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Kinetic Enolate Formation by Lithium Arylamide: Effects of Basicity on Selectivity

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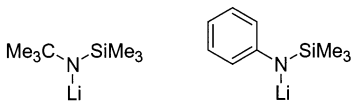
Abstract: Five ketones $R_1COCH_2R_2$ (**1a**−**e**) were enolized in tetrahydrofuran solvent employing lithium arylamides with different electron-withdrawing and -donating substituents on the phenyl ring (**4a**−**e**). Enolate selectivity is unaffected by a moderate electron-releasing or -withdrawing group, but significantly enhanced by strong electron-withdrawing substituents to yield predominantly *Z*-enolate. Outstanding selectivity was achieved with lithium trichloroanilide (**5**) and lithium diphenylamide (**6**). The results are rationalized in terms of electronic effects on the tightness of the transition states.

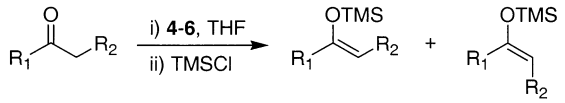
Enolates are an important reactive intermediate that has found wide applications in organic synthesis.[1] The geometry of enolates and related silyl enol ethers (*E* or *Z*) is essential to the control of stereochemistry (diastereo- or enantioselectivity) in the subsequent reactions. In an earlier effort to understand the role of steric and electronic effects of lithium amides in governing enolate *E*/*Z* selectivity, we investigated kinetic enolization of simple ketones (**1a**: R_1 = Et, R_2 = Me; **1b**: R_1 = *i*-Pr, R_2 = Me; **1c**: R_1 = Ph, R_2 = Me; **1d**: R_1 = Me, R_2 = Et; **1e**: R_1 = *i*-Bu, R_2 = *i*-Pr) in tetrahydrofuran (THF) with several alkyl-, aryl-, and trimethylsilyl-substituted lithium amide bases.[2] The kinetic *E*/*Z* selectivity varied widely with different substitution patterns on the nitrogen. Excellent *E*-selectivity was achieved with lithium *tert*-butyltrimethylsilylamide (**2**) at room temperature while very high *Z* preference was obtained by using lithium trimethylsilylanilide (**3**) at −78 °C. We established that



2 **3**

these were the results of kinetic enolization, as the enolization of unsymmetric 2-pentanone and 2-methyl-3-pentanone yielded the major enolate derived from the removal of the less hindered proton. In light of the seemingly similar steric hindrance in **2** and **3**, the completely opposite *E*- and *Z*-selectivity is both surprising and interesting. We hypothesized that the enhanced *Z*-selectivity displayed by **3** was due to its much more stabilized nitrogen as compared to **2**, which resulted in a highly loose transition state leading to the *Z* preference. We now report further evidence supporting this hypothesis.

SCHEME 1



1a: R_1=Et, R_2=Me (Z) (E)
1b: R_1=*i*-Pr, R_2=Me
1c: R_1=Ph, R_2=Me
1d: R_1=Me, R_2=Et
1e: R_1=*i*-Bu, R_2=*i*-Pr

To make unbiased comparisons on the electronic nature of amide bases, we must maintain a consistent steric effect among the amide bases used. We chose various substituted lithium anilides ($X-C_6H_4NHLi$, **4a**: X = H; **4b**: X = *p*-CH_3O; **4c**: X = *o*-Cl; **4d**: X = *m*-Cl; **4e**: X = *p*-CH_3CO_2; **4f**: X = *p*-CN) for this purpose. The steric influence on the reactive nitrogen center imposed by the ring substituents, especially those on the meta and para positions, is expected to be negligible. This allows us to assess the electronic effects of substituents on enolate selectivity. As a comparison, we also included in our study two other highly stabilized nitrogen bases: lithium 2,4,6-trichloroanilide (**5**) and lithium diphenylanilide (**6**). **4**−**6** were prepared by treating their corresponding amine precursors with butyllithium in THF. They were then allowed to react with ketones **1a**−**e** and the resulting enolates were quenched with chlorotrimethylsilane to yield trimethylsilyl enol ethers (Scheme 1). The enol ethers, after workup, were subject to GCMS and NMR analysis and the isomeric enolate ratios determined. The *E*/*Z* ratios derived from **1a**−**e** by lithium arylamides **4a**−**f** are listed in Table 1.

