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Communication

Hetero diacylation of 1,1-diborylalkanes: Practical synthesis of 1,3-diketones

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ABSTRACT

An efficient protocol for the synthesis of asymmetric 1,3-diketones was reported through diacylation of 1,1-diborylalkanes using two different acyl sources. In this transformation, an enolate boron species was initially formed by introducing an acyl group, then it was trapped by another acyl group to form 1,3-diketone. This method not only provided the gateway to obtain a series of 1,3-diketones, but also afforded an operationally simple and efficient access to pyrazoles and isoxazoles.

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Many natural products containing 1,3-diketone moiety exhibit broad biological activities, such as antimicrobial, antiviral, and antifungal activities [1]. They can also act as bidentate ligands in metal catalysis and luminescent materials [2,3]. Besides, 1,3-diketones are widely used as versatile synthons for the construction of various heterocycles [1,4–6] or C—C bond formation [7–15]. Therefore, considerable efforts have recently been devoted to the synthesis of this useful scaffold [1,4]. So far, several strategies have been developed for the synthesis of 1,3-diketones, including (a) Enolate strategy (Scheme 1a) [16–22], (b) Umpolung strategy (Scheme 1b) [23–25], and (c) carbonylation of ketones (Scheme 1c) [26]. Despite these advances, there are still some important challenges, such as the requirement of multistep preparation of precursors, the use of toxic or expensive reagents, and limited substrate scope, that need to be addressed for the synthesis of 1,3-diketones. Hence, the development of new and efficient protocols in which such challenges can be overcome are of great significance in synthetic organic chemistry.

1,1-Diborylalkanes, as a linkage with two binding sites, have attracted increasing attention due to their significant application in mono- or difunctionalization and the fact that they can be employed as a good platform molecule for bifunctional transformation [27]. However, the difunctionalization of the two C—B bonds of 1,1-diborylalkanes is still underdeveloped [27]. Usually, this transformation is realized through cross-coupling reactions under transition metal catalyzed conditions [28–35]. Furthermore, the 1,1-diborylalkanes could be used in nucleophilic addition to carbonyl compounds for the synthesis of enolate boron species through the boron-stabilized carbanion intermediates. These enolate boron species acted as nucleophiles, which could be further trapped by another electrophile to build new chemical structures through the difunctionalization of 1,1-diborylalkanes [36]. Based on this concept, our group recently first introduced carboxylic acid as an acyl synthon to form an enolate boron species, followed by trapping with various electrophiles to build ketones [37]. We reasoned that 1,3-diketones could be formed when the enolate boron species were formed, in combination with the insertion of another acyl source. Herein, we report an efficient protocol for the synthesis of asymmetric 1,3-diketones through diacylation of 1,1-diborylalkanes using two different acyl sources (Scheme 1d).

In our previous report, we developed a dual functionalization of α-monoboryl carbanions through deoxygenative enolization with carboxylic acids [37], in which the α-monoboryl carbanions was formed using CH_3Li to activate 1,1-diborylalkane, followed by addition to carboxylic acids, and then a new enolate boron specie was formed and trapped by another acyl source to afford 1,3-diketones. In this report, the substrate scope was extensively explored under the optimized reaction conditions. In the

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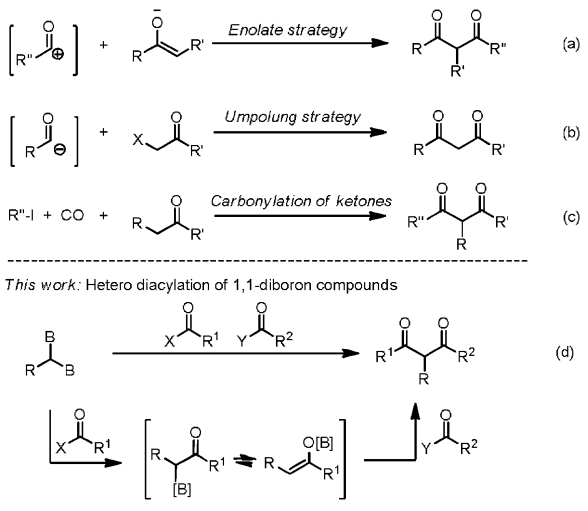


