1-Pyrrolyldiisobutylalane. A Stereoselective Reducing Agent for Reduction of Cyclic Ketones to Thermodynamically More Stable Alcohols

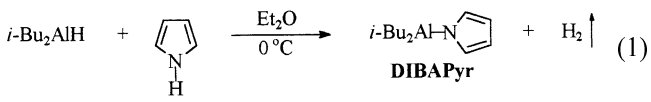
Oh Oun Kwon and Jin Soon Cha*

Department of Chemistry and Institute of Natural Science, Yeungnam University, Kyongsan 712-749, Korea
Received February 2, 2000

Recently, we have reported a series of diisobutylalane derivatives, such as *Al*-chloro-, *Al*-alkoxy-, and *Al*-dialkylaminodiisobutylalanes,[1-3] as selective reducing agents: all these reagents show very high selectivities in the reduction of α,β-unsaturated different carbonyl compounds to allylic alcohols as well as in the competition between carbonyl compounds. In addition, *Al*-isopropoxydiisobutylalane,[2-c,d] one of the *Al*-alkoxy derivatives, can also convert cyclic ketones to the corresponding thermodynamically more stable alcohols in high stereoselectivities. In continuation of our efforts to explore new reducing systems for such transformations, we examined the reducing action of 1-pyrrolyldiisobutylalane (DIBAPyr), an aromatic derivative of diisobutylalane, toward various organic functional groups. In the course of a systematic study, we have found that the reagent shows an excellent stereoselectivity in the cyclic ketone reductions to provide the corresponding thermodynamically more stable alcohols. This paper describes the stereoselective reduction of our new reagent.

Results and Discussion

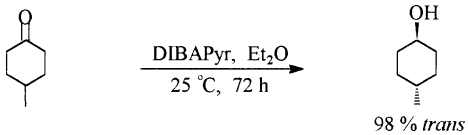
1-Pyrrolyldiisobutylalane (DIBAPyr) is readily prepared by a simple reaction of diisobutylaluminum hydride (DIBAH) with pyrrole in ethyl ether (Eq. 1). The results of this reagent



(1)

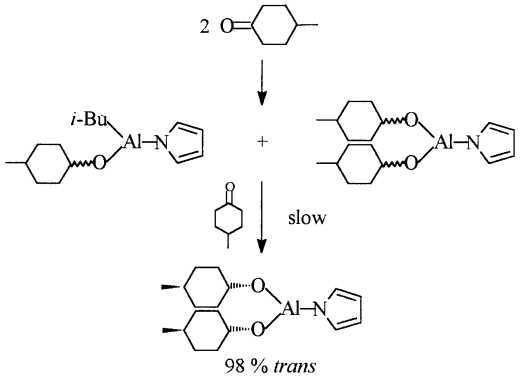
toward representative cyclic ketones at 25 °C are summarized in Table 1.

The characteristic features of the Table 1 are (1) the reagent readily reduces one or two equivalents of the cyclic ketones examined except camphor, even though the second equivalent of ketone is reduced in a relatively slower rate than the first; (2) the stereochemistry of the product alcohol with one equivalent of DIBAPyr is unchangeable during the course of the reaction, whereas the stereochemistry with half equivalent of this reagent is apparently dependent on the reaction time. The stereoselectivity increases consistently



(2)

with the increase of reaction time to result in the exclusive formation of thermodynamically more stable alcohol (Eq. 2), with the exception of camphor which is resistant to such isomerization under the reaction conditions. This seems to be the phenomenon that must rise from the isomerization where the initially formed thermodynamically less stable isomer, one of the two isomer produced by reduction with DIBAPyr, is converted to the more stable one in the course of a Meerwein-Ponndorf-Verley type reduction[2-c,4] (Eq. 3).



(3)

In the case where one equivalent of ketone was used, all the ketones in the reaction mixture were rapidly consumed by one or two isobutyl groups of the reagent. Therefore, there was no ketone molecule to be involved in the slow, second process diagramed in Eq. 3 which leads to the increase of isomeric ratio. On the other hand, in the case of two equivalents of ketone were used a part of the second extra ketone remained in the reaction mixture until all the isobutyl moiety was removed from the reagent *via* reduction. Therefore, the isomer equilibration process became effective and lasted until the reduction completed.

It is noteworthy that the pyrrole moiety, increases the Lewis acidity of aluminum atom of DIBAPyr, so as to cause remarkable reactivity enhancement and hence the ready involvement of both two isobutyl groups in the reduction. All other derivatives of diisobutylalane aforementioned can utilize only one of the two isobutyl group in the ketone reduction. This indicates that the reagent, DIBAPyr, can also be effectively applicable to the reduction of other organic functional groups. In fact, our preliminary results show that DIBAPyr reduces acid chlorides and epoxides as well as aldehydes and ketones, whereas other derivatives can reduce only aldehydes and ketones. We are currently exploring this selectivity issue in a great detail.