We noted from Table 1, extries 1, 7, and 13, that the unsubstituted lithium anilide (**4a**) gave better *Z*-selectivity than LDA or lithium *N*-isopropylanilide used in our previous study in the same solvent. This is presumably due to the less steric hindrance in **4a**, and can be explained by the Ireland's transition state model (Scheme 2).[3] In the transition states involving **4a**, the less hindered hydrogen is expected to favor the axial position while the aryl group occupies the equatorial position. The less sterically hindered interaction, H ↔ R_2, results in a lower energy for the transition state $B^‡$ leading to *Z*-enolate preference. It is also clear from Table 1 that **4b**−**d** gave nearly identical *E*/*Z* selectivity to that by **4a** for the three ketones (**1a**, **1b**, and **1d**) studied. We have previously concluded that *E*/*Z* selectivity is a result of balancing steric (bulkiness of the amide base and R_1 and R_2) and electronic factors (electron density on the nitro-

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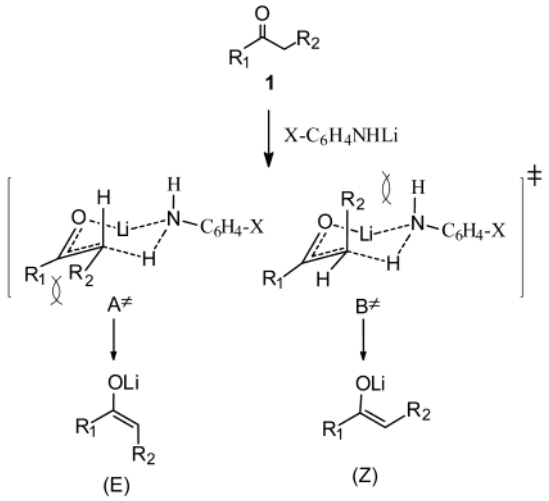
TABLE 1. Kinetic Enolate Selectivity from Ketones 1a−e by Bases 4a−f at 0 °C in THF[a]

entry	ketones	bases	*E*:*Z*
1	**1a**	**4a**	21:79
2	**1a**	**4b**	22:78
3	**1a**	**4c**	24:76
4	**1a**	**4d**	25:75
5	**1a**	**4e**	10:90
6	**1a**	**4f**	8:92
7	**1b**	**4a**	11:89[b]
8	**1b**	**4b**	8:92[b]
9	**1b**	**4e**	4:96[b]
10	**1b**	**4f**	2:98[b]
11	**1c**	**4e**	2:98
12	**1c**	**4f**	2:98
13	**1d**	**4a**	50:50[c]
14	**1d**	**4b**	40:60[c]
15	**1d**	**4c**	44:56[c]
16	**1d**	**4d**	44:56[c]
17	**1d**	**4e**	26:74[c]
18	**1d**	**4f**	21:79[c]
19	**1e**	**4e**	14:86
20	**1e**	**4f**	9:91

[a] All results were obtained with a base-to-ketone ratio of 1.1:1. [b] A small amount of the more substituted regioisomer was also obtained. [c] Deprotonation from the primary carbon constitutes ≥80% of the overall yield.

