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Stereoselective Synthesis of 2-Alkylamino-*N*-(2'-alkylphenyl)succinimide Conformers

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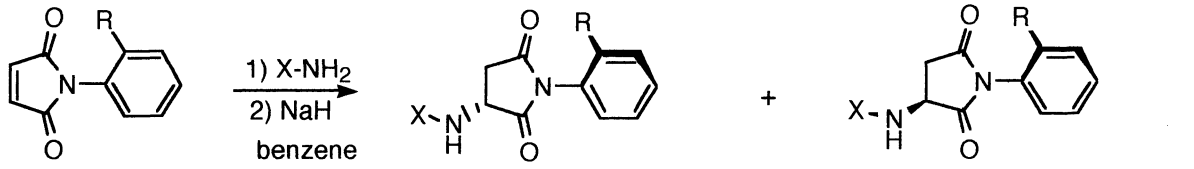
Isolable conformers of 2-alkylamino-*N*-(2'-alkylphenyl)succinimide were stereoselectively synthesized by amination of *N*-(2'-alkylphenyl)maleimides. The rotational barrier and the α-methylation of them were investigated.

Synthesis of stable conformers is important to investigate the relation between the reactivity and the conformation.[1] Recently, our laboratory and Curran et al. reported the synthesis of isolable conformers by atropselective reaction of *N*-(2'-alkylphenyl)maleimide **3**.[2] We now describe our results of the atropselective amination, the rotational barrier measurement, and the cis-selective α-methylation of the obtained conformers.



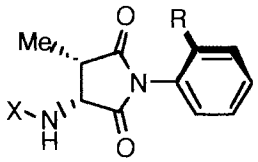
1 (R = H)
2 (R = Me)
3 (R = t-Bu)

4 (R = H, X = Bn)
5a (R = Me, X = Bn)
6a (R = t-Bu, X = Bn)
7a [R = t-Bu, X = CH(CH$_3$)Ph]

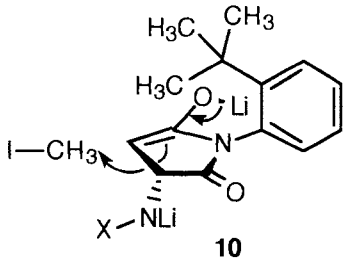
4 (R = H, X = Bn)
5b (R = Me, X = Bn)
6b (R = t-Bu, X = Bn)
7b [R = t-Bu, X = CH(CH$_3$)Ph]

N-Phenylmaleimides **1-3** were prepared by condensation of maleic anhydride and 2-substituted aniline. Amination of **1-3** was performed in benzene at room temperature with deprotonated amines [benzylamine and (*S*)-1-phenylethylamine] by sodium hydride.[4] In the case of **1** (R = H), polymerization of the maleimide was mainly proceeded and the yield of **4** was poor (9%). The amination of **2** (R = Me) gave the better yield (**5a** and **5b**, 68%) without selectivity due to the free rotation around the N-Ar single bond between the imide and the benzene ring. Benzylamine reacted with **3** (R = *t*-Bu) to give the products **6a** and **6b** with moderate selectivity (29%, 81 : 19). The amination of **3** with phenylethylamine was perfectly controlled to give **7a** (56%, **7a** : **7b** = >99 : 1).[5] The high stereoselectivity originates in the steric repulsion between the ortho substituent (R) and the amine.

The rotational barrier of the N-Ar single bond was measured by ^{1}H NMR study.[6] The rotational barriers $\Delta G^{\neq}$ of **5a**,**5b** (R = Me, X = benzyl), **6a** (R = t-Bu, X = benzyl) and **7a** (R = *t*-Bu, X = 1-phenylethyl) were 20.7, 28.4, and 28.6 kcal/mol, respectively. Accordingly, the imide **5** freely rotates around the N-Ar single bond at room temperature. On the other hand the rotation of **6** and **7** is locked at room temperature to give the isolable conformers.



8 (R = t-Bu, X = Bn)
9 [R = t-Bu, X = CH(CH$_3$)Ph]



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The α-methylation of **6a** and **7a** was carried out by the addition of *n*-butyllithium followed by methyl iodide in THF at -78 °C under nitrogen atmosphere, to give the cis isomers **8** (10%) and **9** (52%). The attack of methyl iodide is favorable from the down side of the intermediate dianion **10** to give the cis isomers **8** and **9**, because of steric hindrance due to the bulky ortho *t*-butyl group.

In both amination and α-methylation the stereoselectivity is controlled by the *t*-butyl group on the benzene ring although it is at the ε-position from the reaction center.

