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[5,5] Sigmatropic shift of *N*-phenyl-*N*′-(2-thiazolyl)hydrazines and *N*,*N*′-bis(2-thiazolyl)hydrazines into 2-amino-5-(*p*-aminophenyl)thiazoles and 5,5′-bis(2-aminothiazole) derivatives†

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Abstract

[5,5] Sigmatropic shift of *N*-phenyl-*N*′-(2-thiazolyl)hydrazines and *N*,*N*′-bis(2-thiazolyl)hydrazines in acid-catalyzed benzidine-type rearrangement into 2-amino-5-(*p*-aminophenyl)thiazoles and 5,5′-bis(2-aminothiazole) derivatives is described, respectively.

Keywords: thiazole; hydrazine; thiourea; benzidine-type rearrangement; acid catalyst.

The acid-catalyzed [5,5] sigmatropic shift of hydrazobenzene to 4,4′-diaminobiphenyl is well known and the related studies were published numerously.[1] We wish to report examples where *N*-phenyl-*N*′-(2-thiazolyl)hydrazines and *N*,*N*′-bis(2-thiazolyl)hydrazines could perform [5,5] sigmatropic shift in acid-catalyzed benzidine-type rearrangement, respectively.

Because of our interest in the thiazole compounds, we attempted the condensation of *N*-anilinothiourea (**1**)[2a] and α-chloroacetone to give *N*-phenyl-*N*′-[2-(4-methyl)thiazolyl]hydrazine (**3a**) according to the Hantzsch method.[3] It was found that when the mixture was refluxed in MeOH under neutral conditions, 2-amino-5-(*p*-aminophenyl)-4-methylthiazole (**5a**) was obtained in 81% isolated yield. Otherwise, when it was carried out at room temperature, hydrazine derivative **3a** was obtained in 82% isolated yield.

In order to investigate this phenomena stepwise, as illustrated in Scheme 1, a series of hydrazine derivatives (**3**) have been prepared in high yield by the treatment of **1** with α-chlorocarbonyl compounds for 12–15 h at room temperature or 45°C [pathway (A)].

In the next step of pathway (A) in Scheme 1, compound **3** (5 mmol) was refluxed in 0.5 ml of 35% HCl and 20 ml of H_2O solution to rearrange to compound **5** which, otherwise, was prepared by refluxing directly [pathway (B)] compound **1** and α-chlorocarbonyl compounds in MeOH (refluxed in H^+/H_2O for **5b**). The reactions in Scheme 1 are summarized in Table 1.

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† Dedicated to Professor T. H. Chan on the occasion of his 60th birthday.

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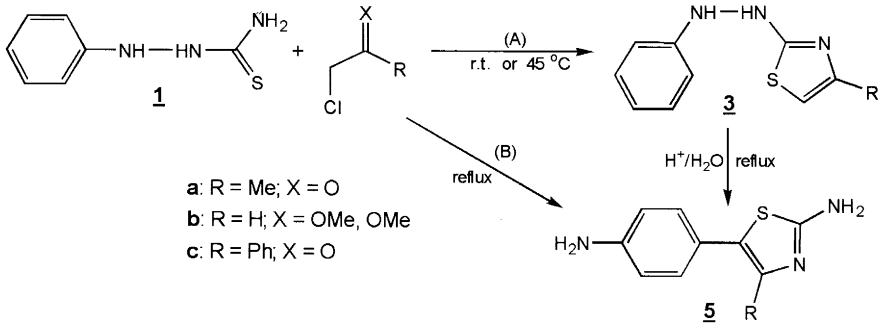
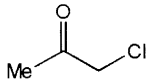
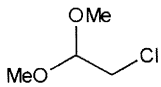
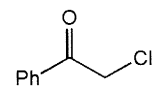


Scheme 1.

