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Thiourea-catalyzed nucleophilic addition of TMSCN and ketene silyl acetals to nitrones and aldehydes

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Abstract—The effect of hydrogen bonding between nitrones and urea derivatives in the nucleophilic addition reaction was examined. Thioureas bearing an electron-withdrawing group on an aromatic ring, behave like Lewis acid to promote the addition of TMSCN and ketene silyl acatals to various nitrones and aldehydes. Presumed interaction between nitrones and thioureas was supported by NMR experiments.

The invention and development of catalytic enantioselective reactions are important research topics among the most challenging and intensively studied frontiers in organic synthesis. Thus far, many useful catalytic systems, most of which contain metallic ions in the active site, have been developed. From the viewpoint of the environmentally benign nature, easiness of handling, and cost of the reaction process, metal-free organocatalysts recently attracted much attention to organic chemists and are intensively studied.[1–4] In addition, different from metallic Lewis acids, these organocatalysts could be recovered and reused for a second reaction. In contrast to the enantioselective reactions catalyzed by L-proline,[1] chiral Lewis bases,[2] and phase-transfer catalysts,[3] there are a few reactions catalyzed by urea derivatives as acid catalysts.[5–7] Curran et al. found that addition of ureas improved diastereoselectivity of the radical-mediated allylation of cyclic α-sulfonyl halides.[5] They also reported Claisen rearrangement catalyzed by the same urea.[6] Schreiner et al. recently revealed that thioureas promoted Diels–Alder reaction of *N*-crotonyloxazolidin-2-one with cyclopentadiene and affected the diastereoselectivity of the products.[7] However these effects on the stereoselectivity were relatively small and the substrates employed were limited. Then, with the aim of expanding the applicability of ureas as an acid catalyst, we started to explore the nucleophilic addition to nitrones and aldehydes catalyzed by urea derivatives.[8] Having the negatively charged oxygen atom, nitrones are known to coordinate effectively to the metallic Lewis acids to be activated.[9] Similarly, it is reasonable to consider that two N–H bonds of ureas would interact with the oxygen of nitrone concurrently through the hydrogen-bonding (Fig. 1). Herein, we report the thiourea-catalyzed nucleophilic addition of TMSCN and ketene silyl acetals to nitrones and aldehydes.

To examine the catalytic potential of ureas,[10] we initially carried out the reaction of 6-methyl-2,3,4,5-tetrahydropyridine *N*-oxide **1a**[11] and TMSCN (5 equiv.) in the presence of 0.5 equiv. of ureas or thioureas in CH_2Cl_2 at −78°C (Table 1). Although even amide **3a** with only one N–H group accelerated the cyanation reaction of **1a** moderately, the reaction with urea **3b** bearing two N–H groups completed within 90 min to give the desired product **2a** in 77% yield (entries 1–3). In addition, acidity of the N–H group should be enhanced by changing urea **3b** to thiourea **4a** and introducing an electron-withdrawing group (CF_3) on the aromatic rings. As expected, the reaction rate dramatically increased when thioureas **4a**–**c** were employed

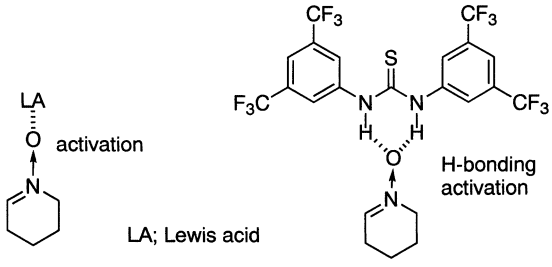

Figure 1. Presumed activation mechanism of nitrones.

