

Copper-Mediated C–N Bond Formation
via Direct Aminolysis of Dithioacetals

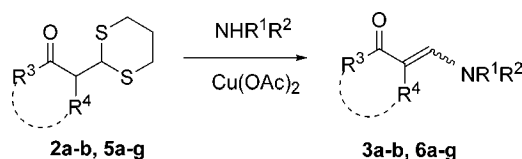
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ABSTRACT



Mediated by copper acetate, an efficient approach to the C–N bond formation via direct aminolysis of dithioacetals **2** and **5** with ammonia, primary or secondary amines are developed under mild conditions. Enaminones **3** and **6** were thus obtained in high to excellent yields with high chemoselectivity. This type of aminolysis reaction presents a new synthetic application of the dithioacetal functionality.

Dithioacetals, which are easily obtained by the condensation of aldehydes/ketones with thiols,¹ odorless thiol equivalents,² or 1,3-propanedithiol copolymers,³ have proven to be very useful in organic synthesis. Besides its use as a latent carbonyl,^{1–3} methylene group⁴ and an umpolung of the carbonyl group (dithiane method according to Seebach),^{5,6} the synthetic potential of the dithioacetal functionality has been widely expanded in recent years. For example, Luh and co-workers demonstrated the nickel-catalyzed olefination reactions of benzylic, allylic, aliphatic, and propargylic dithioacetals (which function as germinal dication synthons)

with Grignard reagents⁷ and the synthesis of furans, pyrroles, and oligoaryls with propargylic dithioacetals as zwitterion synthons.⁸ Takeda et al. reported the desulfurizative metalation of dithioacetals to form titanium-alkylidens species which could produce a C–C double bond with aldehydes, ketones, and esters.⁹ Additionally, the dithiane-/trithiane-based photolabile scaffolds for molecular recognition¹⁰ and some useful transformations¹¹ have also been reported.

In our research on the exploration of the synthetic applications of functionalized ketene dithioacetals,^{12,13} a series

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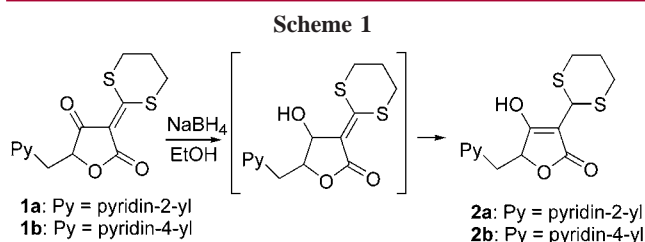
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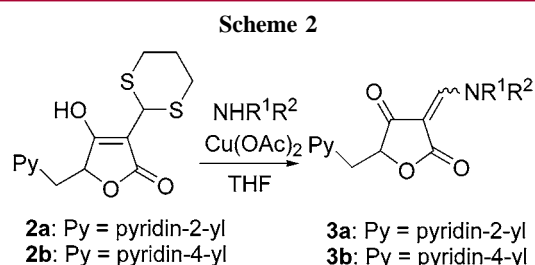
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of 3,5-disubstituted tetronic acid derivatives (TADs) (Scheme 1, compounds **1**) with a 1,3-dithiolane- or 1,3-dithiane-2-ylidene moiety at the 3-position of a TAD were obtained in excellent yields.¹⁴ In addition to the biological features, TADs are useful precursors for syntheses of peptide analogues or HIV-1 protease inhibitors.¹⁵ In continuation of our work, we are interested in the modification at the 3-position of TADs **1** with a goal to find new synthetic applications for the dithioacetal moiety and thus improve their activity for pharmaceutical studies.¹⁶ As a result, we have discovered a new C–N bond-forming reaction via direct aminolysis of dithioacetals. In this communication, the preliminary results on the copper-mediated aminolysis of dithioacetals **2** and **5** with ammonia and primary and secondary amines are described.

Dithianes **2** were prepared from the corresponding TADs **1**.¹⁴ Upon reduction with NaBH₄ (1.1 equiv) in ethanol at 0 °C for about 20 min, dithianes **2a** and **2b**, with the structure of 2-hydroxyvinyl dithioacetals, were obtained in 97% and 98% isolated yields, respectively (Scheme 1).¹⁷

In our study on the C–N cross-coupling reaction of dithianes **2** with amines, a model reaction between **2a** and *n*-butylamine was first examined to optimize the reaction conditions (Scheme 2). The reaction conditions, including catalysts (Cu(OAc)₂·H₂O; Cu(NO₃)₂·3H₂O; CuSO₄·5H₂O), solvents (THF, DMF, CH₂Cl₂), and reaction temperature (room temperature to 50 °C), were investigated. After optimization and treatment of **2a** (1.0 mmol) with *n*-



butylamine (1.5 mmol) in the presence of Cu(OAc)₂·H₂O (0.5 mmol) in THF at 50 °C for 1 h, the product, enaminone **3ad** (Table 1, entry 4), was obtained in 96% isolated yield.¹⁷

