Organic & Biomolecular Chemistry

Dynamic Article Links

Cite this: *Org. Biomol. Chem.*, 2011, **9**, 6484

www.rsc.org/obc

COMMUNICATION

Highly stereoselective synthesis of tetrasubstituted alkenes *via* hydroamination of alkynes and C–H acetoxylation†

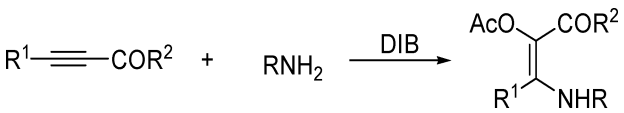
Weibing Liu,* Cui Chen and Qing Zhang

Received 14th June 2011, Accepted 13th July 2011
DOI: 10.1039/c1ob05958k

A novel reaction including the sequence of hydroamination of alkynes and subsequent oxidative C–H bond functionalization has been developed in the presence of diacetoxyiodobenzene (DIB). The method allows us to synthesize a wide range of tetrasubstituted (*E*)-alkenes and provides a potential method to construct densely functionalized carbonyl compounds.

Tandem C–C, C–hetero bond formation leading to useful molecular structures is one of the most interesting and challenging research topics in organic chemistry.[1] Indeed, direct oxidative C–H bond functionalization provides an atom-economical and efficient pathway to achieve these goals. Representative examples have been elegantly utilized not only in abundant academic research studies, but also in the production of a variety of fine chemicals, such as pharmaceuticals, agrochemicals, and intermediates.[2] Notably, hypervalent iodine compounds, serving as mild and chemoselective oxidants, have received significant attention from chemists in recent years owing to their environmentally benign nature and ready availability;[3] furthermore, considering the high toxicity of metal oxidants, such as Pb(IV), Tl(III), and Hg(II),[4] hypervalent iodine reagents are considered as attractive alternatives to those toxic metal oxidants, and they have been widely applied in synthetic organic chemistry in oxidative couplings to form novel C–C, C–O, and C–N bonds.[5] Recently, we observed a notable outcome including hydroamination of an alkyne and subsequent diacetoxyiodobenzene (DIB) mediated C–H bond acetoxylation, representing an example to construct new tetrasubstituted (*E*)-alkenes (Scheme 1). Interestingly, a further oxidative C–H bond alkoxylation leading to the formation of densely functionalized β-imino ketones was also disclosed, when alcohol was introduced into the reaction system. The structures of product **3aa** and **5** have been confirmed by ^{1}H NMR, ^{13}C NMR and NOE.[6]

Initially, we tried to establish an effective reaction system based on the above-mentioned transformation. A brief optimization concerning the effects of several organic solvents, temperature and time on the model reaction was carried out (see the ESI†). The best result was obtained in CH_2Cl_2 in the presence of 1.2 equivalent of DIB at 0 °C for overnight.



Scheme 1 The synthesis of tetrasubstituted (*E*)-alkenes.