Table 1. Stereoselective Reduction of Cyclic Ketones with 1-Pyrrolyldiisobutylalane (DIBAPyr) in Ethyl Ether at 25 °C

Ketone	One equiv of ketone[a]			Two equiv of ketone[b]		
	Reaction time (h)	Ratio of more stable isomer (%)[c]	Yield of alcohol (%)[c]	Reaction time (h)	Ratio of more stable isomer (%)[c]	Yield of alcohol (%)[c]
2-Methyl-cyclohexanone	1	44	100	1	64	94
	24	44	100	24	83	98
	72	44	100	72	88	99
				120	90	100
3-Methyl-cyclohexanone	24	64	100	1	76	99
	72	64	100	24	91	>99.9
				72	97	100
				120	97	100
4-Methyl-cyclohexanone	24	73	100	1	80	99
	72	73	100	24	93	>99.9
				72	98	100
				120	98	100
4-*tert*-Butyl-cyclohexanone	24	75	100	1	97	99
	72	75	100	24	97	100
				120	97	100
3,3,5-Trimethyl-cyclohexanone	1	54	100	1	83	81
	24	54	100	24	97	90
	72	54	100	72	>99.9	99
				120	>99.9	100
Norcamphor	24	27	100	1	53	86
	72	27	100	24	76	95
				72	84	99
				120	97	100
				144	97	100
Camphor	24	7	67	1	9	4
	72	8	97	24	9	41
	120	8	100	72	10	56
				144	15	69

[a]A 1 : 1 ratio for reagent to ketone was utilized. [b]A 1 : 2 ratio for reagent to ketone was utilized. [c]Analyzed by GC.

Experimental Section[5]

Preparation of 1-Pyrrolyldiisobutylalane (DIBAPyr) in Ethyl Ether. The following procedure served for the preparation of the reagent. An oven-dried, 200-mL, round-bottomed flask, equipped with a side arm, a condenser, and an adaptor connected to a mercury bubbler, was cooled to room temperature under a stream of nitrogen and maintained under a static pressure of nitrogen. To this flask was added 14.22 g of *i*-Bu_2AlH (100 mmol) and 25 mL of ethyl ether, and the flask was maintained at 25 °C by immersion in a water bath. A 7.2 g of pyrrole (105 mmol) was added to the solution of *i*-Bu_2AlH dropwise with vigorous stirring at 25 °C. After the complete evolution of hydrogen, the solution was diluted with ethyl ether to a total volume of 100 mL to be 2.0 M.

Reduction of Cyclic Ketones. The following procedure was used to explore the stereoselectivity of this reagent. In a 50-mL, round-bottomed flask was placed 5.0 mL of the 2.0 M solution of the reagent in ethyl ether (10.0 mmol). The flask was maintained at 25 °C by immersion in a water bath. To the flask was added 10 mL of 2-methylcyclohexanone solution in ethyl ether (1.0 or 2.0 M in ketone), and the reaction mixture was stirred at 25 °C. After the appropriate time intervals, the reaction aliquot was withdrawn and then quenched by addition of 3 N HCl. The aqueous layer was saturated with $MgSO_4$, and the organic layer was dried over anhydrous K_2CO_3. The isomeric ratio of alcohol product analyzed by GC using a capillary column are listed in Table 1.

Acknowledgment. The authors wish to acknowledge the financial support of the Korea Research Foundation made in the program year of 1998. The ^{27}Al NMR spectra were recorded on a Bruker AMX 300 spectrometer at the Yeungnam University Instrumental Analysis Center.

References and Notes

1. (a) Cha, J. S.; Kwon, O. O.; Kwon, S. Y.; Kim, J. M.; Seo, W. W.; Chang, S. W. *Synlett* **1995**, 1055. (b) Cha, J. S.; Kwon, O. O.; Kwon, S. Y. *Bull. Korean Chem. Soc.* **1995**, *16*, 1009.
2. (a) Cha, J. S.; Kwon, O. O.; Kwon, S. Y.; Kim, J. M.; Seo, W. W.; Chang, S. W. *Bull. Korean Chem. Soc.* **1996**, *17*,

221. (b) Cha, J. S.; Kwon, O. O.; Kwon, S. Y. *Org. Prep. Proced. Int.* **1996**, *28*, 355. (c) Cha, J. S.; Kwon, O. O. *J. Org. Chem.* **1997**, *62*, 3019. (d) Cha, J. S.; Kwon, O. O. *Bull. Korean Chem. Soc.* **1997**, *18*, 689. (e) Cha, J. S.; Kwon, O. O.; Kim, J. M.; Chun, J. H.; Lee, Y. S.; Lee, H. S.; Cho, S. D. *Ibid.* **1998**, *19*, 236.

3. Cha, J. S.; Kwon, S. Y.; Kwon, O. O.; Kim, J. M. *Bull. Korean Chem. Soc.* **1996**, *17*, 900.
4. (a) Haubenstock, H.; Davidson, E. B. *J. Org. Chem.* **1963**, *28*, 2772. (b) Heinsohn, G. E.; Ashby, E. C. *Ibid.* **1973**, *38*, 4232. (c) Cha, J. S.; Kwon, O. O.; Kim, J. M.; Cho, S. D. *Synlett* **1997**, 1465.
5. All reactions were performed under a dry N_2 atmosphere. All chemicals used were commercial products of the highest purity available; ethyl ether was dried over 4-Å molecular sieves and distilled from sodium-benzophenone ketyl prior to use. Gas chromatographic analyses were carried out with a Varian 3300 chromatograph using a 30 m DB-WAX capillary column.