Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron Letters 45 (2004) 9315–9317
Tetrahedron Letters

Organoaluminum-mediated selective 1,2-rearrangement of γ,γ-disubstituted γ-amino α,β-unsaturated carbonyl compounds leading to unsymmetrically substituted pyrroles

Takashi Ooi, Kohsuke Ohmatsu, Hiroki Ishii, Akira Saito and Keiji Maruoka*

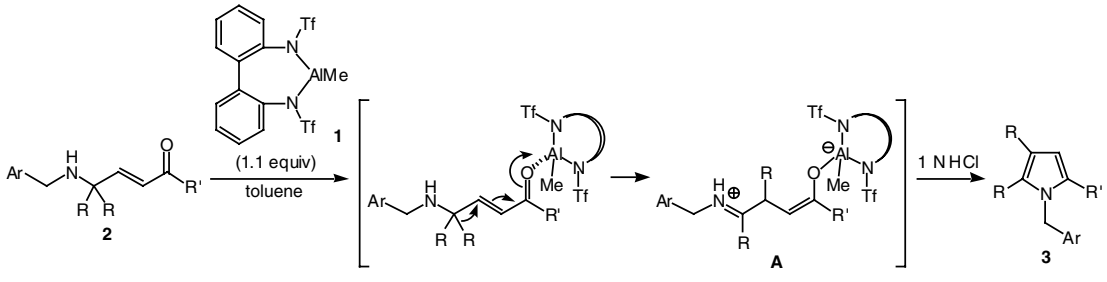
Department of Chemistry, Graduate School of Science, Kyoto University Sakyo, Kyoto 606-8502, Japan

Received 25 September 2004; revised 23 October 2004; accepted 25 October 2004

Abstract—γ,γ-Dialkyl-γ-amino-α,β-unsaturated carbonyl compounds were found to undergo selective skeletal rearrangement under the influence of modified organoaluminum Lewis acid to give unsymmetrically substituted pyrroles through the rapid Paal–Knorr type cyclization upon acidic hydrolysis. This new structural reorganization of amino carbonyl compounds triggered by the 1,2-alkyl shift provides a unique entry to the synthesis of pyrroles, an important class of heterocycles with diverse biological activities.

The reactions involving carbon-to-carbon migrations have been regarded as an important yet useful synthetic tool for the structural reconstruction of various organic molecules.[1] α-Amino ketones and aldehydes readily derived from the corresponding α-amino acids are known to undergo such rearrangement under thermal or acidic conditions.[2,3] However, concurrent intervention of several reaction pathways seemed to devalue the synthetic utility, and studies on *directing* the rearrangement have remained elusive mainly due to the lack of suitable activators. As part of our recent research effort to establish the selective skeletal rearrangement of α,α-disubstituted α-amino aldehydes using organoaluminum Lewis acids,[4] we considered it intriguing to expand our approach to the selective 1,2-alkyl shift in the γ,γ-disubstituted γ-amino-α,β-unsaturated carbonyl substrate **2**. Herein we wish to report the realization of this possibility by the employment of modified organoaluminum Lewis acid **1**, leading to the exclusive formation of unsymmetrically substituted pyrroles via acidic treatment (Scheme 1).[5]

To evaluate the feasibility of the requisite 1,2-rearrangement, we first attempted the reaction of *N*-(α-naphthylmethyl)-γ,γ-dibenzyl-γ-amino enone **2a** under the influence of Me_2AlCl as an activator. Treatment of **2a** with 1.1 equiv of Me_2AlCl in toluene at −78 °C for 5 h showed gradual consumption of the starting amino enone. An additional stirring at room temperature for

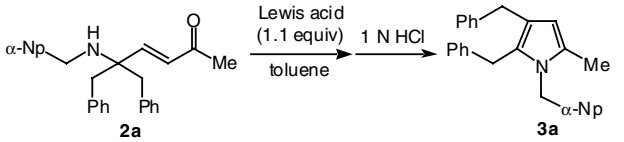


Scheme 1.