Table 1
The reactions of *N*-anilinothiourea (**1**) with α-chlorocarbonyl compounds

chlorocarbonyl	reaction condition	product	yield, %[a]	^{1}H-nmr data (DMSO-d_6), δ
	MeOH/r.t/12 h	**3a**	82	2.18 (s, 3H), 6.23 (s, 1H), 6.7-7.2 (m, 5H), 8.15 (s, 1H), 9.17 (s, 1H)
	MeOH/reflux/12 h	**5a**	81(78)[b]	($CDCl_3$); 2.2 (s, 3H), 4.2 (bs, 2H), 6.2 (bs, 2H), 6.62 (d, J = 9Hz, 2H), 7.05 (d, J = 9 Hz, 2H)
	H^+/H_2O/45 ℃/15 h	**3b**	78	($CDCl_3$); 7.4 (d, J = 3.8Hz, 1H), 8.05 (d, J = 3.8Hz, 1H), 7.45-8.1 (m, 7H)
	H^+/H_2O/110 ℃/12 h	**5b**	83(72)[b]	4.0 (bs, 2H), 6.6 (d, J = 9Hz, 2H), 6.7 (bs, 2H), 6.9 (s, 1H), 7.15 (d, J = 9Hz, 2H)
	MeOH/r.t/12 h	**3c**	85	6.1 (s, 1H), 6.9-7.75 (m, 12H)
	MeOH/reflux/13 h	**5c**	88(88)[b]	4.7 (bs, 2H), 6.65 (d, J = 9Hz, 2H), 6.7 (bs, 2H), 6.9 (d, J = 9Hz, 2H), 7.2-7.4 (m, 5H)

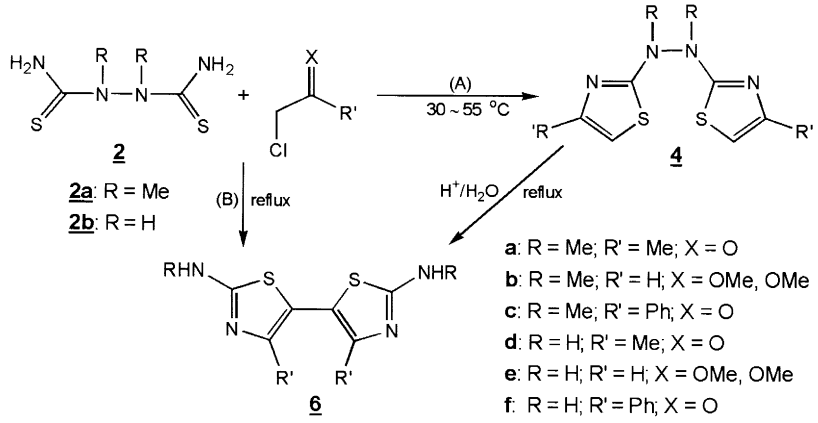
[a]*yield isolated after column chromatography.* [b]*yield rearranged to* **5** *by refluxing* **3** *(H^+/H_2O).*

The structure of **5** was evident from ^{1}H NMR spectroscopic data. After the rearrangement of **3** to **5**, the thiazole 5-H signal in the region δ 6.1–7.4 of **3** disappeared and the pattern of *N*-phenyl proton peaks changed to doublet and doublet (J=9.0 Hz) in the region δ 6.60–7.15.

From the fact that **5a** and **5c** could be directly obtained by refluxing **1** and α-chlorocarbonyl compounds (chloroacetone and 2-chloroacetophenone) in MeOH under neutral conditions, we assume that the HCl generated from the first step in Scheme 1, acted as an acid catalyst for the [5,5]-shifts of **3a** and **3c** to **5a** and **5c**, respectively.

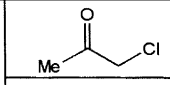
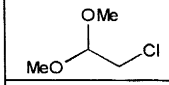
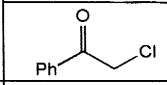
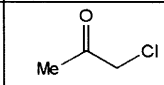
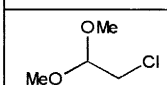
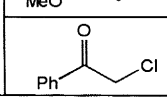
On the other hand, we examined the condensation of 2,5-dithiobiurea (**2**) with α-chlorocarbonyl compounds according to the same way as shown in Scheme 1. We have also found the condensation of **2**[2b–d] with α-chlorocarbonyl compounds at 30–55°C, followed by rearrangement of the resultant *N*,*N*′-bis(2-thiazolyl)hydrazine derivatives (**4**) under the acidic condition to give 5,5′-bis(2-aminothiazole) derivatives (**6**), as illustrated in Scheme 2. After the rearrangement of **4** to **6**, disappearance of thiazole 5-H signal in the region δ 6.2–7.0 of **4** is characteristic. The overall result of pathway (A) in Scheme 2 was consistent with that of pathway (B) and is summarized in Table 2.