SCHEME 2



gen) in the transition state, and strong electron-withdrawing substituents on the nitrogen result in a loose transition state favoring the *Z*-enolate. In the current case, the similar selectivities given by **4b** and **4a** are not particularly surprising, as the negative nitrogen would resist any further electron donation from the *p*-OCH_3. Moreover, the *p*-methoxy group should cause no change in steric hindrance. Thus, the perturbation in both steric and electronic nature of **4b** is negligibly small to change the energy difference between transition states $A^{\ddagger}$ and $B^{\ddagger}$. Likewise, the effect of *o*- and *m*-Cl (**4c** and **4d**) on the *E*/*Z* ratio is relatively small (compare entries 1, 3, and 4, and 13, 15, and 16). Although a small increase in the steric hindrance of **4c** might be expected due to the *o*-Cl, it is conceivable that this effect may be counter-balanced by the electronic effect of the moderate electron-withdrawing *o*-Cl (due to its proximity to the nitrogen and its ability to coordinate to the lithium counterion). In the case of *m*-Cl, both steric and inductive electron-withdrawing effects of the chlorine diminish, thus resulting in a very small selectivity change.

TABLE 2. *E*/*Z* Selectivity from Ketones 1a−e by 3, 5, and 6 in THF[a]

entry	ketones	bases	*E*:*Z*
1	**1a**	**5**	11:89[b]
2	**1b**	**5**	2:98[b]
3	**1c**	**5**	6:94[b]
4	**1d**	**5**	24:76[b]
5	**1e**	**5**	6:94[b]
6	**1a**	**3**	7:93[c]
7	**1a**	**6**	5:95[c]
8	**1b**	**3**	5:95[c]
9	**1b**	**6**	0:100[c]
10	**1c**	**3**	0:100[c]
11	**1c**	**6**	0:100[c]
12	**1d**	**3**	10:90[c]
13	**1d**	**6**	4:96[c]
14	**1e**	**3**	2:98[c]
15	**1e**	**6**	0:100[c]

[a] In the case of unsymmetric ketones, deprotonation occurred mainly on the less substituted carbon. [b] The reactions were run at 0 °C. [c] The reactions involving **3** and **6** were both carried out at −78 °C to achieve the best selectivity.

On the other hand, strong electron-withdrawing CH_3-CO_2 (**4e**) and CN (**4f**) groups on the para position of the phenyl ring enhance the *Z*-selectivity significantly. Since these groups on the para position are expected to cause negligible change in the steric hindrance of the base, the enhanced *Z*-selectivity must come from the substantial electronic delocalization of the anionic nitrogen through the resonance effect. This is indeed consistent with our previous report that substantial stabilization of the electron density on the amide nitrogen leads to a significantly loose transition state thus favoring the *Z*-enolate.[2]

Table 2 summarizes *E*/*Z* selectivity for **1a**−**e** by **5** and **6** in THF, along with the selectivity by **3** that we reported previously. It is clear that both **5** and **6** produced very high *Z* preference, with lithium diphenylamide giving the best *Z*-selectivity. If the steric hindrance of the amide bases were the only factor governing the *E*/*Z* selectivity, then **3**, **5**, and **6** would all seem more hindered than the other bases used in this study and be expected to give higher *E*-selectivity—opposite of what we observed. Other examples of steric effect on enolate selectivity was previously reported.[4] The enhanced *Z*-selectivity is consistent with the fact that the nitrogen in **5** and **6** is extensively stabilized, just as in **3**, by the strong electron-withdrawing nature of the three Cl's in **5** and the phenyl groups in **6**. Comparisons between selectivity by **4c, 4d**, and **5** provide further evidence that sufficient electronic delocalization on the nitrogen (three Cl's vs one Cl) is necessary to achieve significantly enhanced *Z*-selectivity. Strong evidence also came from the comparisons of the substituent effects on the *E*/*Z* selectivity along the series LDA → lithium *N*-isopropyltrimethylsilylamide → **3** and the series LDA → lithium *N*-isopropylanilide → **6**. While the first isopropyl replacement in LDA by a trimethylsilyl or phenyl group yields nearly identical *E*/*Z* selectivity, the second replacement by a phenyl group (leading to **3** and **6**, respectively) results in a dramatic *Z* enhancement. Although these results are in complete agreement with