Table 1. Copper-Catalyzed C–N Cross-Coupling Reaction between Dithianes **2** and Amines

entry	substrates	R ₁	R ₂	products	time (h)	yield (%) ^a
1 ^b	2a	H	H	3aa	3	84
2	2a	H	CH ₃	3ab	2.5	87
3	2a	H	C ₂ H ₅	3ac	2.5	92
4	2a	H	<i>n</i> -C ₄ H ₉	3ad	1	96
5	2a	H	PhCH ₂	3ae	1.5	93
6	2a	C ₂ H ₅	C ₂ H ₅	3af	1.5	92
7	2a	CH ₂ CH ₂ OCH ₂ CH ₂		3ag	2	96
8	2a	H	Ph	3ah	8	76
9	2a	H	<i>p</i> -CH ₃ C ₆ H ₄	3ai	8	66
10	2a	H	CH ₂ CH ₂ OH	3aj	2	85
11 ^b	2b	H	H	3ba	3	80
12	2b	H	CH ₃	3bb	3	88
13	2b	H	C ₂ H ₅	3bc	2.5	91
14	2b	H	<i>n</i> -C ₄ H ₉	3bd	1	95
15	2b	H	PhCH ₂	3be	1.5	90
16	2b	C ₂ H ₅	C ₂ H ₅	3bf	1.5	92
17	2b	CH ₂ CH ₂ OCH ₂ CH ₂		3bg	2	96
18	2b	H	Ph	3bh	8	73
19	2b	H	<i>p</i> -CH ₃ C ₆ H ₄	3bi	8	64
20	2b	H	CH ₂ CH ₂ OH	3bj	2	75

^a Isolated yields over silica gel chromatography. ^b 3 equiv of NH₄OAc was adopted.

It should be noted that 0.5 equiv of Cu(OAc)₂·H₂O was enough to accomplish the reaction, but the cases with a low amount of catalyst, for example, the reaction of **2a** with *n*-butylamine in the presence of 0.25 equiv of Cu(OAc)₂·H₂O under otherwise the same conditions, gave **3ad** in 32% yield with a longer reaction time (more than 12 h). Under the optimized conditions as described above, the corresponding enaminones **3** were obtained in high to excellent yields when TADs **2** reacted with ammonium acetate (Table 1, entries 1 and 11), primary aliphatic amines (Table 1, entries 2–5 and 12–15), and secondary aliphatic amines (Table 1, entries 6, 7, 16, and 17). In particular, when the bisnucleophilic reagent, 2-aminoethanol, was adopted to react with **2a** and **2b**, the corresponding enaminones **3aj** and **3bj** were obtained in high yields with high chemoselectivity (Table 1, entries 10 and 20), respectively. Moreover, even the less-

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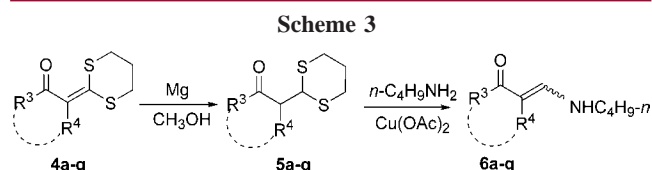
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(17) For details for the preparation of dithioacetals **2** and **5** and the C–N cross-coupling reaction, please see the Supporting Information.

reactive amines, such as aniline and *p*-toluidine, could afford the corresponding enaminones **3ah**, **3ai**, **3bh**, and **3bi** in good yields (Table 1, entries 8, 9, 18, and 19), although the reaction time was prolonged to 8 h. All the results described above indicate the efficiency of this C–N cross-coupling reaction and the generality of this reaction to amines. Also, it is noticeable that this reaction presents an alternative synthetic route to useful enaminones.¹⁸

As an extension of the new C–N coupling reaction, dithioacetals **5a–g** were then synthesized via the reduction of **4a–g**¹⁹ by magnesium in methanol²⁰ (Scheme 3) and were



subjected to the reaction sequence. Under conditions identical to those above, the C–N cross-coupling reaction of **5a–g** with *n*-butylamine (Scheme 3) was proven to be successful and the corresponding enaminones **6a–g** were synthesized in high to excellent yields (Table 2). To understand the scope

Table 2. Copper-Catalyzed C–N Cross-Coupling Reaction between Dithioacetals **5** and *n*-Butylamine

entry	substrates	R ₃	R ₄	products	time (min)	yield (%) ^a
1	5a	CH ₂ CH ₂ CH ₂ CO		6a	15	90
2	5b	CH ₂ C(Me) ₂ CH ₂ CO		6b	30	89
3	5c	Me	COMe	6c	60	94
4	5d	Me	CO ₂ Et	6d	30	95
5	5e	OEt	CO ₂ Et	6e	20	70
6	5f	Me	CONH ₂	6f	20	84
7	5g	Me	CN	6g	20	84

^a Isolated yields over silica gel chromatography.

of the aminolysis reaction explored here, dithioacetals **7a** and **7b** were selected to react with *n*-butylamine. As a result, no reaction was found for **7a** (the substrate was recovered quantitatively). As for **7b**, an inseparable mixture was produced (Figure 1).