In another interesting Hantzsch synthesis, the reaction of 2,5-dibromo-3,4-hexanedione or 1,4-dibromo-2,3-butanedione with 2 equiv. of thiourea in refluxing MeOH (Eq. (1)) gave the corresponding 4,4′-bis(2-aminothiazole) derivative (**7a** or **7b**).[4] Compound **7a** or **7b** was in contrast to **6d** or **6e** in Scheme 2 (Eq. (2)) in terms of site selectivity, respectively.

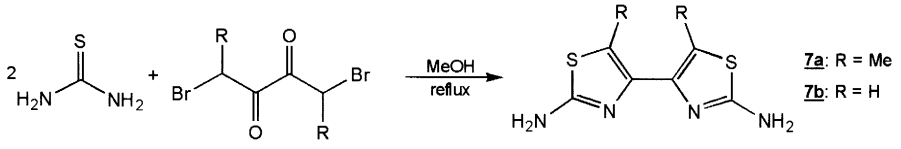


Scheme 2.

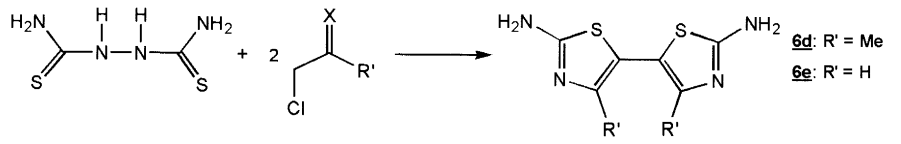
Table 2
The reactions of 2,5-dithiobiureas (**2**) with α-chlorocarbonyl compounds

2	chlorocarbonyl[a]	reaction condition	product	yield,%[b]	^{1}H-nmr data (DMSO-d_6), δ
2a		MeOH/40 ℃/12 h	**4a**	77	($CDCl_3$); 2.25 (s, 6H), 3.25 (s, 6H), 6.2 (s, 2H)
		H_2O/120 ℃/14 h	**6a**	81 (80)[c]	2.0 (s, 6H), 2.77 (d, 6H), 7.45 (q, 2H)
		H^+/H_2O/45 ℃/15 h	**4b**	70	($CDCl_3$); 3.3 (s, 6H), 6.7 (d, 2H), 7.25 (d, 2H)
		H^+/H_2O/125 ℃/17 h	**6b**	78 (77)[c]	2.85 (d, 6H), 6.95 (s, 2H), 7.6 (q, 2H)
		MeOH/30 ℃/12 h	**4c**	75	($CDCl_3$); 3.4 (s, 6H), 6.9 (s, 2H), 7.3-7.9 (m, 10H)
		MeOH/75 ℃/13 h	**6c**	88 (85)[c]	2.93 (s, 6H), 3.4 (bs, 2H), 7.2-7.7 (m, 10H)
2b		MeOH/40 ℃/12 h	**4d**	74	2.1 (s, 6H), 5.75 (s, 2H), 6.25 (s, 2H)
		H_2O/120 ℃/14 h	**6d**	75 (75)[c]	1.95 (s, 6H), 6.8 (s, 4H)
		H^+/H_2O/55 ℃/15 h	**4e**	70	6.85 (d, 2H), 7.25 (d, 2H), 7.7 (bs, 2H)
		H^+/H_2O/130 ℃/16 h	**6e**	58 (52)[c]	7.0 (s, 2H), 7.6 (bs, 4H)
		MeOH/30 ℃/12 h	**4f**	78	7.0 (s, 2H), 7.3-7.8 (m, 12H)
		MeOH/75 ℃/13 h	**6f**	78 (77)[c]	6.8 (bs, 4H), 7.2-7.7 (m, 10H)

[a] *2 equivalents of α-chlorocarbonyl compounds were used.* [b] *yield isolated after column chromatography.*
[c] *yield rearranged to* **6** *by refluxing* **4** *(H^+/H_2O).*



(1)



(2)

Those reactions are simple and effective, and also possess interesting potential as a new method in polythiazole synthesis.