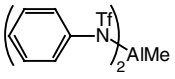
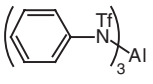
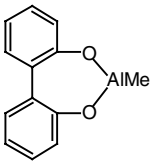
Keywords: Amino carbonyl compounds; Organoaluminum Lewis acids; Paal–Knorr reaction; Pyrroles; 1,2-Rearrangement.
* Corresponding author. Tel./fax: +81 (0)757534041; e-mail: maruoka@kuchem.kyoto-u.ac.jp

0040-4039/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2004.10.126

Table 1. Screening of various Lewis acids for selective rearrangement–cyclization of **2a** to pyrrole **3a**[a]

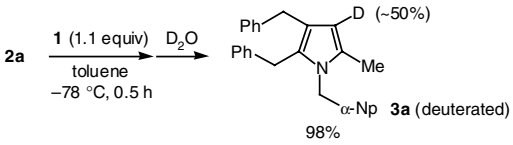


2a **3a**

Entry	Lewis acid	Condition (°C, h)	% Yield[b]
1	Me_2AlCl	−78, 5; rt, 12	64
2	$SnCl_4$	−78, 5; rt, 12	10
3	$TiCl_4$	−78, 5; rt, 12	33
4	$BF_3{\cdot}OEt_2$	−78, 5; rt, 12	8
5		−78, 5	61
6		−78, 5	58
7	**1**	−78, 0.5	98
8		−78, 5; rt, 12	12

[a] The reaction was carried out with 1.1 equiv of Lewis acid in toluene under the given reaction conditions.
[b] Isolated yield.

12 h and subsequent workup with 1 N HCl resulted in the production of pyrrole **3a** in 64% isolated yield (Table 1, entry 1). This interesting result suggested that the selective 1,2-migration of γ-alkyl substituent toward the β-carbon of the enone moiety indeed took place, giving the corresponding aluminum enolate. Once the ketone carbonyl was regenerated upon acidic workup, subsequent Paal–Knorr type intramolecular cyclization–dehydration seemed to occur instantaneously to afford **3a**.[6] Although other conventional Lewis acids such as $BF_3{\cdot}OEt_2$, $SnCl_4$, and $TiCl_4$ effected the rearrangement, chemical yields of **3a** were uniformly lowered (entries 2–4). In contrast, however, aluminum Lewis acids bearing a trifluoromethanesulfonylamino ligand exhibited significantly higher reactivity (entries 5 and 6). Further, we found that the reaction of **2a** with **1**, prepared from Me_3Al and 2,2′-bis(trifluoromethanesulfonylamino)-1,1′-biphenyl, at −78 °C for 0.5 h followed by the treatment with 1 N HCl yielded **3a** almost quantitatively (entry 7). It should be added that the 2,2′-biphenol-derived aluminum phenoxide was ineffective for this rearrangement (entry 8).

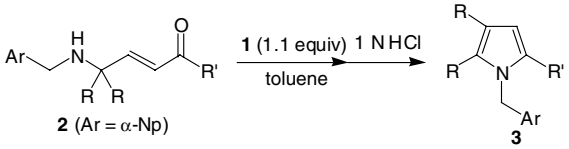


Scheme 2.

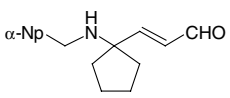
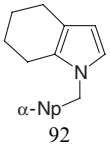
To gain information supporting the plausible reaction pathway of this new transformation, we conducted deuterium quenching with D_2O in the rearrangement of **2a** mediated by Lewis acid **1**, which led to the isolation of **3a** incorporating approximately 50% deuterium at 4-position of the pyrrole unit (Scheme 2). This result certainly indicates that the assembly of the pyrrole structure occurs at hydrolysis stage and hence implies in situ formation of the zwitterionic intermediate of type **A** after the initial 1,2-alkyl shift.

