

# Direct Use of Unprotected Aliphatic Amines to Generate N-Heterocycles via $\beta$ -C–H Malonylation with Iodonium Ylide

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**S** Supporting Information



ABSTRACT: An unprecedented method that enables the direct transformation of unprotected secondary aliphatic amines into functionalized N-heterocycles in the absence of transition metals was developed. The activation of these NH-free amines by the iodonium ylide induces a site-selective  $\beta$ -C-H malonylation process, allowing the construction of three  $\sigma$ -bonds and one  $\pi$ bond in a simple operation.

ransformation of amines is fundamentally important in broad chemical contexts, such as organic synthesis, pharmaceutical industries, and materials science. While the functionalization of inert  $C(sp^3)$ -H bonds of amines is a straightforward strategy, current methods are largely incompatible with unprotected aliphatic amines because they not only deactivate transition metals but also readily undergo deterioration under oxidative conditions.<sup>1</sup> In this context, the vast majority of established methods focused on the  $\alpha$ -C-H functionalization of tertiary amines (often N-aryl)<sup>2</sup> or protected cyclic amines (Figure 1a).<sup>1,3</sup> The second important strategy, transition-metal-mediated C-H functionalization, frequently involves the installation of a protecting or auxiliary group, converting a free amino group to an amide.<sup>4</sup> These tailored directing groups guide the C-H functionalization processes to take place at the  $\gamma$ - or  $\delta$ -position of amine derivatives via a 5- or 6-membered metallacyclic intermediate (Figure 1b). Other noteworthy strategies include the formation of a transient directing group<sup>5</sup> or the complexation of the amine to a Lewis or Brønsted acid.<sup>6</sup> The latter complexation deactivates the C-H bonds proximal to the nitrogen, thus directing functionalization of C-H bonds at more distal positions.

Despite these significant progresses made in the transformation of amines,  $\beta$ -functionalization of unprotected secondary aliphatic amines is rare yet remains an elusive problem. A more ideal solution to this problem is the direct  $\beta$ functionalization of unprotected aliphatic amines in the absence of transition metals. Although the presence of an N-H bond remarkably increases the challenge associated with this transformation, the further exploitation of the free-NH functionality could potentially transform aliphatic amines into N-heterocycles.

(a) α-position: tertiary aromatic amines or protected cyclic amines



Figure 1. Different strategies in the transformation of amines.

Recently, we found that iodonium ylides could react with aromatic amines to achieve N- and  $\alpha$ -functionalization reactions.<sup>8,9</sup> However, without an aromatic-ring-stabilized effect, the numerous attempts to use aliphatic amines in the presence of iodonium ylides are not successful,<sup>9</sup> probably owing to the difficulties in manipulating the highly unstable intermediates and differentiating multiple  $C(sp^3)$ -H bonds.

Received: November 24, 2019

Herein, we report an unprecedented transformation that directly generates functionalized N-heterocycles from unprotected secondary aliphatic amines via a  $\beta$ -C–H malonylation process (Figure 1c).

At the outset of our study, a model reaction of dicyclohexylamine and iodonium ylide was investigated (Table 1). Initially,

Table 1. Optimization of Reaction Conditions<sup>a</sup>

N H 1a	MeO <sub>2</sub> C CO <sub>2</sub> Me solvent, + I temperature Ph <sup>-1</sup> Ar	MeO <sub>2</sub> C CO <sub>2</sub> Me		D <sub>2</sub> Me CO <sub>2</sub> Me =O y
entry	solvent	$T(^{\circ}C)$	<i>t</i> (h)	yield ( <b>3a</b> %) <sup>b</sup>
1	DCM	40	12	<5
2	DCE	40	12	<5
3	THF	40	12	<5
4	CH <sub>3</sub> CN	40	12	<5
5	toluene	40	12	<5
6	CH <sub>3</sub> OH	40	12	<5
7	ethyl acetate	40	12	<5
8	1,4-dioxane	40	12	23
9 <sup>c</sup>	other solvents	40	12	<5
10	1,4-dioxane	rt	12	<5
11	1,4-dioxane	50	2.5	63
12	1,4-dioxane	70	0.4	71
13	1,4-dioxane	80	0.3	64
14 <sup>d</sup>	1,4-dioxane	70	0.4	64
15 <sup>e</sup>	1,4-dioxane	70	0.4	29