Acknowledgements

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References

1. (a) Shine, H. J. In *Aromatic Rearrangement*; Elsevier: New York, 1967; pp. 126–179. (b) Shine, H. J. In *Mechanism of Molecular Migration*; Thyagarajan, B. S., Ed.; Interscience: New York, 1969; Vol. 2, pp. 191–247. (c) Dewar, M. J. S. In *Molecular Rearrangements*; de Mayo, P., Ed.; Interscience: New York, 1969; Vol. 1, pp. 323–343. (d) Cox, R. A.; Buncel, E. In *The Chemistry of the Hydrazo, Azo and Azoxy Groups*; Patai, S., Ed.; Wiley: New York, 1975; pp. 775–859. (e) Banthrope, D. V. *Chem. Rev.* **1970**, *70*, 295–322. (f) Olah, G. A.; Dunne, K.; Kelly, D. P.; Mo, Y. K. *J. Am. Chem. Soc*. **1972**, *94*, 7438–7447. (g) Bunton, C. A.; Rubin, R. J. *J. Am. Chem. Soc*. **1976**, *98*, 4236–4246. (h) Park, K. H.; Kang, J. S. *J. Org. Chem*. **1997**, *62*, 3794–3795.
2. (a) The procedure for the synthesis of *N*-anilinothiourea (**1**) is as follows: To 20 ml of H_2O was dissolved 5 mmol of phenylhydrazine hydrochloride and 5 mmol of NH_4SCN. The mixture was refluxed for 12 h at 120°C and the solvent was evaporated under reduced pressure. Pale brown solid was recrystallized from H_2O. Yield: 88%, ^{1}H NMR (DMSO-d_6) δ: 6.7–7.2 (m, Ph), 7.5 (bs, NH), 9.25 (s, NH), ^{13}C NMR (DMSO-d_6) δ: 113, 118.7, 128, 147.5, 182. (b) Typical procedure for the synthesis of 3,4-dimethyl-2,5-dithiobiurea (**2a**) is as follows: To 20 ml of H_2O was dissolved 10 mmol (1.33 g) of 1,2-dimethylhydrazine dihydrochloride and 20 mmol (1.52 g) of NH_4SCN. After the mixture was refluxed for 15 h at 120°C, solid was filtered and washed 3 times with 20 ml of H_2O and dried. Yield: 75%, mp=208–210°C (dec.), ^{1}H NMR (DMSO-d_6) δ: 3.3 (s, 6H) 7.7 (bs, NH_2), ^{13}C NMR (DMSO-d_6) δ: 36.5, 181.5 (c) For 2,5-dithiobiurea (**2b**), yield: 58%, mp=209–211°C (lit.[2d] 212°C), ^{1}H NMR (DMSO-d_6) δ: 7.6 (bs, NH_2), 9.4 (s, NH), ^{13}C NMR (DMSO-d_6) δ: 180. (d) Compound **2b** is also commercially available from Aldrich Chem. Co.
3. (a) Hantzsch, A.; Wever, J. H. *Ber.* **1887**, *20*, 3118–3128. (b) Hantzsch, A.; Traumann, V. *Ber.* **1888**, *21*, 938–946.
4. NMR data for **7a** and **7b**. (a) **7a**; yield: 85%, mp=263–265°C, ^{1}H NMR (DMSO-d_6) δ: 2.35 (s, 6H), 6.60 (s, NH_2), ^{13}C NMR (DMSO-d_6) δ: 13.5, 117.5, 141, 163.5. (b) **7b**; yield: 88%, mp=246–248°C, ^{1}H NMR (DMSO-d_6) δ: 6.62 (s, 2H), 6.95 (s, NH_2), ^{13}C NMR (DMSO-d_6) δ: 102.5, 146.5, 168.