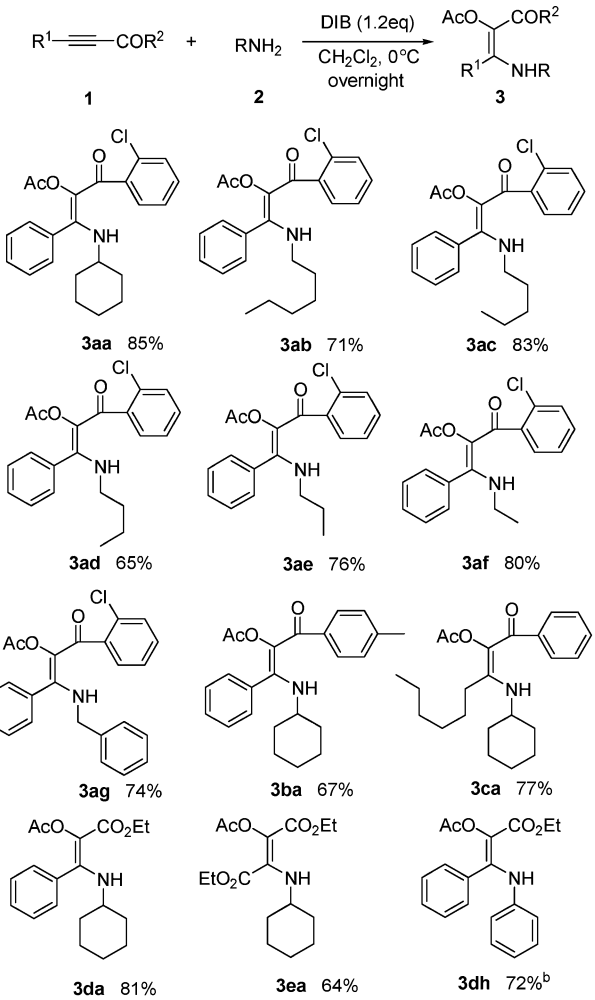
To explore the substrate scope and limitations of this reaction, a range of electron-deficient alkynes, including alkynones and alkynoates, and primary alkylamines were then examined under the optimized reaction conditions. As shown in Scheme 2, all of the reactions proceeded smoothly and gave the (*E*)-tetrasubstituted alkenes exclusively in good to excellent isolated yields. It was found that the electronic property of the substituents on the alkynes has little effect on the reaction efficiency (**3aa–3ea**). In general, alkylamines react more readily with electron-deficient alkynes under the optimized reaction conditions as compared to arylamines. Thus, *N*-alkylated alkenes could be effectively prepared. However, the reaction between electron-deficient alkynes and arylamines failed to result in the corresponding alkene products. These results are attributed to the enhanced nucleophilicity of alkylamines, which favors hydroamination of the alkynes and the formation of tetrasubstituted alkenes, and is consistent with the mechanistic proposal.

Although arylamines were inert under the standard reaction conditions, earlier reported literature showed that cationic silver salts can effectively promote the hydroamination of alkynones and alkynoates to form enamines.[7] Enlightened by these elegant examples, an arylamine was then employed as a coupling partner and was expected to form *N*-arylated alkene products. The catalytic system of $AgBF_4$ (5 mol%)/L-proline(5 mol%) was utilized in the reaction of ethyl 3-phenylpropiolate and aniline in CH_2Cl_2. The resulting mixture was stirred at room temperature for 30 min, and 1.2 equivalent of DIB was then introduced into the reaction system at 0 °C and stirred overnight. Gratifyingly, the result showed that this sequential one-pot reaction proceeded smoothly and afforded the expected product (*E*)-ethyl 2-acetoxy-3-phenyl-3-(phenylamino)acrylate (**3dh**) in 72% isolated yield.

Interestingly, β-imino ketones containing a quaternary α-carbon atom were efficiently obtained when methanol was introduced into the reaction system. For example, the reaction

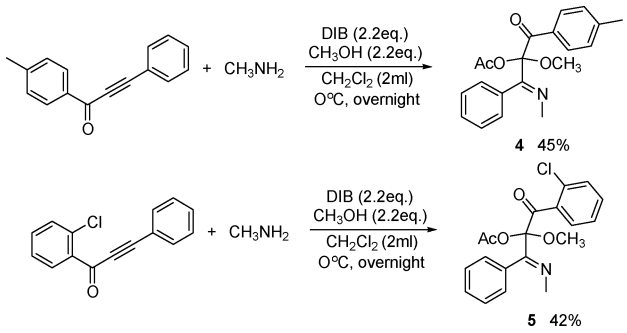
School of Chemistry and Life Science, Guangdong University of Petrochemical Technology, 139 Guangdu Two Road, Maoming 525000, P. R. China. E-mail: lwb409@yahoo.com.cn; Fax: +86-668-2923575; Tel: +86-668-2923956

† Electronic supplementary information (ESI) available: Full experimental details, and copies of NMR spectral data. See DOI: 10.1039/c1ob05958k