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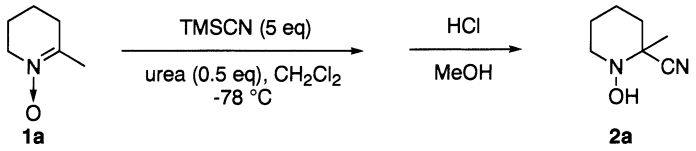
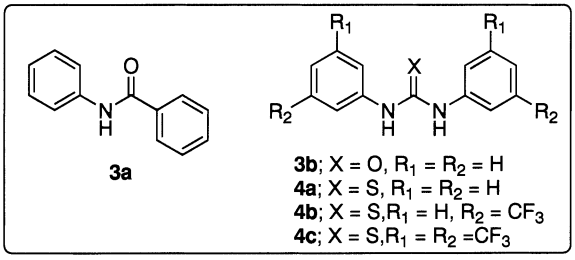
Table 1. Relationship between activity and structure of ureas derivatives



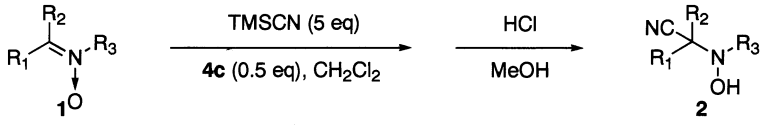
entry	urea	time (min)	cy (%)
1	-	300	79
2	**3a**	180	83
3	**3b**	90	77
4	**4a**	45	81
5	**4b**	15	75
6	**4c**	15	81

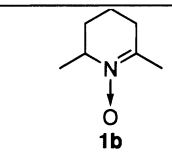
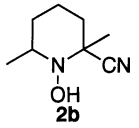
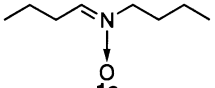
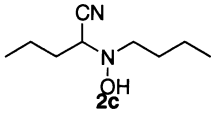
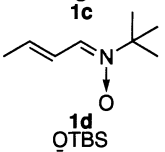
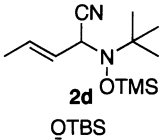
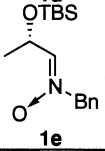
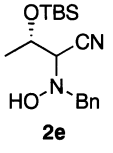


as the catalyst (entries 4–6). These results indicate that positive correlation is observed between the acidity of the N–H bond of thioureas and their catalytic activity, and also, bidentate coordination of the ureas with **1a** is important for the catalytic activation. Among these ureas, we selected thiourea **4c** as the best catalyst for the nucleophilic addition.

The scope of the urea-catalyzed cyanation was demonstrated by the reaction of nitrones **1b–e** with TMSCN catalyzed by thiourea **4c** as shown in Table 2. The cyanation of cyclic nitrone **1b** was efficiently accelerated in the presence of **4c** to give the product **2b** bearing the quaternary carbon center in good yield (entry 1). This method could be applied to acyclic nitrones **1c** and **1d**. The same treatment of **1c** and **1d** as **1b** provided the corresponding adducts **2c** and **2d** in 85–92% yields (entries 2 and 3). In the case of entry 3, it is worthy to note that only 1,2-adduct was obtained, while the conjugated nitrone **1d** has two reactive sites (α- and γ-positions). Finally, to investigate the effect of **4c** on diastereoselectivity of the cyanation, chiral nitrone **1e**[12] was subjected to the reaction conditions (entry 4). Unfortunately, although **4c** shortened the reaction time

Table 2. Thiourea-catalyzed addition of TMSCN to various nitrones



entry	SM	TM	temp. (°C)	time (h)	cy (%)
1	 **1b**	 **2b**	-78	1.5 (15)[a]	75 (79)[b]
2	 **1c**	 **2c**	0	0.25 (7.5)[a]	92 (95)[b]
3	 **1d**	 **2d**	rt	1.5 (20)[a]	85 (85)[b]
4	 **1e**	 **2e**	rt	1 (24)[a]	96[c] (72[d])[b]

[a] The value in parenthesis is the reaction time of the reaction without **4c**.

[b] The value in parenthesis is the yield of **2** of the reaction without **4c**.

