Shanghai, China 200032, Analytical Center, Institute of Chemical Defense, Beijing, China 102205, and Department of Chemistry, Shanghai University, Shanghai, China 200436

zhaih@mail.sioc.ac.cn

Received June 19, 2005

ABSTRACT



We describe here a direct, efficient, one-step construction of γ,γ-difunctionalized γ-butyrolactones from benzoins or benzaldehydes via a tandem reaction promoted by 1,3-dimethyl imidazolin-2-ylidene, an N-heterocyclic carbene (NHC).

Since the isolation and characterization of the stable N-heterocyclic carbene (NHC) species by Arduengo[1] in 1991, there has been considerable attention[2] given to exploring and developing NHC-mediated organic transformations such as benzoin condensation,[3] Stetter reaction,[4] and transesterification.[5] Recently, several successful cases of NHC-triggered multicomponent reactions (MCRs) were reported by Nair[6] and Ma,[7] respectively.

Having been fascinated by the attractive characteristics of NHCs, we decided to investigate the reaction of benzoin (**1a**, Scheme 1) and methyl acrylate in the presence of 1,3-

---

[†] Shanghai Institute of Organic Chemistry.

[‡] Institute of Chemical Defense.

[§] Shanghai University.

(1) Arduengo, A. J., III; Harlow, R. L.; Kline, M. *J. Am. Chem. Soc.* **1991**, *113*, 361.

(2) For recent reviews on NHCs, see: (a) Enders, D.; Balensiefer, T. *Acc. Chem. Res.* **2004**, *37*, 534. (b) Nair, V.; Bindu, S.; Sreekumar, V. *Angew. Chem., Int. Ed.* **2004**, *43*, 5130. (c) César, V.; Bellemin-Laponnaz, S.; Gade, L. H. *Chem. Soc. Rev.* **2004**, *33*, 619. (d) Herrmann, W. A. *Angew. Chem., Int. Ed.* **2002**, *41*, 1290.

(3) For selected examples, see: (a) Knight, R. L.; Leeper, F. J. *J. Chem. Soc., Perkin Trans. 1* **1998**, 1891. (b) Enders, D.; Kallfass, U. *Angew. Chem., Int. Ed.* **2002**, *41*, 1743. (c) Dvorak, C. A.; Rawal, V. H. *Tetrahedron Lett.* **1998**, *39*, 2925. (d) Linghu, X.; Johnson, J. S. *Angew. Chem., Int. Ed.* **2003**, *42*, 2534. (e) Pesch, J.; Harms, K.; Bach, T. *Eur. J. Org. Chem.* **2004**, 2025.

(4) For selected examples, see: (a) Kerr, M. S.; Read de Alaniz, J.; Rovis, T. *J. Am. Chem. Soc.* **2002**, *124*, 10298. (b) Mattson, A. E.; Bharadwaj, A. R.; Scheidt, K. A. *J. Am. Chem. Soc.* **2004**, *126*, 2314. (c) Kerr, M. S.; Rovis, T. *J. Am. Chem. Soc.* **2004**, *126*, 8876. (d) Kerr, M. S.; Rovis, T. *Synlett* **2003**, 1934. (e) Ciganek, E. *Synthesis* **1995**, 1311. (f) Pesch, J.; Harms, K.; Bach, T. *Eur. J. Org. Chem.* **2004**, 2025. (g) Barrett, A. G. M.; Love, A. C.; Tedeschi, L. *Org. Lett.* **2004**, *6*, 3377.

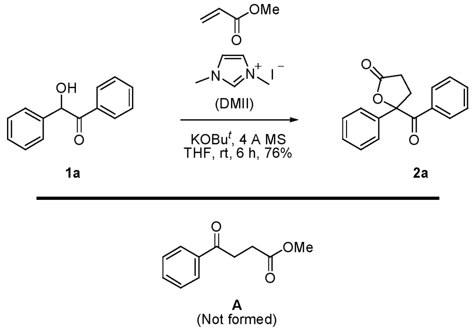
(5) For selected examples, see: (a) Nyce, G. W.; Lamboy, J. A.; Connor, E. F.; Waymouth, R. M.; Hedrick, J. L. *Org. Lett.* **2002**, *4*, 3587. (b) Grasa, G. A.; Güveli, T.; Singh, R.; Nolan, S. P. *J. Org. Chem.* **2003**, *68*, 2812. (c) Kano, T.; Sasaki, K.; Maruoka, K. *Org. Lett.* **2005**, *7*, 1347. (d) Singh, R.; Kissling, R. M.; Letellier, M.-A.; Nolan, S. P. *J. Org. Chem.* **2004**, *69*, 209.

(6) (a) Nair, V.; Bindu, S.; Sreekumar, V.; Rath, N. P. *Org. Lett.* **2003**, *5*, 665. (b) Nair, V.; Sreekumar, V.; Bindu, S.; Suresh, E. *Org. Lett.* **2005**, *7*, 2297.

(7) Ma, C.; Yang, Y. *Org. Lett.* **2005**, *7*, 1343.

