The Regioselective Amino-exchange Reaction of β-Amino Conjugated Enones

Choji KASHIMA* and Yasuhiro YAMAMOTO

Department of Chemistry, University of Tsukuba, Sakura-mura, Niihari-gun, Ibaraki 300-31

(Received September 21, 1978)

By heating with various amines, the amino-exchange reaction of β-amino conjugated enones was regioselectively accomplished on β-carbon to give the corresponding β-amino conjugated enones. The resulting β-dialkylamino conjugated enones could then be used for the synthesis of β,β-disubstituted conjugated enones by treatment with Grignard reagents.

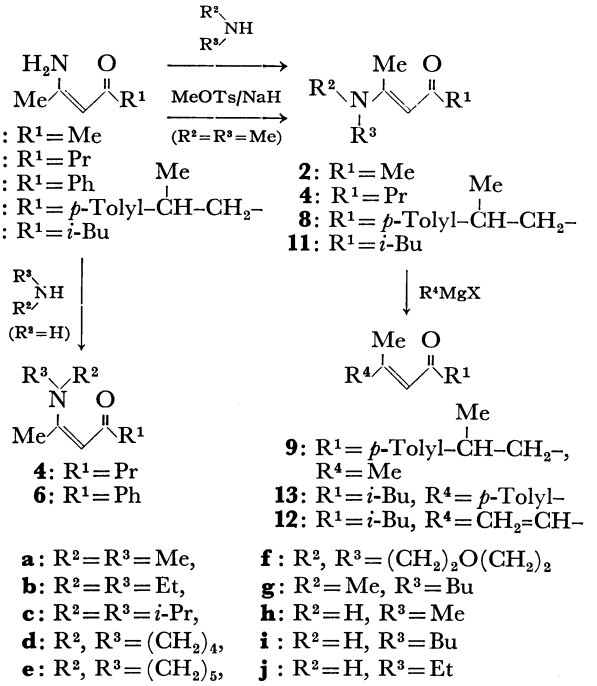
Previously, it has been reported that *cis*-1-substituted-4-amino-3-penten-2-ones were regioselectively prepared from 2,4-pentanedione through 5-substituted 3-methylisoxazoles by catalytic hydrogenation.[1] Benary described[2] how β-dialkylamino conjugated enones reacted with Grignard reagents to afford β,β-disubstituted conjugated enones. However, *N*-unsubstituted and *N*-monosubstituted β-amino conjugated enones are inert toward Grignard reagents, even under forced conditions. Therefore, the conversion from *N*-unsubstituted β-amino conjugated enones to *N*,*N*-disubstituted analogues seems to be the key step in the regioselective synthesis of β,β-disubstituted conjugated enones.

The reactions of β-amino conjugated enones with hydroxylamine[3] and ureas[4] have already been reported. In both cases, nucleophiles attack first the β-carbon of β-amino conjugated enones as a Michael-type addition, and then eliminate the amine or ammonia to afford the corresponding heterocycles. By analogy, we expected the amino-exchange reaction of β-amino conjugated enones upon the treatment with a primary or secondary amine to afford *N*-monosubstituted or *N*,*N*-disubstituted β-amino conjugated enones. (Scheme 1).