[c] Syn/anti = 42/58

[d] Syn/anti = 50/50

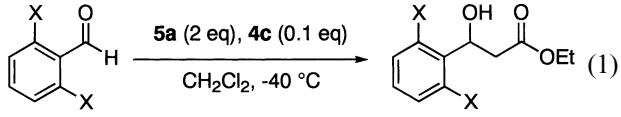
effectively, improvement of the diastereoselectivity (*syn*/*anti* = 42/58) was minimal.

As thiourea **4c** was revealed to promote the cyanation of nitrones, we next examined the reaction of nitrones with ketene silyl acetals **5a–c** (Table 3).[13] Reactions of various nitrones with ketene silyl acetal **5a** derived from ethyl acetate were catalyzed by thiourea **4c**, giving rise to 1,2-isoxazolidin-5-ones **6a–c**, and **6f** in moderate to good yields (entries 1–4).[14] It should be noted that no or negligible amounts of the desired adducts was obtained without **4c** in all cases. In addition, the reaction of nitrone **1f** with sterically hindered ketene silyl acetals **5b** and **5c** proceeded smoothly to afford the corresponding adducts **6g** and **6h** possessing tertiary and quaternary carbon centers (entries 5 and 6). Moreover, reduction of the amount of **4c** from 0.5 to 0.1 equiv. did not affect the reaction of the nitrone **1f** with **5c**, giving the same result (entry 7).

Our assumption that ureas would activate nitrones by the hydrogen-bonding was supported by NMR experiments. ^{1}H NMR titration of a solution of nitrone **1c** in $CDCl_3$ with thiourea **4a** resulted in a downfield shift of the N=C–H of **1c** and upfield shift of the N–H of **4a**, and these shifts were enhanced with increase of the ratio of **6a**/**1c**, respectively. In addition, downfield shift of the N=C–H of **1c** was also observed by ^{13}C NMR of 1:1 mixture of **4a**/**1c**. These results support the activation of nitrone **1c** by the hydrogen bonding with the urea N–H in the manner of a Lewis acid and the experimental data shown in Table 1.

The benefit of ureas as organocatalyst is the easiness of recycle and reuse. In the reaction of nitrone **1a** with TMSCN, thiourea **4c** was recovered quantitatively and no loss of activity was observed on using the recovered thiourea (1st: 20 min, 76%; 2nd: 20 min, 86%).

Finally, we investigated the thiourea-catalyzed Mukaiyama–aldol reaction of aldehydes **7a** and **7b** with ketene silyl acetal (Eq. (1)). In the same manner as described for nitrones, arylaldehydes **7a** and **7b** were reacted with ketene silyl acetal **5a** in the presence of **4c** (0.1 equiv.). Interestingly, benzaldehyde **7a** gave the desired product **8a** in low yield, while the same reaction of **7b** bearing the methoxy groups at the *ortho* position of the aromatic ring proceeded smoothly, resulting in good chemical yield. At this stage, the reason is not clear, but we now assume that both oxygens of the carbonyl and methoxy groups of **7b** might coordinate to thiourea **6c** to form a highly activated intermediate.

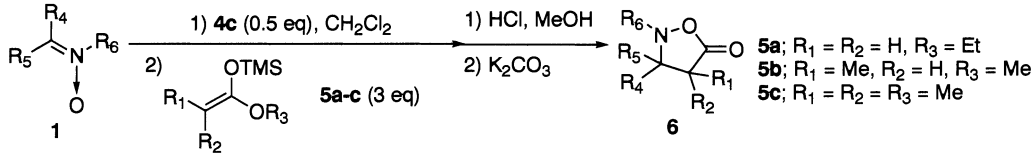


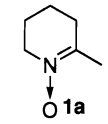
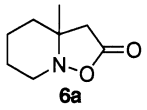
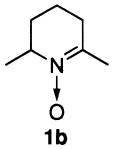
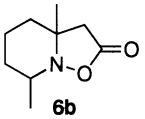
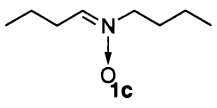
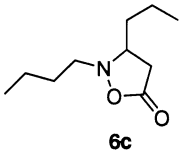
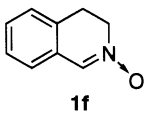
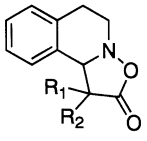
(1)