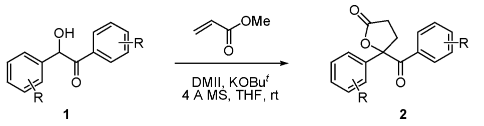
10.1021/ol051422m CCC: $30.25

Scheme 1. Reaction of Benzoin with Methyl Acrylate Catalyzed by Imidazolin-2-ylidene



dimethyl imidazolin-2-ylidene (20 mol %) generated in situ by deprotonating 1,3-dimethylimidazolium iodide (DMII) with an appropriate base. As the original objective, we speculated that an equilibrium-driven, tandem retro-benzoin condensation/Stetter reaction would take place to furnish 1,4-ketoester **A**. As a matter of fact, when potassium *tert*-butoxide was chosen as a base and the reaction was run in THF containing 4 Å molecular sieves (MS) at room temperature for 6 h, a formal [3 + 2] cyclization product, γ-benzoyl-γ-phenyl-γ-butyrolactone[8] (**2a**), was formed in 76% yield. The 1,4-ketoester **A** was not isolable at all. Simply switching the base from potassium *tert*-butoxide to sodium hydride caused the chemical yield to drop to 65% after the mixture was allowed to react for 8 h. In contrast, with triethylamine used as the base, no desirable γ-butyrolactone product was generated after 10 h of stirring in THF or dichloromethane as the solvent. The presence of 4 Å MS seemed to exert a favorable effect on the NHC-mediated formal [3 + 2] cyclization. With potassium *tert*-butoxide as the base, the γ-lactone was afforded in only 53% (10 h) in the absence of 4 Å MS. Furthermore, the presence of DMII was found to be crucial for the formal [3 + 2] cyclization since potassium *tert*-butoxide or sodium hydride alone could not drive the transformation to proceed, which indicated that the NHC might be the catalytic species required for the tandem reaction. This was further confirmed by the fact that no reaction occurred even after 12 h at room temperature in the presence of DMII without addition of potassium *tert*-butoxide or sodium hydride. On the basis of our experimental results, we tend to believe that the role of DMII should not be merely to provide a counterion. It is also noteworthy that an excess of methyl acrylate (20 equiv) was introduced into the system in order to ensure a reasonably clean transformation by inhibiting possible side reactions.

Table 1. Reaction of Various Benzoins with Methyl Acrylate Catalyzed by Imidazolin-2-ylidene[9]



entry	R	time (h)	product	yield[a] (%)
1	H	6	**2a**[8a,8b]	76
2	*p*-Br	8	**2b**	65
3	*o*-Cl	8	**2c**	60
4	*m*-Cl	8	**2d**	72
5	*p*-Cl	8	**2e**	67
6	*p*-F	8	**2f**[8b]	70
7	*m*-Me	8	**2g**	62
8	*p*-Me	8	**2h**	60
9	*p*-MeO	44	**2i**[8b]	32

[a] Isolated yield.

To examine the generality of the methodology, another eight benzoin substrates were scrutinized (Table 1). The following observations have been made. (i) The benzoins with substituents of F, Cl, Br, or Me on the phenyl rings gave the γ-butyrolactone products in similar and moderate yields (60−72%, entries 2−8) that were slightly lower than those given by the parent molecule benzoin itself (76%, entry 1). The substitution pattern on the phenyl rings apparently affects the reaction to some extent. With the same substituent of Cl on the phenyl rings, the chemical yields of the products were discovered to be slightly different and seemed to follow a trend of *o*- < *p*- < *m*- (entries 3−5). A similar trend was observed with methyl-substituted benzoins as well (*p*- < *m*-, entries 7 and 8). (ii) In the case of 4,4′-dimethoxybenzoin, the transformation was rather sluggish, and the corresponding γ-butyrolactone was afforded in only 32% yield after prolonged reaction time (44 h, entry 9). (iii) The reaction seems to be very sensitive to the identity of the Michael acceptors. Replacement of methyl acrylate with methyl methacrylate (**3**), crotonate (**4**), or cinnamate (**5**) resulted in no formation of the corresponding γ-butyrolactones (Figure 1).

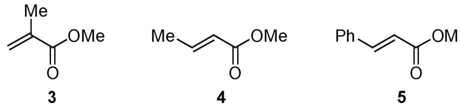


Figure 1.

At this stage, the precise reaction mechanism for the current efficient transformation remains puzzling to us. As

---

[8] Ruthenium carbonyl-mediated cycloaddition was reported to lead to the same γ-butyrolactone. See: (a) Chatani, N.; Tobisu, M.; Asaumi, T.; Fukumoto, Y.; Murai, S. *J. Am. Chem. Soc.* **1999**, *121*, 7160. (b) Tobisu, M.; Chatani, N.; Asaumi, T.; Amako, K.; Ie, Y.; Fukumoto, Y.; Murai, S. *J. Am. Chem. Soc.* **2000**, *122*, 12663.