<sup>*a*</sup>Unless otherwise noted, all the reactions were carried out with 1a (0.3 mmol) and 2 (0.9 mmol) in 1.0 mL of solvent. <sup>*b*</sup>Isolated yield. <sup>*c*</sup>Et<sub>2</sub>O, *i*-PrOH, hexane, and DMF were used. <sup>*d*</sup>1.2 mmol of 2 was used. <sup>*e*</sup>0.6 mmol of 2 was used.

a range of different solvents were tested. The experimental results indicate that this reaction was quite dependent on solvent since 1,4-dioxane gave a promising result, while the desirable reaction did not proceed well in the other tested solvents (Table 1, entries 1-9). Then we evaluated the temperature effect on this cyclization reaction (Table 1, entries 10-13). The reaction can be significantly accelerated upon being conducted at an elevated temperature. For instance, the cyclization reaction was finished within 25 min at 70 °C, and the desirable product 3a was obtained in 71% yield (Table 1, entry 12). The further investigation of the concentration and amount of iodonium ylide (Table 1, entries 14-15) enabled the establishment of an optimal reaction condition. As the double bond of product 3a tends to isomerize to form 3a', 3a was converted to 3a' in the presence of a Brønsted acid, such as CH<sub>3</sub>SO<sub>3</sub>H, CF<sub>3</sub>SO<sub>3</sub>H, TsOH·H<sub>2</sub>O, and CF<sub>3</sub>CO<sub>2</sub>H, etc., in a range of frequently used solvents (see the Supporting Information for details). The optimal condition of isomerization was established when 3a was treated with CF<sub>3</sub>CO<sub>2</sub>H in methanol and 3a' was obtained in 84% yield.

With the optimized reaction conditions, the scope of secondary aliphatic amines was investigated. Initially, a range of acyclic amines bearing one or two alicyclic substitutions were examined in this cyclization reaction (Scheme 1, amines 1a-1i). As a result, a diverse array of bicyclic N-heterocycles (3a-3i) was constructed. The alicyclic substitutions (1c-f) are flexible, thus generating a range of prevalent bicyclic N-heterocyclic N-heterocyclic scaffolds in a distinct way.

# Scheme 1. Scope of Acyclic Amines Bearing Alicyclic Substitution $^{a,b}$



<sup>*a*</sup>Unless otherwise noted, all the reactions described in Schemes 1–3 were carried out with 1 (0.3 mmol) and 2 (0.9 mmol) in 1.0 mL of 1,4-dioxane at 70 °C (see the Supporting Information for details). <sup>*b*</sup>Isolated yield. <sup>*c*</sup>1.0 mL of 1:1 1,4-dioxane/toluene was used. <sup>*d*</sup>3g' was obtained through treatment of corresponding 3g with TsOH-H<sub>2</sub>O in toluene at 100 °C.

Previous studies showed that the open-chain acyclic secondary aliphatic amines constantly cause problems, and they were generally not tolerated in the C–H functionalization processes.<sup>1–3</sup> Then open-chain acyclic amines were investigated (Scheme 2). The experimental results revealed that these previously problematic amines (1j-1p) could be tolerated in this transformation, affording a range of functionalized  $\gamma$ -lactams (3j-3p). Powerfully, even using an aliphatic amine as simple as *N*-methylisopropylamine (1j), the desirable transformation was successful to give a  $\gamma$ -lactam product (3j). This highly concise feature makes this approach attractive in the synthesis of  $\gamma$ -lactams. Furthermore, as shown in Scheme 3, piperidine derivatives (1q-1s) could be used as effective substrates to give tetrahydroindolizinones 3q-3s, thus providing a distinct access to this widely distributed scaffold.

