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Reactions of ketone dilithio α,β-dianions with imines and hydrazones: an anionic access to γ-amino ketones

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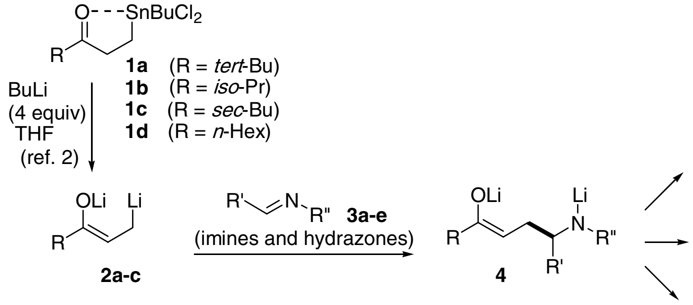
Abstract—The reactions of ketone dilithio α,β-dianions with imines and hydrazones were investigated. The nucleophilic addition reaction to C–N double bonds took place selectively at the β-position of dianions to form lithium Z-enolates containing a lithium amide portion, which is then transformed into γ-amino ketones and related compounds by the subsequent reaction with electrophiles.

γ-Amino ketones are potent intermediates for the synthesis of pyrollines.[1] We have recently shown that ketone dilithio α,β-dianions, having *Z*-form enolate/allyl anion structure **2**, can be conveniently generated by treating β-dichlorobutylstannyl ketones **1** with 4 equiv of *n*-BuLi. We also reported their use for some synthetic transformations.[2–4] In this letter, we report that ketone dilithio α,β-dianions **2** react with imines and hydrazones, **3**, at the β-anion portion selectively to give *Z*-form lithium enolates **4**, which serve as precursors to γ-amino ketones and related nitrogen heterocycles (Scheme 1).

Firstly, we examined the reactions of ketone α,β-dianion **2a**, which was generated from β-butyldichlorostannyl ketone **1a** and *n*-BuLi in THF, with an imine **3a** (Scheme 2). The addition reaction of **2a** with **3a** was sluggish at −78 °C, however, warming up the reaction mixture to 0 °C resulted in the complete addition. After proton quenching with MeOH γ-amino ketone **5** was afforded in 83% isolated yield.

Results of the reaction of dianions **2** with imines and hydrazones are summarized in Table 1. In contrast with the result of aromatic imine **3a**, the reaction of **2a** with an aliphatic imine **3b** gave the addition product **6** in a rather poor yield (entry 2).[5] Then, we examined hydrazones **3c** and **3d**, which are easily prepared from formaldehyde and benzaldehyde by condensation with *N*-methyl-*N*-phenylhydrazine and dimethylhydrazine,



Scheme 1. Reaction of ketone α,β-dianions and C–N double bonds.

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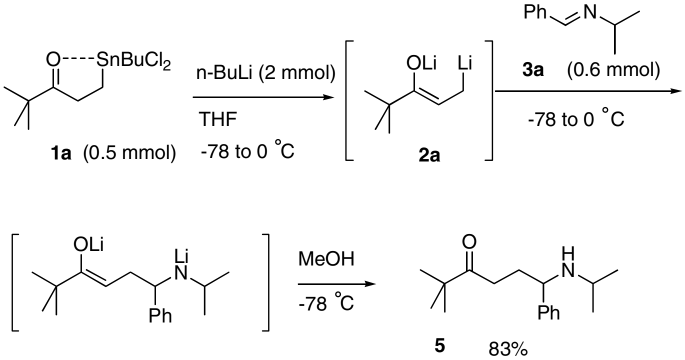
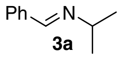
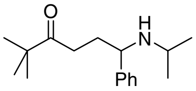
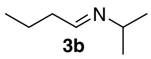
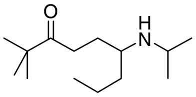
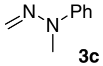
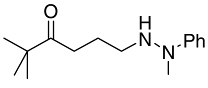
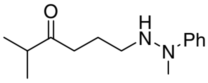
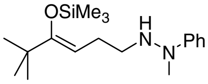
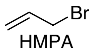
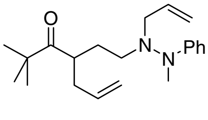
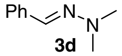
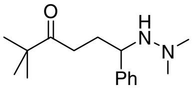
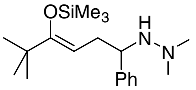
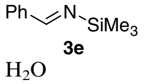
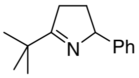
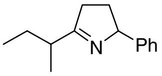
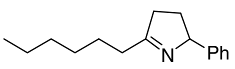
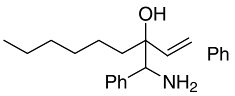


Scheme 2. Reaction of ketone α,β-dianion **2a** with imine **3a**.