Other selected examples are summarized in Table 2. The substrate **2b** with phenyl ketone moiety also experienced

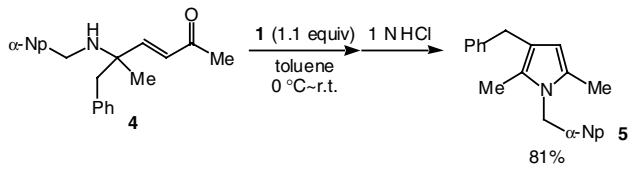
Table 2. Organoaluminum-promoted selective 1,2-rearrangement–cyclization of **2** to unsymmetrically substituted pyrrole **3**[a]



2 (Ar = α-Np) **3**

Entry	R	R′	Condition (°C, h)	% Yield[b]	Prod.
1	CH_2Ph	Ph (**2b**)	0, 1; rt, 12	98	**3b**
2	CH_2Ph	H (**2c**)	−78, 0.25	99	**3c**
3[c]	CH_2Ph	Me (**2d**)	−78, 0.5; 0, 1	93	**3d**
4	$CH_2CH{=}C(CH_3)_2$	H (**2e**)	−78, 1	97	**3e**
5	$CH_2CH{=}C(CH_3)_2$	Me (**2f**)	0, 3; rt, 20	82	**3f**
6	$CH_2CH{=}CHPh$	Me (**2g**)	0, 3; rt, 20	81	**3g**
7	$CH_2CH{=}CHPh$	*p*-Cl–C_6H_4 (**2h**)	−78, 1; 0, 3	87	**3h**
8		(**2i**)	−78, 1	 92	**3i**

[a] Unless otherwise specified, the reaction was carried out with 1.1 equiv of **1** in toluene under the given reaction conditions.
[b] Isolated yield.
[c] With **2** (Ar = *p*-MeO–C_6H_4) as substrate.



Scheme 3.

clean rearrangement under the influence of **1** (entry 1). The reaction of γ-amino enal **2c** was found to complete within 15 min at −78 °C, leading to the quantitative formation of the corresponding pyrrole **3c** (entry 2). Here, the presence of α-naphthylmethyl substituent on nitrogen was not necessarily essential as evident from the attempt with **2d** having *p*-methoxybenzyl group (entry 3).[4] The present system tolerated allylic γ-substituents in accommodation with both enal and enone moieties (entries 4–7). Further, the rearrangement involving ring expansion process appeared feasible to afford pyrrole fused with a cyclohexane unit (**3i**) (entry 8).

Finally, the migratory aptitude of γ-amino enone **4** possessing different alkyl substituents at γ-position was examined. When **4** was treated with **1** in toluene at 0 °C for 3 h and at room temperature for an additional 12 h, pyrrole **5** was obtained as the sole isolable product in 81% yield after acidic treatment, indicating selective transfer of the benzyl group (Scheme 3).[7] This represents an additional synthetic utility of the present transformation.

In summary, we have discovered a unique skeletal rearrangement of γ,γ-dialkyl-γ-amino-α,β-unsaturated carbonyl compounds smoothly facilitated by modified organoaluminum Lewis acid **1**, which gives rise to unsymmetrically substituted pyrroles through the rapid Paal–Knorr type cyclization upon acidic hydrolysis. This new method provides a unique entry to the synthesis of pyrroles, an important class of heterocycles with diverse biological activities. The mechanistic details are being further investigated in our laboratory.

Typical experimental procedure is as follows (Table 1, entry 7): to a solution of 2,2′-bis(trifluoromethanesulfonylamino)-1,1′-biphenyl (98.6 mg, 0.22 mmol) in freshly distilled toluene (2 mL) was added a 1 M hexane solution of trimethylaluminum (220 μL, 0.22 mmol) at room temperature under argon atmosphere, and the mixture was heated at 110 °C for 30 min with stirring. After being cooled to −78 °C, **2a** (84.0 mg, 0.2 mmol) in toluene (1 mL) was added and the stirring was maintained at −78 °C for 30 min. The resulting mixture was poured into 1 N HCl at 0 °C and the whole mixture was stirred for 30 min. Extractive workup was performed with ether and the organic extracts were washed with brine and dried over anhydrous Na_2SO_4. Evaporation of solvents and purification of the residual oil by column chromatography on silica gel (ether/hexane = 1:10 as eluant) gave the corresponding pyrrole **3a** (78.8 mg, 0.196 mmol, 98% yield) as colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.86–7.89 (1H, m, Ar-H), 7.78–7.81 (1H, m, Ar-H), 7.71 (1H, d, J = 8.3 Hz, Ar-H), 7.49–7.53 (2H, m, Ar-H), 7.08–7.32 (9H, m, Ar-H), 6.95 (2H, d, J = 7.5 Hz, Ar-H), 6.36 (1H, d, J = 7.5 Hz, Ar-H), 5.87 (1H, s, C=CH), 5.25 (2H, s, α-NpCH_2N), 3.88 (2H, s, PhCH_2), 3.80 (2H, s, PhCH_2), 2.07 (3H, s, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 142.7, 140.2, 134.1, 133.3, 130.0, 128.8, 128.6, 128.3, 128.2, 128.1, 128.0, 127.3, 126.7, 126.2, 125.9, 125.9, 125.7, 125.5, 122.5, 122.1, 119.4, 107.4, 44.7, 32.7, 30.4, 12.1; IR (neat) 3059, 3024, 2907, 1599, 1493, 1452, 1398, 1352, 1028, 792, 769, 731, 698 cm^{-1}. HRMS (ESI-TOF) calcd for $C_{30}H_{28}N$ ($[M+H]^+$): 402.2216, found: 402.2217.