Despite the presence of similar  $\beta$ -C–H bonds in several aliphatic amines, unconventional site selectivity was obtained as the malonylation reaction exclusively took place at the  $\beta$ -carbon adjacent to a more steric tertiary  $\alpha$ -carbon bearing less acidic hydrogen. As three  $\sigma$ -bonds and one  $\pi$ -bond were



<sup>*a*</sup>Isolated yield. <sup>*b*</sup>1.0 mL of 1:1 1,4-dioxane/toluene was used. <sup>*c*</sup>The reaction was run at 60 °C. <sup>*d*</sup>3m' was obtained through treatment of the corresponding 3m with TsOH·H<sub>2</sub>O in toluene at 100 °C.



 $^a$  Isolated yield.  $^b$  The reaction was run in 1.0 mL of 1:1 1,4-dioxane/ toluene.

formed in this complicated transformation, the overall yields of the final products were obtained in a reasonable range considering the efficiency of the per chemical bond. However, ketoester-derived iodonium ylides could not been tolerated under the optimized reaction conditions. Furthermore, the use of diethylamine-type secondary amines that lack an  $\alpha$ -tertiary carbon are unsuccessful to give the desired lactam products.

As shown in Scheme 4, the further transformation of product, i.e., 3a', was carried out. The ester groups could be



easily removed to give a valuable lactam product **4** in 84% yield (see the Supporting Information for details).

Based on the obtained data and our previous studies on iodonium ylide chemistry,<sup>8,9</sup> a plausible mechanism was depicted in Scheme 5. Initially, an electron-transfer process





occurs between the halogen-bonding complexes (M1) of an amine and an iodonium ylide, generating a radical ion pair (M2). The proton transfer between a radical ion pair generates a nitrogen-centered radical M4 and a precursor of the malonyl radical M3. Subsequently, iodonium ylide selectively abstracts a hydrogen atom from the  $\alpha$ -C-H bond of M4 to give an enamine intermediate M5, which is trapped by a malonyl radical in situ generated from M4 upon losing one molecule of iodobenzene. It has been reported that  $\alpha$ -aminoalkyl radicals are strongly reducing species.<sup>10</sup> The  $\alpha$ -aminoalkyl radical M6 could be oxidized by the iodonium ylide to generate

carbocation M7. The further proton transfer between M7 (or M7') and the radical anion gives enamine M8. ESI-HRMS analysis of the reaction mixture in toluene found a strong signal at 310.2018, suggesting the presence of enamine M8 or its corresponding imine (calcd  $[M + H]^+$  310.2018). The intramolecular cyclization of enamine M8 gives M9. Finally, an amine-catalyzed umpolung coupling reaction generates N-heterocyclic product 3. It should be noted that the reported approach to this type of umpolung coupling reaction requires the presence of a halogen-bonding activator.<sup>11</sup>

In conclusion, we have established an unprecedented approach to N-heterocycles through site-selective  $\beta$ -malonylation of a diverse array of unprotected secondary aliphatic amines with iodonium ylide. In this transformation, iodonium ylide alone can manage all the distinct bond-formation events through properly manipulating the highly unstable intermediates. As this approach provides a very concise way to synthesize N-heterocycles, we expect this method will find significant utility in medicinal and synthetic chemistry.

#### ASSOCIATED CONTENT

#### **Supporting Information**

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.9b04213.

Full experimental procedures and compound characterization (PDF)

#### **Accession Codes**

CCDC 1935992, 1935998, 1936001–1936002, and 1971974 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.ca-m.ac.uk/data\_request/cif, or by emailing data\_request@ccdc. cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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# Notes

The authors declare no competing financial interest.

# ACKNOWLEDGMENTS

We gratefully acknowledge the National Natural Science Foundation of China (21772113, 21971147) and the Natural Science Foundation of Shandong Province for Distinguished Young Scholars (ZR2019JQ08). We thank Prof. Di Sun of Shandong University for assistance with the X-ray crystal structure analysis.

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