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a loose transition state due to the strong electronic delocalization on the nitrogen, it is possible that they may also result from the change in the aggregation state of the lithium amides. It is possible that different aggregates (monomers, dimers, or higher aggregates solvated by a different number of solvent molecules) may become the active deprotonating species when the electronic property (basicity) of our lithium amides is drastically altered. Extensive aggregation studies on alkyllithium and lithium amides (particularly LDA) have been reported by Collum and co-workers.[5]

In conclusion, we reported further evidence on the effect of electronic delocalization in lithium amide bases on the enolate stereoselectivity. *Z*-enolate selectivity can be significantly enhanced by modifying amide bases with strong electron-withdrawing substituents. Excellent *Z*-selectivity can be achieved with lithium diphenylamide, which is of practical value in organic synthesis.

Experimental Section

General. Glassware and syringe needles were dried at 140 °C overnight in an oven. Gastight syringes were dried in a desiccator under vacuum (≤0.1 Torr) for at least 1 h before use. The enolization experiments were carried out in Schlenk flasks under a nitrogen atmosphere. ^{1}H NMR was obtained on a 270-MHz FT-NMR spectrometer. The quantitative analysis of trimethylsilyl enol ethers was carried out on GC-MS and NMR.

Solvent. Tetrahydrofuran (99.5%) was dried over Na/benzophenone under N_2 until a purple color persists, and distilled immediately prior to use.

***n*-Butyllithium.** *n*-Butyllithium (1.6 M in hexane) was titrated with reagent grade diphenylacetic acid for its exact concentration. In most cases *n*-butyllithium concentration was found to be within 10% of what was labeled on the bottle.

Ketones. 1a, **1b**, and **1d** were distilled on a B/R Model 8T micro spinning band distillation system, and dried over 3 Å molecular sieves. **1c** and **1e** were dried over 3 Å molecular sieves and used without further purification. The identity and purity of all ketones were confirmed by ^{1}H NMR to indicate no detectable amount of impurity or water.

Amines. The precursor amines for the preparation of **4**−**6** are all commercially available. Unless otherwise noted, liquid amines (**4b**−**d**) were dried over molecular sieves and used without further purification. They were kept from any light source as much as possible and their purity was checked by ^{1}H NMR and GCMS. Solid amines (**4e**,**f**, **5,** and **6**) were used directly after their mp was checked for purify and identify.

Aniline. Aniline (**4a**) was distilled under reduced pressure and dried over molecular sieves before use.

General Procedure of Enolization. Lithium amide bases **4**−**6** were prepared by adding 1.1 mmol of *n*-butyllithium to a stirring solution of 1.2 mmol of corresponding amine in 5 mL of dry THF at 0 °C under nitrogen. The solution was allowed to stir for 15 min. The solution was then kept at 0 °C or lowered to −78 °C, depending on the conditions desired. Ketone (1 mmol) was then slowly added by a gastight syringe, and the reaction was stirred for an additional 15 min before the enolates were quenched with 1.2 mmol of freshly distilled chlorotrimethylsilane (over CaH_2). After being stirred for 10 min, the reaction mixture was allowed to warm to room temperature and poured into 10 mL of pentane in a small separatory funnel. The mixture was washed twice with 5 mL each of saturated sodium bicarbonate solution and once with brine solution, and the organic layer was dried over anhydrous magnesium sulfate. The solution was filtered and the product ratios determined on GC/MS. At least two individual experiments (normally 3−4 experiments) for each entry in Tables 1 and 2 were run to ensure reproducible results. Usually 2−3 GC injections were made for each experimental run. To ensure kinetically controlled conditions, we also carried out the above reactions using a base/ketone molar ratio of 2:1. The E/Z ratios showed no difference from those obtained with a base/ketone ratio of 1.1:1.

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