Table 1. Reaction of ketone α,β-dianions with imines and hydrazones[a]

Entry	α,β-Dianion	Conditions		Product (yield[b])
1	**2a**	(1)  **3a** (2) H_2O	−78 °C to 0 °C 0 °C	 **5** (83%)
2	**2a**	(1)  **3b** (2) H_2O	−78 °C to 0 °C 0 °C	 **6** (37%)
3	**2a**	(1)  **3c** (2) H_2O	−78 °C to 0 °C 0 °C	 **7** (84%)
4	**2b**	(1) **3c** (2) H_2O	−78 °C to 0 °C 0 °C	 **8** (58%)
5	**2a**	(1) **3c** (2) Me_3SiCl	−78 °C to 0 °C −78 °C to 0 °C	 **9** (76%)
6	**2a**	(1) **3c** (2)  HMPA	−78 °C to 0 °C −78 °C to 20 °C	 **10** (77%)
7	**2a**	(1)  **3d** (2) H_2O	−78 °C to 0 °C 0 °C	 **11** (74%)
8	**2a**	(1) **3d** (2) Me_3SiCl	−78 °C to 0 °C −78 °C to 0 °C	 **12** (74%)
9	**2a**	(1)  **3e** (2) H_2O	−78 °C to 0 °C 0 °C	 **13** (90%)
10	**2c**	(1) **3e** (2) H_2O	−78 °C to 0 °C 0 °C	 **14** (84%) (54/46)[c]
11	**2d**	(1) **3e** (2) H_2O	−78 °C to 0 °C 0 °C	 **15** (58%)  **16** (18%)

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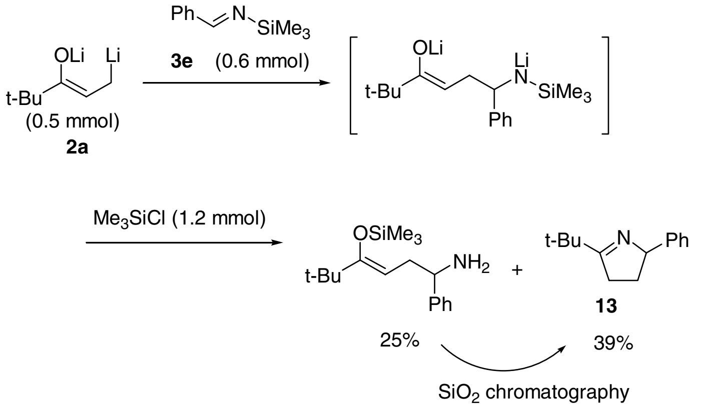
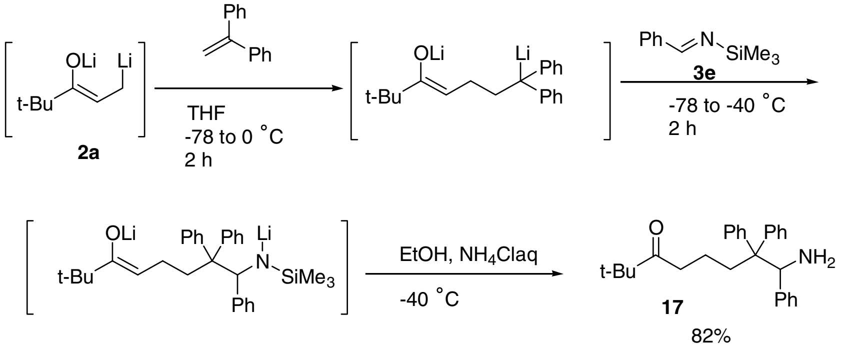
[a] Reactions were conducted on 0.5 or 1 mmol scale.

[b] Isolated yield by column chromatography on silica gel.

[c] Determined by ^{1}H NMR.



Scheme 3. Reaction of ketone α,β-dianion **2a** with silylimine **3e**.



Scheme 4. Consecutive reaction of ketone α,β-dianion **2a** with 1,1-diphenylethylene and silylimine **3e**.

respectively. Again the C–C bond forming reactions took place selectively at the β-position of dianions **2** (entries 3-7). For example, the reaction of **2a** with hydrazone **3c** gave the adduct **7** in 84% yield (entry 3).[6] When the reaction was quenched by TMSCl (2.2 mol equiv), an enol silyl ether containing a hydrazide moiety, **9**, was obtained in 76% yield (entry 5). A ^{1}H NMR of the crude reaction mixture confirmed the formation of bis-silylated product, however, during the silica gel chromatography the TMS-N moiety was hydrolyzed to give **9**. On the other hand, quenching the reaction mixture with allyl bromide gave bis-allylated product **10** in 77% yield (entry 6). Similarly, **3d** also served as an efficient dianion trap to give the corresponding adducts (entries 7 and 8).