References

1) M. Oki, *Angew. Chem., Int. Ed. Engl.*, **15**, 87 (1976).
2) Presented in part at the 67th Spring Meeting of the Chemical Society of Japan, Aoyama in Tokyo, March 29, 1994.
3) D. P. Curran, H. Qi, S. J. Grieb, and N. C. DeMello, *J. Am. Chem. Soc.*, **116**, 3131 (1994).
4) An example of amination of maleimides; Maleimide **3** (100 mg, 0.436 mmol) and (*S*)-1-phenylethylamine (0.084 ml, 0.654 mmol) were dissolved in 5 ml of benzene. After addition of sodium hydride (20 mg), the solution was stirred at room temperature for 3 h. The reaction was quenched by addition of water and the organic phase was washed with water and dried over anhydrous magnesium sulfate. The oily products were separated by column chromatography on silica gel eluting with hexane-ethyl acetate to give **7a** (82.5 mg, 56%).
5) The stereochemistry of **7a** (consisted from two regioisomers) was estimated by its NOE experiments.
6) C. E. Looney, W. D. Phillips, and E. L. Reilly, *J. Am. Chem. Soc.*, **79**, 6136 (1957).
7) Data of key compounds:

6a: Colorless oil; ^{1}H NMR ($CDCl_3$, 270 MHz) δ 1.26 (s, 9H), 2.70 (dd, J = 18.1, 5.4 Hz, 1H), 3.02 (dd, J = 18.1, 8.4 Hz, 1H), 3.91 (s, 2H), 3.92 (dd, J = 8.4, 5.4 Hz, 1H), 6.86-7.59 (m, 9H).

6b: Colorless oil; ^{1}H NMR ($CDCl_3$, 270 MHz) δ 1.32 (s, 9H), 2.70 (dd, J = 17.7, 5.3 Hz, 1H), 3.02 (dd, J = 17.7, 7.9 Hz, 1H), 3.91 (dd, J = 7.9, 5.3 Hz, 1H), 3.93 (s, 2H), 6.79-7.61 (m, 9H).

7a: (diastereomer A) Colorless crystals; mp 137-137.5 °C; ^{1}H NMR ($CDCl_3$, 270 MHz) δ 1.23 (s, 9H), 1.45 (d, J = 6.5 Hz, 3H), 2.33 (dd, J = 18.7, 5.7 Hz, 1H), 2.55 (dd, J = 18.7, 8.5 Hz, 1H), 3.81 (dd, J = 8.5, 5.7 Hz, 1H), 4.05 (q, J = 6.4 Hz, 1H), 6.82-7.57 (m, 9H). (diastereomer B) Colorless crystals; mp 117.5-118 °C; ^{1}H NMR ($CDCl_3$, 270 MHz) δ 1.21 (s, 9H), 1.45 (d, J = 6.5 Hz, 3H), 2.75 (dd, J = 17.5, 5.1 Hz, 1H), 2.95 (dd, J = 17.5, 8.3 Hz, 1H), 3.64 (dd, J = 8.3, 5.1 Hz, 1H), 3.84 (q, J = 6.5 Hz, 1H), 6.88-7.58 (m, 9H).

Diastereomer **7b** was synthesized by heating **7a** in a sealed tube at 160 °C.

7b: (Rotational isomer of diastereomer A) Colorless oil; ^{1}H NMR ($CDCl_3$, 270 MHz) δ 1.32 (s, 9H), 1.44 (d, J = 6.6 Hz, 3H), 1.84 (dd, J = 18.1, 5.7 Hz, 1H), 2.08 (dd, J = 18.1, 8.3 Hz, 1H), 3.80 (dd, J = 8.3, 5.7 Hz, 1H), 4.11 (q, J = 6.6 Hz, 1H), 6.74-7.59 (m, 9H).

8: Colorless oil; ^{1}H NMR ($CDCl_3$, 270 MHz) δ 1.29 (s, 9H), 1.41 (d, J = 7.5 Hz, 3H), 3.13 (dq, J = 7.5, 7.5 Hz, 1H), 3.95 (d, J = 7.5 Hz, 1H), 3.96 (s, 2H), 6.79-7.59 (m, 9H).

9: Colorless oil; ^{1}H NMR ($CDCl_3$, 270 MHz) δ 1.25 (s, 9H), 1.26 (d, J = 7.8 Hz, 3H), 1.45 (d, J = 6.7 Hz, 3H), 2.75 (dq, J = 7.9, 7.8 Hz, 1H), 3.74 (d, J = 7.9, 1H), 4.25 (q, J = 6.7 Hz, 1H), 6.76-7.57 (m, 9H).

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