When *cis*-4-amino-3-penten-2-one (**1**) was treated with dimethylamine, *trans*-4-dimethylamino-3-penten-2-one (**2a**) was formed in a quantitative yield. In this reaction, the β-amino conjugated enone has two reaction sites, on the β-carbon and on the carbonyl carbon atoms. In the case of the reaction of *cis*-2-amino-2-hepten-4-one (**3**) with dimethylamine, four reaction products, *trans*-2-dimethylamino-2-hepten-4-one (**4a**), *trans*-4-dimethylamino-3-hepten-2-one, and their *cis* isomers, could be expected. When **3** was treated with dimethylamine under the same conditions, however, only one product was obtained. This product was independently prepared from **3** by direct methylation on nitrogen in the presence of sodium hydride. This result showed that the amino-exchange reaction occurred regioselectively on β-carbon to afford 2-dimethylamino-2-hepten-4-one. For determining the configuration, the NMR spectrum of this product was compared with those of **1**, **2a**, **2d**, **2e**, **2f**, and **2h**, which configurations had already been confirmed by means of the IR, UV, and olefinic proton NMR spectra.[5] The allyl methyl proton signal appeared at δ 2.49 ppm, and the molarinduced shift (Δδ) by $Eu(fod)_3$ was larger than that of the olefinic proton signal. This was similar not to the cases of **1** and **2h**, but to those of **2a**, **2d**, **2e**, and **2f** (*cf.* Table 2). These results indicated that *trans*-2-dimethylamino-2-hepten-4-one (**4a**) was more favorable for the reaction product from **3** and dimethylamine.

Similarly, **1** and **3** were treated with various secondary amines to give the corresponding β-amino conjugated enones, **2** and **4**, with *trans* configurations, as are listed in Table 1. On the contrary, the reaction products from primary amines with **3** and **5** were found to be the corresponding *cis*-β-(*N*-monosubstituted)-amino conjugated enones, **4h**, **4i**, and **6j**, which showed allyl methyl protons and the chelated NH signals at about δ 1.9 and 10.5 ppm in NMR respectively. These results suggested that the configurations of the resulting β-amino conjugated enones were easily changed to the thermodynamically stable form under an amino-exchange reaction or on alkylation reaction. In the cases of piperidine, morpholine, diethylamine, diisopropylamine, aniline, *N*-methylaniline, acetamide, and *N*-methylacetamide, the reaction did not occur, even at high temperatures, because of their bulkiness and/or the lack of nucleophilicity.

As applications of this amino-exchange reaction, the syntheses of several terpens, such as ar-turmerone (**9**)[6] and targetone (**12**),[7] were demonstrated. The synthesis of **11** was carried out from *cis*-2-amino-6-*p*-tolyl-2-



Scheme 1.

TABLE 1. THE YIELDS OF AMINO-EXCHANGE REACTION PRODUCTS

	Product			Temp (°C)	Time (h)	Yield (%)
	R^1	R^2	R^3			
2a	Me	Me	Me	90	12	90
2b	Me	Et	Et	150	24	0
2c	Me	*i*-Pr	*i*-Pr	150	24	0
2d	Me	$-(CH_2)_4-$		90[a]	6	98
2e	Me	$-(CH_2)_5-$		105[a]	24	0
2e	Me	$-(CH_2)_5-$		125	12	13
2f	Me	$-(CH_2)_2O(CH_2)_2-$		130[a]	48	0
2g	Me	Me	Bu	90[a]	48	46
4a	Pr	Me	Me	90	12	92
4b	Pr	Et	Et	150	24	0
4d	Pr	$-(CH_2)_4-$		90[a]	6	100
4e	Pr	$-(CH_2)_5-$		105[a]	24	0
4f	Pr	$-(CH_2)_2O(CH_2)_2-$		130[a]	24	0
4h	Pr	H	Me	120	12	96
4i	Pr	H	Bu	130	12	79
6j	Ph	H	Et	110	24	95
8d	*p*-Tolyl-CH(Me)-CH_2-	$-(CH_2)_4-$		90[a]	12	65
11d	*i*-Bu	$-(CH_2)_4-$		90[a]	12	73

a) The reaction was carried out under refluxing without benzene.