We thought that the use of *N*-silyl imines would lead to 1-pyrollines via [3+2]-annulation method. The reaction of dianion **2a** with silyl imine **3e**[7] followed by the treatment with TMSCl gave a mixture of a 4-amino-substituted enol silyl ether and 1-pyrolline **13** after silica gel chromatography (Scheme 3). Since the NMR chart of the crude reaction mixture does not contain peaks ascribed to **13**, **13** is likely to be obtained by in situ hydrolysis of bis-silylated product during silica gel chromatography. When the reaction mixture was quenched with EtOH–NH$_4$Cl aq at 0 °C, the cyclized product 1-pyrolline **13** was obtained as the sole product in 90% yield (entry 9). Using a similar procedure, pyrolline **14** was obtained from dianion **2c** in 84% yield (entry 10). Ketone dilithio α,β-dianions rarely exhibit an ambident character as an allylic anion. An exceptional case was the reaction with aldehydes, which led to a mixture of 4-hydroxyketones and homoallylic alcohols.[2b] We encountered such an ambident behavior in the case of *n*-hexyl substituted dianion **2d** (entry 11). The reaction gave 1-pyrolline **15** as the major product (58%) together with amino alcohol **16** as the byproduct (18%). The sterically less hindered lithioxy carbon of **2d** may allow for the partial formation of **16**. Since ketone α,δ-dianions can be readily generated by vinylogous extension of ketone α,β-dianions,[3c] we examined a sequential reaction, comprising dianion **2a**, 1,1-diphenylethene, and imine **3e**. The reaction worked well to give the envisaged 6-amino-substituted ketone **17** (Scheme 4).

In summary, we have shown that ketone α,β-dianions **2** react with imines and hydrazones selectively at the β-anion portion to give *Z*-form lithium enolates of γ-amino ketones. The use of TMS-imine as a dianion trap, coupled with the standard aqueous workup, led to a convenient access to 1-pyrollines.

Acknowledgements

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References and notes

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6. Typical procedure: 2,2-dimethyl-6-(*N*-methyl-*N'*-phenylhydrazino)-3-hexanone (**7**). To a solution of β-dichlorobutylstannyl ketone **2a** (360 mg, 1.0 mmol) in THF (10 mL) was added *n*-BuLi (2.63 mL, 1.52 M solution in hexane, 4.0 mmol) dropwise over a period of 5 min at −78 °C. This solution was allowed to warm to 0 °C and stirred for 30 min. After cooling to −78 °C, hydrazone **3c** (127 mg, 0.95 mmol, 0.95 equiv) was added. The mixture was allowed to warm to 0 °C and stirred for 30 min. After re-cooling to −78 °C, the resulting yellow solution was quenched with MeOH (1 mL). The quenched mixture was poured into saturated aqueous NH_4Cl (40 mL) and extracted with ether. The aqueous layer was separated and extracted with ether (20 mL × 2). The combined organic solution was dried over $MgSO_4$ and concentrated under reduced pressure. Purification by flash chromatography (elution with hexane/Et_2O) provided the desired adduct **7** (198 mg, 84%) as a colorless oil; ^1H NMR (270 MHz, $CDCl_3$) δ 1.13 (s, 9H, *t*-Bu), 1.72–1.77 (m, 2H), 2.62 (t, 2H, $J = 7.3$ Hz), 2.86 (t, 2H, $J = 6.8$ Hz), 3.01 (s, 3H, Me), 6.75–7.22 (m, 5H, Ph); ^{13}C NMR (68 MHz, $CDCl_3$) δ 22.34, 26.46, 34.09, 39.06, 44.03, 47.09, 113.04, 117.80, 128.69, 151.30, 215.45; EIMS m/z (relative intensity, %) 248 (M^+, 85), 161 (18), 127 (39), 121 (100), 106 (89); IR (neat, cm^{-1}) 1705; HRMS calcd for $C_{15}H_{24}ON_2$: 248.1889. Found: 248.1907; Anal. Calcd for $C_{33}H_{48}OSi_3$: C, 72.73; H, 8.88. Found: C, 72.70; H, 8.64.
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