7a; X = H
7b; X = OMe

8a; X = H (36%)
8b; X = OMe (65%)

Table 3. Thiourea-catalyzed addition of ketene silyl acetals to various nitrones



entry	SM	ketene silyl acetal	TM	temp. (°C)	time (h)	cy (%)
1	 **1a**	**5a**	 **6a**	-60	1	88
2	 **1b**	**5a**	 **6b**	-40	1.25	80
3	 **1c**	**5a**	 **6c**	-40	1	63
4	 **1f**	**5a**		**6f**	-20	0.25	52
5		**5b**		**6g**	-20	0.25	70
6		**5c**		**6h**	rt	1.5	80
7		**5c**		**6h**	rt	1.5	79

*0.1 eq. of **4c** was used.

In summary, thiourea-catalyzed nucleophilic addition to various nitrones were developed. The reactions of both TMSCN and ketene silyl acetal to nitrones were greatly accelerated by the hydrogen bonding between ureas and nitrones, and the Lewis acid-like activation mechanism was supported by ^{1}H and ^{13}C NMR analysis. Moreover, the urea employed could be recovered quantitatively and the reuse of the catalyst **4c** was also demonstrated. Now we are engaged in an asymmetric version of these reactions catalyzed by chiral thiourea derivatives.

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14. *Experimental procedure*: Under an argon atmosphere, to a solution of 3,4-dihydroisoquinoline-*N*-oxide **1f** (20.9 mg, 0.142 mmol) and bis-(3,5-bis-trifluoromethylphenyl)urea **4c** (0.5 equiv., 35.5 mg) in dry CH_2Cl_2 (0.71 ml) was added 1-methoxy-2-methyl-1-(trimethylsiloxy)propene **5c** (3.0 equiv., 0.088 ml) at rt. The reaction mixture was stirred 1.5 h and then 0.3 M HCl in MeOH (0.25 ml) was added. After desilylation was completed, K_2CO_3 (38.2 mg) was added to convert hydroxylamine to cyclic compound. The reaction mixture was diluted with $CHCl_3$ and saturated NH_4Cl aq. The organic layer was separated and the aqueous layer was extracted with $CHCl_3$. The combined organic extracts was dried over Na_2SO_4. Evaporation of solvents and purification of the residual oil by column chromatography on silica gel (ether/hexane = 1/3) gave the desired product (24.8 mg, 80% yield) as white solid. An analytical sample was prepared by recrystalization from hexane. Mp 96–97°C (hexane); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.26–7.23 (m, 2H), 7.18 (dd, J = 3.9, 5.2 Hz, 1H), 7.09 (dd, J = 3.9,

4.3 Hz, 1H), 4.83 (br s, 1H), 3.61 (br s, 1H), 3.42 (br s, 1H), 3.04 (br s, 1H), 2.89 (br s, 1H), 1.61 (s, 3H), 1.11 (s, 3H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$): δ 181.2, 134.0, 131.0, 128.8, 127.4, 126.4, 70.0, 51.0, 45.2, 27.5, 25.6, 22.6 ppm; IR ($CHCl_3$): ν 3030, 2980, 2940, 2876, 1773, 1112 cm^{-1}; MS (EI^+): 217 (M^+, 12), 131 (100). Anal. calcd for $C_{13}H_{15}NO_2$: C, 71.87; H, 6.96; N, 6.45. Found: C, 72.06; H, 7.11; N, 6.39%.