Light promoted aqueous phase amine synthesis via three-component coupling reactions

Lina Zhang a,b, Youquan Deng a, Feng Shi a,⇑

a Center for Green Chemistry and Catalysis, Lanzhou Institute of Chemical Physics, CAS, Lanzhou 730000, China
b University of the Chinese Academy of Sciences, Beijing 100049, China

A R T I C L E   I N F O

Article history:
Received 29 April 2013
Revised 3 July 2013
Accepted 11 July 2013
Available online 17 July 2013

Keywords:
Amine
Imine
Heterogeneous catalysis
Light

A B S T R A C T

By applying a simple TiO2–(NH4)2S2O8 system and promoted by UV light, the three-component reactions of cyclic ether, aniline and aldehyde can be progressed efficiently. 29 substituted amines with different structures were synthesized with up to 97% isolated yields. Isotope effect study revealed that the rate-determining step might be the nucleophilic addition step but not radical generation.

© 2013 Elsevier Ltd. All rights reserved.

The selective C–H bond functionalization is one of the fundamental problems in chemistry. 1 Due to the stability of C–H bond, especially the unactivated sp3 C–H bond, the pre-functionalization is necessary in order to realize the selective transformation reactions, which results in low atomic efficiency and serious environmental pollution. The development of a new catalyst to realize the selective transformation of C–H bond under mild reaction conditions will undoubtedly be interesting in the synthesis of many functional substrates. The application of transition metal catalyst is an efficient method to carry out the C–H bond activation. 1 Normally, the transition metal can react with C–H bond to produce C–M bond and it can be selectively transformed into desired product. In the last years, a variety of catalytic C–H bond activation processes have been developed with excellent performance.

Except the catalytic activation of C–H bond via the formation of C–M bond, the C–H bond activation through the formation of radical is also an attractive route. 2 Since 1980s the radical chemistry based synthetic methods have been studied extensively, which is strictly related to the development of new radical precursors. Therefore, the discovery of a specific radical initiator for a specific reaction is one of the major tasks for researchers in order to find a valuable synthetic method. In the last decades, many radical initiators such as azo compounds or peroxides, 3 samarium iodide, 4 triethylborane, 5 hexabutylditin, 6 indium 7 and dimanganese decacarbonyl 8 have been reported and many good results were obtained. Recently, great progresses have been achieved in the catalytic addition of RX, 9 HCONH2, 10 olefins 11 and Mitsunobu’s reagent 12 to imines. Besides the reactions discussed above, the selective addition of cyclic ethers to C=N bond is one of the challenging reactions in this field. About this transformation, 13–17 good results were obtained under ionizing radiation 13 or in the presence of large excess of Me2Zn, 14,15 TiCl4/PhN2 2b,c,17 as radical initiator. Undoubtedly, the usage of large excess of radical initiators is one of the big disadvantages of the radical based synthetic method. It makes the reaction complicated and difficult for the treatment of the reaction. Meanwhile, the generality of the methodology is usually limited and the selectivities to the desired products are not good enough. It would be an ideal choice if a clean, economic and general method can be developed for this transformation. Herein, we would like to present our new results about the light promoted activation of cyclic ether and its application in the three-component coupling reactions with aldehydes and anilines. The reaction was initiated with TiO2–(NH4)2S2O8 and promoted by UV-light.

The catalytic performance of this system was first explored using the reaction of p-toluidine, benzaldehyde and 1,4-dioxane as model reaction. Table 1. Clearly, the combination of TiO2 and UV is essential to gain the selective transformation of the three-component reaction. The desired product 3a was not detectable in the absence of TiO2, entry 1. The three-component reaction can progress well if a suitable amount of TiO2 was added and the selectivity to 3a increased to 66%, entry 2. The addition of water as co-solvent is indispensable to realize the transformation. Almost no nucleophilic addition product of 1,4-dioxane was observed under water free condition, entry 3. As a radical initiator is extensively used, the applying...
of (NH₄)₂S₂O₈ as co-catalyst can promote the reaction significantly. The selectivity of 3a was 97% and (E)-N-benzyldiene-4-toluidine was observed as byproduct. Meanwhile, the isolated yield of 3a was 86%, entries 4 and 5. Moreover, other sulfate and sulfide inorganic salts as co-catalysts were also studied but no better result was obtained, entries 6–9. It is noteworthy, as a classical combination for radical generating, the co-addition of (NH₄)₂S₂O₈ and NaHSO₃ was tested, too, and a similar result as (NH₄)₂S₂O₈ itself as co-catalyst was observed, entry 10. Thus, according to the above results, it can be concluded that the applying of TiO₂ is indispensable for the three-component reaction. Meanwhile, (NH₄)₂S₂O₈ as co-catalyst can promote the reaction.