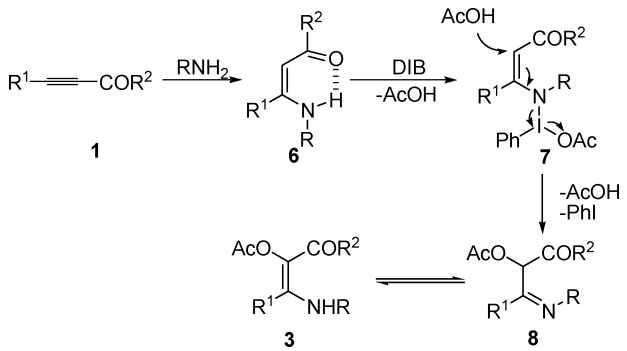


[a] All the reactions are carried out using 1.0 mmol of **1**, 1.0 mmol of **2** in CH_2Cl_2 (2.0 mL) at 0 °C overnight and the isolated yields are listed; [b] Reaction conditions: $AgBF_4$(5 mol %)/L-proline (5 mol %), DIB (1.2 equiv.).

Scheme 2 Synthesis of tetrasubstituted (*E*)-alkenes from alkynes and amines.[a]



Scheme 3 The synthesis of (*E*)-imines.



Scheme 4 A mechanistic rationale for the additive–oxidative reaction.

of methylamine with 3-phenyl-1-*p*-tolylprop-2-yn-1-one or 1-(2-chlorophenyl)-3-phenylprop-2-yn-1-one in the presence of DIB (2.2 equiv.) and CH_3OH (2.2 equiv.) in CH_2Cl_2 (2 mL) at 0 °C for overnight resulted in imine **4** or **5** in moderate isolated yield (Scheme 3). The formation of the unexpected products is the result of further DIB-mediated oxidation and C–H bond methoxylation of the tetrasubstituted alkene. Obviously, this tandem reaction is potentially valuable for the synthesis of densely functionalized β-imino ketones and chiral amino acid derivatives.

A plausible mechanism for this transformation is shown in Scheme 4. The reaction initiates with the formation of (*Z*)-enamine **6** through hydroamination of the alkyne and the effect of intramolecular hydrogen bond.[7] The nucleophilic nitrogen atom of **6** interacts with the electrophilic iodine(III) of $PhI(OAc)_2$, to form intermediate **7** by eliminating one equivalent of acetic acid.[8] Subsequent N–I bond cleavage, along with nucleophilic attack of acetic acid on the C–C double bond, affords imine **8** by eliminating one molecule of iodobenzene and one molecule of acetic acid. Finally, the desired product **9** is produced after isomerization of **8** to the more stably conjugated enamine form.

In summary, we have developed a facile and highly efficient reaction to synthesize tetrasubstituted (*E*)-alkenes by a sequence of hydroamination of an alkyne, DIB-mediated oxidative C–H bond acetoxylation and isomerization. Also this reaction can be further employed to construct densely functionalized β-imino ketones and provides the potential to access new amino acid derivatives in the presence of alcohols. Further investigations concerning the scope of this tandem reaction, applications, and mechanistic details are currently ongoing in our laboratory and will be published in due course.

References

1 (*a*) M. Fagnoni, D. Dondi, D. Ravelli and A. Albini, *Chem. Rev.*, 2007, **107**, 2725; (*b*) E. M. Beccalli, G. Broggini, M. Martinelli and S. Sottocornola, *Chem. Rev.*, 2007, **107**, 5318; (*c*) X. F. Tong, M. Beller and M. K. Tse, *J. Am. Chem. Soc.*, 2007, **129**, 4906; (*d*) J. J. Niu, H. Zhou, Z. G. Li, J. W. Xu and S. J. Hu, *J. Org. Chem.*, 2008, **73**, 7814; (*e*) J. M. Lee, E. J. Park, S. H. Cho and S. Chang, *J. Am. Chem. Soc.*, 2008, **130**, 7824; (*f*) S. Ueda and H. Nagasawa, *J. Org. Chem.*, 2009, **74**, 4272; (*g*) Z. D. Liang, W. Z. Hou, Y. F. Du, Y. L. Zhang, Y. Pan, D. Mao and K. Zhao, *Org. Lett.*, 2009, **11**, 4978; (*h*) Y. Peng, L. Cui, G. Z. Zhang and L. M. Zhang, *J. Am. Chem. Soc.*, 2009, **131**, 5062; (*i*) T. Mizuhara, S. Oishi, N. Fujii and H. Ohno, *J. Org. Chem.*, 2010, **75**, 265.