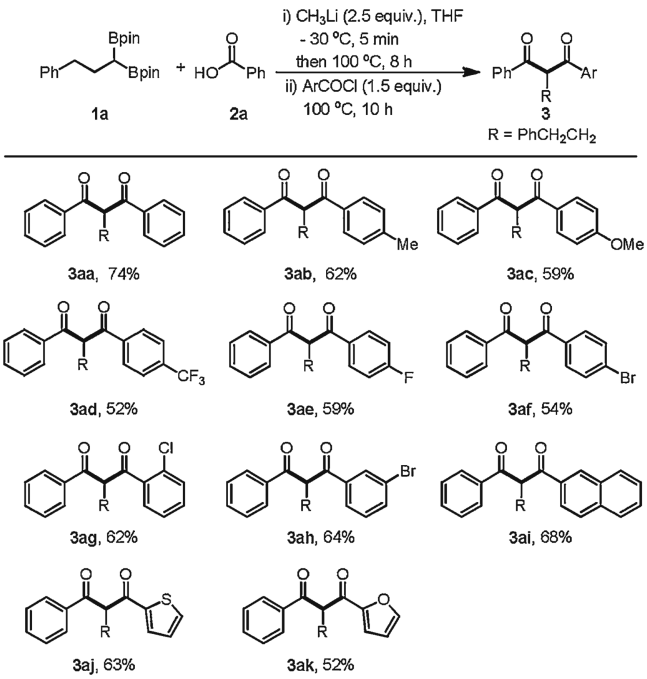
Scheme 1. General approaches to 1,3-diketones.

meanwhile, the application of 1,3-diketones was investigated to synthesize poly-substituted pyrazoles and isoxazoles. Firstly, in order to explore the generality of the reaction, a broad range of aromatic acyl chlorides were investigated under the optimized conditions and the results are summarized in Scheme 2. At first, product **3aa** was obtained in 74% yield. Substrates bearing electron-donating groups –Me and –OMe were also successfully employed in the reaction, providing the corresponding products **3ab** and **3ac** in 62% and 59% yields, respectively. For the substrates containing electron-withdrawing group $-CF_3$, and halogen –F, and –Br, the reaction also afforded products **3ad**-**3af** in good yields (52%, 59% and 54% yields, respectively). Next, the reaction was turned to other substrates with substituents *ortho*-Cl and *meta*-Br affording products **3ag** and **3ah** in 62% and 64% yields, respectively. Furthermore, the substrate bearing 2-naphthyl group also reacted well under the standard conditions, affording product **3ai** in 68% yield. Two heterocycle acyl chlorides were further investigated in the reaction, producing products **3aj** and **3ak** in 63% and 52% yields, respectively.

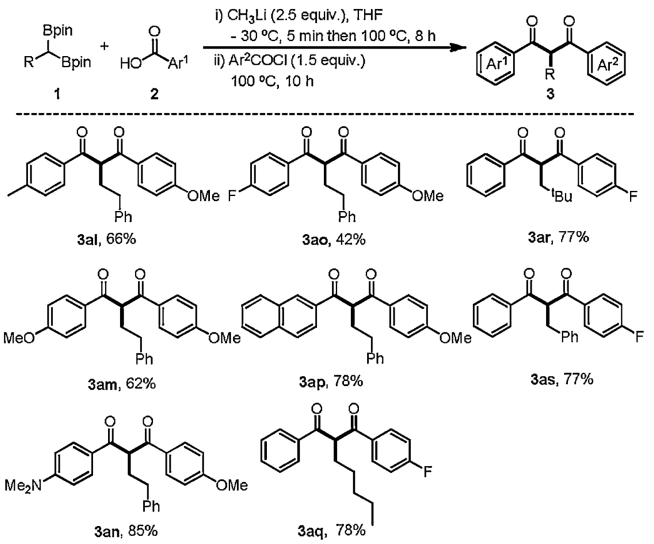
In order to further explore the scope of the reaction, a series of carboxylic acids were investigated and the results are summarized in Scheme 3. Functional groups, such as *p*-Me, *p*-OMe, *p*-NMe_2 and *p*-F, were well tolerated, providing the corresponding products **3al**-**3ao** in good yields. Furthermore, the substrate bearing naphthyl group was also successfully employed in the reaction, affording product **3ap** in 78% yield. Next, several other 1,1-diborylalkanes were then tested. These 1,1-diborylalkanes were easily accessed by our development on the *gem*-diborylation of aldehydes, ketones and carboxylic esters [38–40]. Benzoic acid was applied as the coupling partner, and 4-fluorobenzoyl chloride was used as the electrophilic trapping reagents to demonstrate the advantage of this method for the synthesis of various α-substituted 1,3-diketones. These alkyl and benzyl substituted 1,1-diborylalkanes were suitable for this transformation, affording the desired products in moderate to good yields (**3aq**, **3ar**, **3as**).