On the basis of the above results, a possible mechanism for the copper(II)-catalyzed C–N cross-coupling reaction is tentatively proposed as depicted in Scheme 4 (with the aminolysis of **2** as an example). Initially, a copper complex

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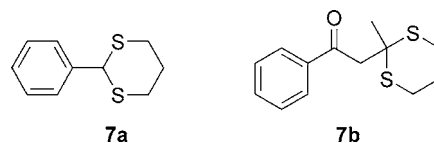
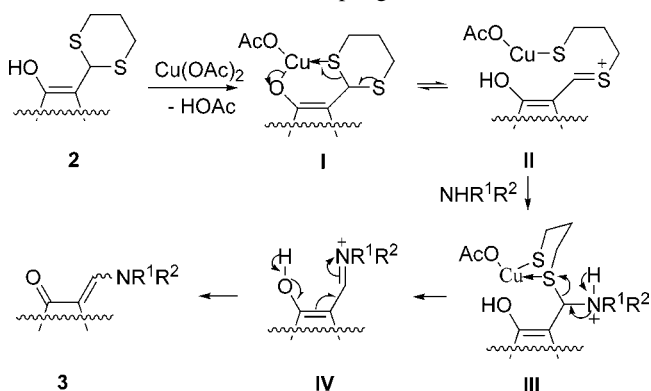


Figure 1. Dithioacetals with more general structures in the explored aminolysis reaction mediated by the Cu(II) catalyst.

I is proposed to be formed by reaction of **2** with Cu(OAc)₂ in which one of the sulfur atoms of the dithioacetal unit coordinates to the Cu(II) ion.²¹ The formation of **I** activates the C–S bond coordinated to the copper(II) ion, and thus, the thionium ion intermediate **II** (or the sulfur-stabilized carbocation intermediate) would be formed by the C–S bond cleavage. After that, the amine attacking at the carbon atom of thionium **II** leads to the formation of enaminones **3**.

Scheme 4. Proposed Mechanism for the Copper-Catalyzed C–N Cross-Coupling Reaction



The C–N coupling reaction is important in organic synthesis.^{22,23} To know more details about the reaction mechanism, the reaction of **2a** with *n*-butylamine was then carried out under optimized conditions with anhydrous Cu(OAc)₂ as the catalyst in absolute THF and monitored by TLC. The reaction was completed at 50 °C within 8 h and gave **3ad** in 81% isolated yield. By comparison, in another experiment without *n*-butylamine added, substrate **2a** was almost entirely recovered (contaminated with traces of the corresponding aldehyde; yield <3%) under the above conditions for 8 h.²⁴ The results, together with the reaction of 2-aminoethanol with **2a** and **2b** (Table 1, entries 10 and 20),

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(24) The corresponding aldehyde, produced by the hydrolysis of **2a**, is likely formed during the workup process. This process was difficult to monitor because dithiane **2a** and the corresponding aldehyde have the same *R_f* value on TLC and the amount of aldehyde was calculated based on the ¹H NMR spectra of the mixture (see the Supporting Information).

clearly support the proposed mechanism of copper(II)-mediated direct aminolysis of dithioacetals (Scheme 4), although the reaction rate between **2a** and *n*-butylamine is a little slower under anhydrous conditions than that with Cu(OAc)₂·H₂O as the catalyst.²⁵

In conclusion, a new C–N bond formation reaction where a thionium ion intermediate was trapped by an amine was realized. This copper(II)-mediated C–N bond formation reaction of a dithioacetal unit with amines could proceed under mild conditions with high chemoselectivity. The functional groups such as carbonyl, cyano, ethoxycarbonyl, and lactone are tolerable to the reaction conditions. This type of aminolysis reaction represents a new synthetic

(25) The substrates **2** were slightly soluble in THF. When even one drop of water was added to the THF of **2**, the solution would become clear immediately. The reason for the prolonged reaction time of **2a** under anhydrous conditions was mainly attributed to the poor solubility of **2a** in absolute THF.

application of the dithioacetal functionality. Further work on the scope of this C–N coupling reaction is underway in our laboratory.

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Supporting Information Available: Experimental details and spectral data for compounds **2** and **3** and **5** and **6**. ¹H NMR spectrum for the mixture of **2a** and the corresponding aldehyde, and the HMBC, HMQC, and ¹H-¹H COSY spectra of compound **3aa**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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