TABLE 2. THE NMR DATA OF β-AMINO CONJUGATED ENONES [R^2R^3N-C(Me)=CH-CO-R^1]

Compd	Conf.	δ^{Me}	δ^{CH}	δ^{R^2}	δ^{R^3}	δ^{R^1}	$\Delta\delta^{Me}$	$\Delta\delta^{CH}$
1	*cis*	1.90	5.01	9.6	6.4	1.99	3.78	6.50
2h	*cis*	1.90	4.98	10.7	2.93	2.00	3.36	5.48
3	*cis*	1.90	4.97	9.7	5.2	0.95, 1.2—1.9, 2.25		
4h	*cis*	1.92	5.00	10.8	2.92	0.92, 1.6, 2.2		
4i	*cis*	1.92	4.95	11.0	0.93, 1.55, 3.25	0.93, 1.55, 2.22		
5	*cis*	2.00	5.70	10.2	5.5	7.2—7.5, 7.7—8.0		
6j	*cis*	2.07	5.66	10.5	1.19, 4.1—4.5	7.2—7.5, 7.7—8.0		
7	*cis*	1.82	4.93	9.6	5.15	1.23, 2.27, 2.5, 3.2, 7.1		
10	*cis*	1.90	5.00	9.7	4.9—5.2	0.93, 2.11		
2a	*trans*	2.41	4.95	2.92		1.96	8.32	5.90
2d	*trans*	2.48	4.95	1.94, 3.14		2.01	8.18	5.74
2e	*trans*	2.42	5.14	1.63, 3.32		1.98	7.81	5.61
2f	*trans*	2.48	5.25	3.52		2.09	8.29	6.34
2g	*trans*	2.35	4.82	2.79	0.88, 1.38, 3.17	1.85		
4a	*trans*	2.49	5.00	2.95		0.92, 1.6, 2.15	5.99[a]	1.31[a]
4d	*trans*	2.51	4.91	1.94, 3.31		0.91, 1.53, 2.25		
8d	*trans*	2.49	4.85	1.9, 3.25		1.23, 2.29, 2.5, 3.25, 7.1		
11d	*trans*	2.45	4.80	2.0, 3.32		1.90, 2.0		

hepten-4-one (**7**) through *trans*-2-(1-pyrrolidinyl)-6-*p*-tolyl-2-hepten-4-one (**8d**). Similarly, **12** was synthesized by the reaction of *cis*-2-amino-6-methyl-2-hepten-4-one (**10**) and pyrrolidine, followed by the reaction with vinylmagnesium bromide. The total yields of **9** and **12** were 22 and 9%, based on the corresponding *N*-unsubstituted β-amino conjugated enones respectively.

In conclusion, the treatment of *N*-unsubstituted β-amino conjugated enones with various amines afforded *N*-substituted β-amino conjugated enones by the regioselective amino-exchange reaction. The resulting β-dialkylamino conjugated enones should be very useful intermediates for the synthesis of β,β-disubstituted conjugated enones in combination with the Grignard reaction.

Experimental

The Preparation of N-*Unsubstituted* β-*Amino Conjugated Enones.* *cis*-4-Amino-3-penten-2-one (**1**) was prepared from 2,4-pentanedione by treatment with anhydrous ammonia in anhydrous ethanol.[8] By hydrogenation on platinum, *cis*-2-amino-2-hepten-4-one (**3**) was prepared from 3-methyl-5-propylisoxazole, which had itself been obtained by the action of ethyl bromide on 3,5-dimethylisoxazole in the presence of sodium amide in liquid ammonia.[1] The configurations of all the β-amino conjugated enones were confirmed by the chemical shifts of the allyl methyl and the chelated NH proton signals, and the

shifts of the allyl methyl and olefinic proton signals induced by Eu(fod)$_3$, on NMR in chloroform-d_1, as are listed in Table 2.

cis-*2-Amino-6-*p*-tolyl-2-hepten-4-one (7).* According to the alkylation method,[1] 3,5-dimethylisoxazole was treated with 1-bromo-1-*p*-tolyl-ethane to afford 3-methyl-5-[1-methyl-2-(*p*-tolyl)ethyl]isoxazole; yield, 37 %. Bp 110 °C/3 mmHg. IR (liquid film): 2950, 1610, 1530, 1450, 1420, 1120, and 815 cm^{-1}. Found: C, 78.09; H, 7.93; N, 6.13%. Calcd for $C_{14}H_{17}NO$: C, 78.10; H, 7.96; N, 6.51 %. This isoxazole derivative was then hydrogenated to Compound **7**, which was purified by distillation *in vacuo*; yield, 95%. Bp 137 °C/4 mmHg. IR (liquid film): 3350, 3200, 2950, 1615, 1530, 1410, 1020, and 815 cm^{-1}.