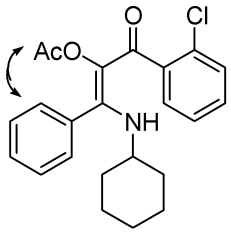
2 (*a*) D. I. Enache, J. K. Edwards, P. Landoin, B. Solsona-Espriu, A. F. Carley, A. A. Herzing, M. Watanabe, C. J. Kiely, D. W. Knight and G. J. Hutchings, *Science*, 2006, **311**, 362; (*b*) J. Piera and J. E. Backvall, *Angew. Chem., Int. Ed.*, 2008, **47**, 3506.

3 (*a*) M. A. Ciufolini, N. A. Braun, S. Canesi, M. Ousmer, J. Chang and D. Chai, *Synthesis*, 2007, 3759; (*b*) A. J. Canty, T. Rodemann and J. H. Ryan, *Adv. Organomet. Chem.*, 2008, **5**, 279; (*c*) S. Quideau, L. Pouys egu and D. Deffiieux, *SynLett.*, 2008, **467**; (*d*) V. V. Zhdankin and P. J. Stang, *Chem. Rev.*, 2008, **108**, 5299.

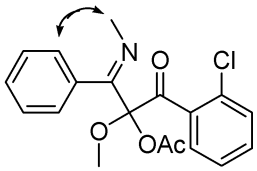
4 R. M. Moriarty, *J. Org. Chem.*, 2005, **70**, 2893; T. Wirth, *Angew. Chem., Int. Ed.*, 2005, **44**, 3656.

5 (*a*) T. Dohi, A. Maruyama, Y. Minamitsuji, N. Takenaga and Y. Kita, *Chem. Commun.*, 2007, 1224; V. V. Zhdankin and P. J. Stang, *Chem. Rev.*, 2008, **108**, 5299; (*b*) T. Dohi and Y. Kita, *Chem. Commun.*, 2009, 2073; (*c*) M. Uyanik and K. Ishihara, *Chem. Commun.*, 2009, 2086; (*d*) H. Ghosh and B. K. Patel, *Org. Biomol. Chem.*, 2010, **8**, 384; (*e*) J. Y. Wang, S. P. Liu and W. Yu, *Synlett*, 2009, 2529; (*f*) I. Papoutsis, s. Spyroudis and A. Varvoglis, *Tetrahedron*, 1998, **54**, 1005; (*g*) A. Liguori, R. Ottana, G. Romeo, G. Sindona and N. Uccella, *Heterocycles*, 1988, **27**, 1365; (*h*) A. R. Thornton, V. I. Martin and S. B. Blakey, *J. Am. Chem. Soc.*, 2009, **131**, 2434; (*i*) Y. Chen, T. Ju, J. W. Wang, W. Q. Yu, Y. F. Du and K. Zhao, *Synlett*, 2010, 231.

6 The configuration of the 1,2-diheteroatom-substituted (*E*)-alkenes was further confirmed by NOE studies on compound **3aa** and **5**:.



3aa



5

7 H. Cao, X. J. Wang, H. F. Jiang, Q. H. Zhu and M. Zhang, *Chem.–Eur. J.*, 2008, **14**, 11623.

8 (*a*) D. S. Bose and M. Idrees, *J. Org. Chem.*, 2006, **71**, 8261; (*b*) A. Correa, I. Tellitu, E. Domínguez and R. SanMartin, *J. Org. Chem.*, 2006, **71**, 3501; (*c*) S. Serna, I. Tellitu, E. Domínguez, I. Moreno and R. SanMartín, *Org. Lett.*, 2005, **7**, 3073.