Acknowledgements

This work was partially supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology, Japan.

References and notes

1. Review: *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: New York, 1991; Vol. 3, Chapter 3, pp 705–1014.
2. For an excellent review on the thermal rearrangement of α-amino ketones, see: Stevens, C. L.; Pillai, P. M.; Munk, M. E.; Taylor, K. G. *Mech. Mol. Migr.* **1971**, *3*, 271, and references cited therein.
3. For the rearrangement of α-amino aldehydes, see: (a) Duhamel, L.; Duhamel, P.; Jarry, A. *Tetrahedron Lett.* **1970**, *13*, 1053; (b) Kirrmann, A.; Nouri-Bimorghi, R.; Elkik, E. *Bull. Soc. Chim. Fr.* **1969**, 2385.
4. Ooi, T.; Saito, A.; Maruoka, K. *J. Am. Chem. Soc.* **2003**, *125*, 3220.
5. For recent representative contributions to the synthesis of pyrroles, see: with transition metal catalysis: (a) Merlic, C. A.; Baur, A.; Aldrich, C. C. *J. Am. Chem. Soc.* **2000**, *122*, 7398; (b) Takaya, H.; Kojima, S.; Murahashi, S.-I. *Org. Lett.* **2001**, *3*, 421; (c) Kel'in, A. V.; Sromek, A. W.; Gevorgyan, V. *J. Am. Chem. Soc.* **2001**, *123*, 2074; (d) Wang, Y.; Zhu, S. *Org. Lett.* **2003**, *5*, 745; (e) Dhawan, R.; Arndtsen, B. A. *J. Am. Chem. Soc.* **2004**, *126*, 468, and references cited therein. Based on the Paal–Knorr reaction:[6] (f) Braun, R. U.; Zeitler, K.; Muller, T. J. J. *Org. Lett.* **2001**, *3*, 3297; (g) Banik, B. K.; Samajdar, S.; Banik, I. *J. Org. Chem.* **2004**, *69*, 213; (h) Raghavan, S.; Anuradha, K. *Synlett* **2003**, 711; (i) Bharadwaj, A. R.; Scheidt, K. A. *Org. Lett.* **2004**, *6*, 2465.
6. (a) Knorr, L. *Ber.* **1884**, *17*, 1635; (b) Paal, C. *Ber.* **1885**, *18*, 367; (c) *Pyrroles, Part II*; Jones, R. A., Ed.; Wiley: New York, 1992; (d) Gribble, G. W. In *Comprehensive Heterocyclic Chemistry II*; Katrizky, A. R., Rees, C. W., Scriven, E. F., Eds.; Pergamon: Oxford, 1996; Vol. 2, p 207.
7. The structure of pyrrole **5** was confirmed by correlation with the authentic sample independently synthesized from 3-benzylhexane-2,5-dione[8] and α-naphthylmethylamine through Paal–Knorr reaction.
8. Ballini, R.; Bosica, G.; Fiorini, D.; Giarlo, G. *Synthesis* **2001**, 2003.