Next, the generality of this system was explored. (Scheme 1). Initially, aniline and benzaldehyde as starting materials were tried and 3c as the major product was obtained with 89% yields. Similar yield, that is 87%, to the desired product 3b was obtained if the p-MeO group was incorporated into benzaldehyde. p-Toluidine also exhibited nice reactivity and 72–86% yields to 3d and 3e were obtained in the reactions with benzaldehyde, p-Me benzaldehyde or p-methoxybenzaldehyde and 1,4-dioxane. The use of m-substituted starting materials does not affect the reactivity significantly. For example, 88% and 85% isolated yields of 3f and 3g were obtained if m-toluidine was used and reacted with benzaldehyde and p-methoxybenzaldehyde. When p-methoxyaniline was employed to react with benzaldehyde and p-methoxybenzaldehyde, 71–80% yields to the 3h and 3i can be achieved. However, the yield to 3j was only 46%. The incorporation of halide substituents into the nucleophilic addition reaction should be interesting because the presence of active C–X bonds is helpful to extend their applications in the synthesis of other compounds. Here, a series of chloro and bromo functionalized aniline derivatives as starting materials were tested. To our delight, they can react with benzaldehyde and 1,4-dioxane smoothly and 3k–3r can be synthesized with up to 97% isolated yields. It should be mentioned that the dr ratios in all the products were close to 45:55. When o-toluidine was used as starting material, the selectivity to the aim product was 74% determined by GC-FID. However, we still do not get the pure products now.

This system is also very efficient in the three-component reactions of 1,3-dioxolane with different aniline and aldehyde derivatives, (Table 2). Similar as the three-component reactions using 1,4-dioxane, aniline and benzaldehyde derivatives with different substituting groups can be used as the starting materials and the yields to products 4a–4j were 65–93%, entries 1–10. The dr ratios of products using 1,3-dioxolane as nucleophile were all close to 15:85.

Except the syntheses of compounds 3 and 4 discussed above, THF can be used as nucleophile for the three-component reaction and the yield to 5a was 58%. It should be mentioned that the dr ratio of 5a was 47:53. If o-toluidine was used as starting material, the reaction can also be carried out and the selectivity to the aimed product was 59% determined by GC-FID.

Following, the isotope effect study was employed to explore the mechanism of the reaction, (Scheme 2). Clearly, there are four steps involved in the nucleophilic addition of THF to imine. It is the reaction of benzaldehyde and p-toluidine to form imine (step 1), radical generation (step 2), nucleophilic addition of radical to imine (step 3) and formation of amine product (step 4), respectively. Among the four steps, step 1 and step 4 should not be the rate determining steps because relatively a large amount of imine can be synthesized. Step 2, that is the generation of THF radical, is the rate-determining step but it cannot be confirmed at this stage. Moreover, the ratio of d₅-5a to d₆-5a is 6.15:1. That means the major deuterated product is d₅-5a, which shows remarkable proton exchange in the presence of water as solvent.

In summary, a simple and efficient method for the three-component reactions of aldehyde, amine and cyclic ethers was developed. Several imines are used as starting materials for the nucleophilic addition reaction.
Three-component reaction of 1,3-dioxolane with aniline and benzaldehyde derivatives

<table>
<thead>
<tr>
<th>Entry</th>
<th>R1</th>
<th>R2</th>
<th>Isolated yields (%) (a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H (1a)</td>
<td>p-MeO (2b)</td>
<td>87% (dr = 14:86) (4a)</td>
</tr>
<tr>
<td>2</td>
<td>H (1a)</td>
<td>p-MeO (2b)</td>
<td>84% (dr = 14:86) (4b)</td>
</tr>
<tr>
<td>3</td>
<td>m-Me (1b)</td>
<td>H (2a)</td>
<td>78% (dr = 14:86) (4c)</td>
</tr>
<tr>
<td>4</td>
<td>m-Me (1b)</td>
<td>p-MeO (2b)</td>
<td>93% (dr = 14:86) (4d)</td>
</tr>
<tr>
<td>5</td>
<td>p-MeO (1c)</td>
<td>H (2a)</td>
<td>71% (dr = 15:83) (4e)</td>
</tr>
<tr>
<td>6</td>
<td>p-MeO (1c)</td>
<td>p-Me (2c)</td>
<td>78% (dr = 14:86) (4f)</td>
</tr>
<tr>
<td>7</td>
<td>p-MeO (1c)</td>
<td>p-MeO (2b)</td>
<td>65% (dr = 11:89) (4g)</td>
</tr>
<tr>
<td>8</td>
<td>p-Cl (1d)</td>
<td>p-MeO (2b)</td>
<td>75% (dr = 15:85) (4h)</td>
</tr>
<tr>
<td>9</td>
<td>m-Br (1e)</td>
<td>p-MeO (2b)</td>
<td>73% (dr = 19:81) (4i)</td>
</tr>
<tr>
<td>10</td>
<td>m-Br (1e)</td>
<td>p-Me (2c)</td>
<td>75% (dr = 19:81) (4j)</td>
</tr>
</tbody>
</table>

* a 0.2 mmol amine, 0.3 mmol aldehyde, 2.5 mL 1,3-dioxolane, 2.5 mL H2O, 0.25 mmol TiO2 (P25), 6 mg (NH4)2S2O8, UV (365 nm LED), argon, rt, 10 h. Diastereomer ratios are given in parenthesis following the yields.

**Scheme 2.** Isotope competition reactions of THF and d7-THF.

- step 1: 1a-e + NH2
- step 2: [cat-H] + [cat-D]
- step 3: 2a-c + 2a-c
- step 4: 4a-j

Scheme 2. Isotope competition reactions of THF and d7-THF.

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.07.060.

**Acknowledgments**

This work was financially supported by the National Natural Science Foundation of China (21073208) and the Chinese Academy of Sciences.

**References and notes**