cis-*2-Amino-6-methyl-2-hepten-4-one (10).* By the hydrogenation of 3-methyl-5-isobutylisoxazole, **10** was obtained and purified by recrystallization from hexane; yield, 57%. Mp 56—57 °C, bp 102—105 °C/5 mmHg. Found: C, 67.82; H, 10.57; N, 9.82%. Calcd for $C_8H_{15}NO$: C, 68.04; H, 10.71; N, 9.82%.

General Procedure of Amino-exchange Reaction. A solution of β-amino conjugated enone (5 mmol) and primary or secondary amine (6 mmol) in 2 ml of benzene was heated in a sealed tube. The mixture was then cooled to room temperature and concentrated. The crude *N*-substituted β-amino conjugated enone was purified by fractional distillation and/or recrystallization. The product was identified with an authentic sample by means of VPC and the spectral data.

trans-*2-Dimethylamino-2-hepten-4-one (4a).* Compound **4a** was prepared from **3** and dimethylamine. The NMR peaks were shifted by Eu(fod)$_3$ (*cf.* Table 2). Bp 100—110 °C/3 mmHg. Mass (*m/e*): 155 (M), 140 (M−15), 138, 127 (M−28), 112 (M−43), 98, 85, 84, 70, 69, 56, and 44. Found: C, 68.80; H, 11.07; N, 8.82%. Calcd for $C_9H_{17}NO$: C, 69.63; H, 11.03; N, 9.02%.

trans-*2-(1-Pyrrolidinyl)-2-hepten-4-one (4d).* Compound **4d** was prepared from **3** and pyrrolidine. Bp 112—114 °C/5 mmHg. IR (liquid film): 2950, 2910, 1630, 1530, 1340, and 1020 cm^{-1}. Found: C, 72.44; H, 10.40; N, 7.88%. Calcd for $C_{11}H_{19}NO$: C, 72.88; H, 10.57; N, 7.73%.

cis-*2-Methylamino-2-hepten-4-one (4h).* Compound **4h** was prepared from **3** and methylamine. Bp 53—55 °C/5 mmHg. Found: C, 68.33; H, 10.46; N, 9.90%. Calcd for $C_8H_{15}NO$: C, 68.04; H, 10.71; N, 9.92%.

cis-*2-Butylamino-2-hepten-4-one (4i).* Compound **4i** was prepared from **3** and butylamine. Bp 105 °C/3 mmHg. IR (liquid film): 2950, 2915, 1605, 1580, 1300, and 735 cm^{-1}. Found: C, 72.19; H, 11.21; N, 7.65%. Calcd for $C_{11}H_{21}NO$: C, 72.08; H, 11.55; N, 7.64%.

trans-*2-(1-Pyrrolidinyl)-6-*p*-tolyl-2-hepten-4-one (8d).* Compound **8d** was obtained from **7** and pyrrolidine, and subsequently purified by distillation. Bp 130 °C/5 mmHg. IR (liquid film): 2950, 1630, 1340, 1020, 815, and 730 cm^{-1}.

trans-*2-(1-Pyrrolidinyl)-6-methyl-4-hepten-2-one (11d).* Compound **11d** was obtained by the amino-exchange reaction from **10** and pyrrolidine, and subsequently purified by recrystallization from hexane. Mp 67—68.5 °C. Found: C, 73.26; H, 10.57; N, 7.15%. Calcd for $C_{10}H_{21}NO$: C, 73.79; H, 10.84; N, 7.17%.