[9] **General Procedure.** A mixture of 1,3-dimethylimidazolium iodide (0.22 mmol) and potassium *tert*-butoxide (0.2 mmol) in THF (4 mL) was stirred at room temperature under N_2 for 45 min [Note: The reaction time (45 min) for carbene generation was consistent with those reported in the literature. The carbene species are reportedly quite stable, and some of them are actually isolable. See: (i) Ref 5a. (ii) Arduengo, A. J., III; Dias, H. V. R.; Harlow, R. L.; Kline, M. *J. Am. Chem. Soc.* **1992**, *114*, 5530. (iii) Burstein, C.; Glorius, F. *Angew. Chem., Int. Ed.* **2004**, *43*, 6205]. Then, 4 Å MS (500 mg), benzoin (1 mmol), and methyl acrylate (1.8 mL, 20 mmol) were added, and the resulting mixture was stirred for the indicated time. The reaction mixture was passed through a short pad of Celite, and the solvent was evaporated under reduced pressure to afford a residue that was purified by flash column chromatography on silica gel to give the product.

Scheme 2

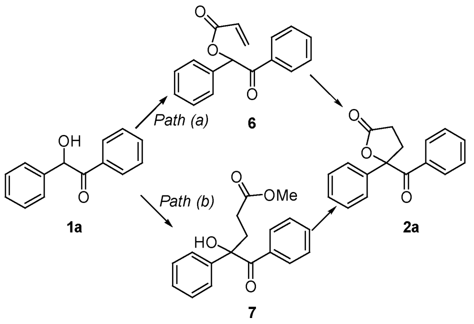
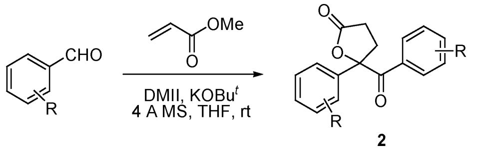


Table 2. Reaction of Various Aromatic Aldehydes with Methyl Acrylate Catalyzed by Imidazolin-2-ylidene[10]



entry	R	time (h)	product	yield[a] (%)
1	H	6	**2a**[8a,8b]	72
2	*p*-Br	8	**2b**	54
3	*o*-Cl	8	**2c**	45
4	*m*-Cl	8	**2d**	65
5	*p*-Cl	8	**2e**	60
6	*p*-F	8	**2f**[8b]	59
7	*m*-Me	8	**2g**	56
8	*p*-Me	8	**2h**	53
9	*p*-MeO	44	**2i**[8b]	27

[a] Isolated yield.

outlined in Scheme 2, the γ-butyrolactone formation might result either from tandem transesterification/intramolecular Michael addition (path a, via intermediate **6**) or from tandem Michael addition/lactonization realized by intramolecular transesterification (path b, via intermediate **7**). The isolation of **6** and/or **7** would be highly useful for us to gain certain detailed mechanistic insights into the current methodology. However, this attempt has not proved to be successful so far despite our active endeavors.

Since NHC species are known to catalyze benzoin condensation,[3] we next turned our attention to probing the feasibility of directly converting benzaldehydes into γ-butyrolactones in the presence of 1,3-dimethyl imidazolin-2-ylidene and methyl acrylate. To our delight, benzaldehyde and its derivatives could indeed give rise to γ,γ-difunctionalized γ-butyrolactones presumably via initial benzoin formation followed by the above-mentioned tandem reaction. Although the chemical yields (45−72%, except a 27% yield obtained for 4-methoxybenzaldehyde as the starting material) were found to be somewhat lower than those of the corresponding transformations from benzoins (Table 2), the overall synthetic efficiency was further enhanced. The lowered yields might be accounted for in part by the fact that 6−18% of unreacted benzaldehydes could be recovered and 4−20% of benzoins could be isolated as well.

In summary, we have described a one-step assembly of γ,γ-difunctionalized γ-butyrolactones from benzoins or benzaldehydes via a tandem reaction promoted by 1,3-dimethyl imidazolin-2-ylidene that showcased the unique utility of N-heterocyclic carbene species. Our direct, efficient, NHC-mediated protocol should find applications in organic synthesis.

Acknowledgment. We thank NSFC (No. 20372073), STCSM ("Venus" Program, No. 02QB14058), Ministry of Human Resources of PRC, and Bureau of Tobacco of PRC for financial support.

Supporting Information Available: Spectroscopic characterization of compounds **2b**−**e**,**g**,**h**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL051422M

---

(10) **General Procedure.** A mixture of 1,3-dimethyl-imidazolium iodide (0.22 mmol) and potassium *tert*-butoxide (0.2 mmol) in THF (4 mL) was stirred at room temperature under N_2 for 45 min. Benzaldehyde (1.0 mmol) was added, and the resulting mixture was stirred for 3 h. Then, 4 Å MS (500 mg) and methyl acrylate (0.90 mL, 10 mmol) were added, and the reaction mixture was stirred for the indicated time. The reaction mixture was passed through a short pad of Celite, and the solvent was evaporated under reduced pressure to afford a residue that was purified by flash column chromatography on silica gel to give the product.