Having successfully developed an efficient method for the preparation of 1,3-diketones, we turned our focus on the utility of these compounds to access heterocyclic scaffolds [35,41–43]. A series of 1,3-diketones were reacted with hydrazine hydrate to produce trisubstituted pyrazoles and the results are summarized in Scheme 4. Generally, almost all the tested examples provided the corresponding products **4aa**-**4ah** in excellent yields. According to literature report, fast tautomerism of the 1*H*-pyrazoles generally occurred in $CDCl_3$ solution [44–46]. Therefore, no isomers were observed for those products and those products were presented in one form. Furthermore, phenylhydrazine was also successfully employed to react with **3aa**, affording terasubstituted pyrazole **5aa** in 78% yield (Scheme 5a). In the meanwhile, condensation of **3aa** with hydroxylamine led to the formation of the corresponding isoxazole **6aa** in 89% yield in the presence of iodine (Scheme 5b).

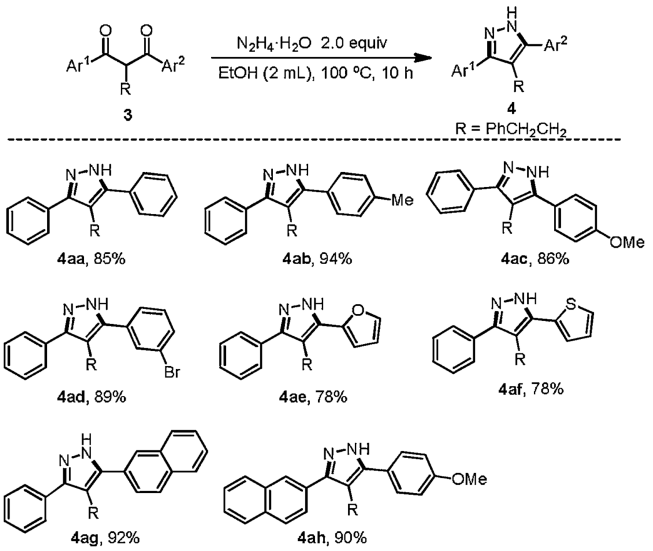
In conclusion, we developed a new method to synthesize various 1,3-diketones via the cross-coupling of 1,1-diborylalkanes and two different acyl sources. In the process, the inert carboxylic acids could be directly transformed to 1,3-diketones and many functional groups were well tolerated. Furthermore, these 1,3-



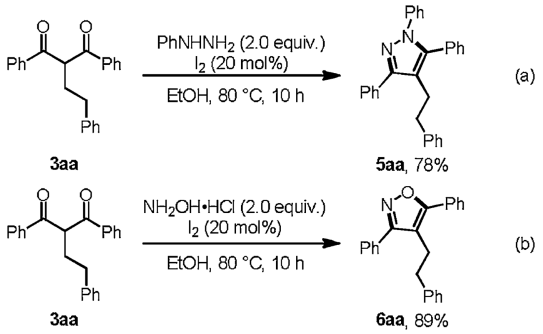
Scheme 2. Substrate scope of various acyl chlorides. Reaction conditions: (i) **1a** (0.375 mmol), **2a** (0.25 mmol), CH_3Li (0.625 mmol), THF (2.0 mL), −30 °C, 5 min then 100 °C, 8 h; (ii) ArCOCl (0.375 mmol), 100 °C, 10 h. Isolated yields of compound **3** were based on carboxylic acid.



Scheme 3. Substrate scope of various carboxylic acids and *gem*-diborylalkanes. Reaction conditions: (i) **1** (0.375 mmol), **2** (0.25 mmol), CH_3Li (0.625 mmol), THF (2.0 mL), -30 °C, 5 min then 100 °C, 8 h; (ii) *p*-$OMeC_6H_4COCl$ or *p*-FC_6H_4COCl (0.375 mmol), 100 °C, 10 h. Isolated yields of compound **3** were based on carboxylic acids.



Scheme 4. The synthesis of trisubstituted pyrazoles. Reaction conditions: **3** (0.25 mmol), $N_2H_4{\cdot}H_2O$ (0.5 mmol), EtOH (2.0 mL), 100 °C, 10 h. Yields based on isolated products.



Scheme 5. The condensation of 1,3-diketones with phenylhydrazine and hydroxylamine. Reaction conditions: **3aa** (0.25 mmol), $PhNNH_2$ or $NH_2OH{\cdot}HCl$ (0.5 mmol), I_2 (0.05 mmol), EtOH (2.0 mL), 80 °C, 10 h. Yields were obtained by isolating the pure products.

diketones have been successfully employed to construct pyrazoles and isoxazoles. Ongoing research, including further mechanistic details and expanding the substrate scope, are currently underway.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.cclet.2019.12.016.

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