The Direct Methylation of 3. Sodium hydride in Bayol was washed with dry ether 2 times. To the suspension of sodium hydride in dry ether, **3** (5 mmol) was then added, drop by drop, at 0 °C to precipitate a pasty mass. Then methyl tosylate (12 mmol) in dry ether was added slowly to the mixture. After the reaction mixture had been stirred at room temperature for 5 h, the reaction mixture was washed with aqueous sodium chloride and dried over anhydrous magnesium sulfate. The ether was evaporated off, and the residue was distilled *in vacuo* to afford **4a**, which was identified with amino-exchange reaction product by means of VPC and the spectral data; yield, 34%.

ar-Turmerone (9). The title compound was obtained from **8d** and methylmagnesium iodide, and the product was identified with authentic sample by means of its spectral data;[6] yield, 28 %.

ar-Dihydroturmerone (14). By the treatment of **11d** with *p*-tolylmagnesium bromide, 2-*p*-tolyl-6-methyl-2-hepten-4-one (**13**) was prepared; yield, 24 %. Bp 70—75 °C/2 mmHg. NMR ($CDCl_3$): 0.92 (d, 6H, J=7.0 Hz), 2.0 (m, 1H), 2.3 (m, 2H), 2.34 (s, 3H), 2.47 (s, 3H), 6.35 (broad s, 1H), 7.04 (d, 2H, J=10.0 Hz), and 7.30 ppm (d, 2H, J=10.0 Hz). IR (liquid film): 2950, 1680, 1600, 1195, 1060, and 810 cm^{-1}. Found: C, 82.23; H, 9.20%. Calcd for $C_{15}H_{20}O$: C, 83.28; H, 9.32%. Compound **13** was hydrogenated on platinum in ethanol to afford Compound **14**; yield, 36 %. Bp 111—114 °C/6 mmHg. NMR (CCl_4): 0.90 (d, 6H, J=7.0 Hz), 1.16 (d, 3H, J=7.5 Hz), 2.06 (m, 3H), 2.27 (s, 3H), 2.48 (m, 2H), 3.21 (m, 1H), and 7.0 ppm (s, 4H). Found: C, 82.95; H, 10.25%. Calcd for $C_{15}H_{22}O$: C, 82.51; H, 10.16%.

The title compound was also obtained by the hydrogenation of **9** on platinum in ethanol; the two products were identical in their spectral data.

Targetone (12). The title compound was prepared from **11d** and vinylmagnesium bromide, and subsequently purified by distillation. The product was identified with an authentic sample by means of its spectral data.[8]

References

1) C. Kashima, S. Tobe, N. Sugiyama, and M. Yamamoto, *Bull. Chem. Soc. Jpn.*, **46**, 310 (1973).

2) E. Benary, *Chem. Ber.*, **64**, 2543 (1931); J. Ficinni and Normant, *Bull. Soc. Chim. Fr.*, **1964**, 1294.

3) C. Kashima, Y. Yamamoto, Y. Omote, and Y. Tsuda, *Bull. Chem. Soc. Jpn.*, **50**. 543 (1977).

4) C. Kashima, Y. Yamamoto, Y. Omote, T. Otsuka, and Y. Tsuda, *Heterocycles*, **4**, 1387 (1976).

5) C. Kashima, H. Aoyama, Y. Yamamoto, T. Nishio, and K. Yamada, *J. Chem. Soc., Perkin Trans. 2*, **1975** 665.

6) R. P. Gandhi, O. P. Vig, and S. M. Mukheji, *Tetrahedron*, **7**, 236 (1959); V. K. Honwad and A. S. Rao, *Tetrahedron*, **20**, 2921 (1964); K. S. Ayyor and G. S. K. Rao, *Can. J. Chem.*, **46**, 1467 (1968).

7) E. E. Boehm, V. Thaller, and M. C. Whiting, *J. Chem. Soc.*, **1963**, 2535.

8) A. Combes and C. Combes, *Bull. Soc. Chim. Fr.*, [3] **7**, 778 (1892).