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1,1,4,7,10,10-Hexamethyltriethylenetetramine: a reagent to enhance the rate of alkylation reaction of the lithium enolate of 1-tetralone with alkyl halides

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Abstract

The rate of the reaction of the lithium enolate of 1-tetralone with alkyl halides was enhanced greatly in the presence of 3 equivalents of 1,1,4,7,10,10-hexamethyltriethylenetetramine. The ratio of the monoalkylated product to the dialkylated product was found to have increased under a shorter reaction time. © 1999 Elsevier Science Ltd. All rights reserved.

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Lithium enolates play a central role in organic synthesis, because they can be prepared easily from the corresponding carbonyl compounds by deprotonation using lithium amides, and they react with various electrophiles to undergo many important reactions, such as alkylation, acylation, aldolization, Michael reaction, protonation etc. In the alkylation, the rate of the reaction is usually slow, and the ratio of the monoalkylated product to the dialkylated product decreases as the reaction time increases. HMPA (hexamethylphosphoric triamide) is known to coordinate to the metal cations, and is a useful reagent to enhance the rate of alkylation reaction of lithium enolates.[1] However, since industrial use of HMPA is not recommended due to its possible carcinogenicity, cyclic urea derivatives such as DMPU (*N,N′*-dimethyl-*N,N′*-propyleneurea) and DMEU (*N,N′*-dimethyl-*N,N′*-ethyleneurea) were developed as safe substitutes of HMPA having similar properties.[2]

We have previously studied enantioselective alkylation reaction of the achiral lithium enolates prepared by deprotonation of cyclohexanone (**1**) and 1-tetralone (**3**) using various chiral lithium amides (**4**–**7**),

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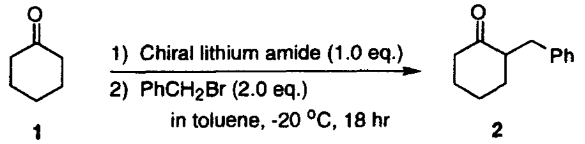
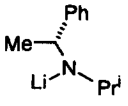
followed by treatment of the resulting solution with reactive alkyl halides in toluene.[3] It is shown that chemical yields of the products depend heavily on the lithium amides employed. Thus, in the benzylation reaction of **1** under the same conditions (in toluene, −20°C, 18 h), chemical yields of **2** were 1%, 7%, 15% and 62%, by using 1 equivalent of **4**, **5**, **6**, and **7**, respectively.[3d] Since the lithium enolate is expected to form a complex in solution with the amine coming from the lithium amide employed,[4] it is conceivable that the rate of the reaction of the lithium enolate with alkyl halide is greatly enhanced by forming a complex with a tetradentate amine coming from **7**.

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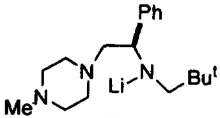
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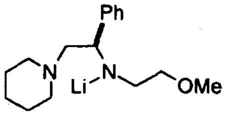
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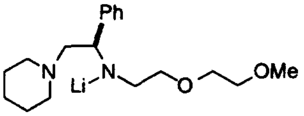
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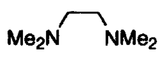
In order to examine the effect of additives on the rate of the reaction of the lithium enolates with alkyl halides, **3** was treated with LDA to give the corresponding lithium enolate, and the resulting solution was treated with 5 equivalents of alkyl halides in the absence and in the presence of 3 equivalents of various additives (HMPA, DMPU, [2.1.1]-cryptand, bidentate (**10**), tridentate (**11**), tetradentate (**12**), and pentadentate (**13**) amines), which are expected to interact with the lithium. The results are summarized in Table 1.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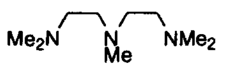
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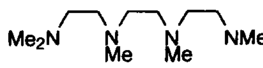
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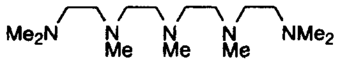
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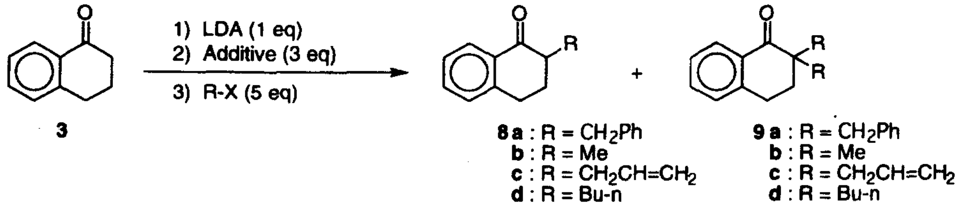

Benzylation reaction of **3** to give **8a** and **9a** was first examined in DME. In the absence of any additives, the reaction was very slow at −23°C, and needed a longer reaction time to get the products in reasonable yields (runs 1, 2). As was expected, HMPA enhances the rate of the reaction with reasonably high selectivity for **8a/9a** after 40 min (run 3), while DMPU has little effect (run 4 vs run 1). In the presence of [2.1.1]-cryptand, the rate of the reaction actually increased, but the ratio of **8a/9a** decreased greatly after 40 min (run 5). This means that further deprotonation of **8a** also enhanced greatly during the reaction in the presence of [2.1.1]-cryptand. Among multidentate amines (**10**–**13**), bidentate amine (**10**) has little effect (runs 6, 7 vs runs 1, 2), while the reaction in the presence of a tridentate (**11**), a tetradentate (**12**), or a pentadentate (**13**) amine gave the products in higher yields (runs 8, 9, 11 vs run 1). It is shown that the tetradentate amine (**12**) is the best, giving **8a** in 72% yield and **9a** in 1% yield after 40 min (run 9), while **8a** in 83% yield and **9a** in 7% yield were obtained after 3 h (run 10).[5] Thus, longer reaction time

Table 1
Alkylation of the lithium enolate of **3**[a]

Run	RX (5 eq)	Additive (3 eq)	Solvent	Temp (°C)	Reaction time	Yield (%)		Recovered **3** (%)
						8	**9**	
1	PhCH$_2$Br	none	DME	- 23	40 min	6	~0	92
2	PhCH$_2$Br	none	DME	- 23	18 hr	54	13	25
3	PhCH$_2$Br	HMPA	DME	- 23	40 min	34	2	58
4	PhCH$_2$Br	DMPU	DME	- 23	40 min	3	~0	93
5	PhCH$_2$Br	[2.1.1] cryptand	DME	- 23	40 min	24	31	36
6	PhCH$_2$Br	**10**	DME	- 23	40 min	6	~0	93
7	PhCH$_2$Br	**10**	DME	- 23	18 hr	42	4	46
8	PhCH$_2$Br	**11**	DME	- 23	40 min	50	1	51
9	PhCH$_2$Br	**12**	DME	- 23	40 min	72	1	24
10	PhCH$_2$Br	**12**	DME	- 23	3 hr	83	7	16
11	PhCH$_2$Br	**13**	DME	- 23	40 min	33	~0	64
12	PhCH$_2$Br	none	THF	- 23	40 min	3	~0	94
13	PhCH$_2$Br	**12**	THF	- 23	40 min	12	~0	85
14	PhCH$_2$Br	none	ether	- 23	40 min	1	~0	98
15	PhCH$_2$Br	**12**	ether	- 23	40 min	45	2	51
16	PhCH$_2$Br	none	toluene	- 23	40 min	1	~0	88
17	PhCH$_2$Br	**12**	toluene	- 23	40 min	75	6	15
18	MeI	none	DME	- 23	40 min	27	~0	65
19	MeI	**12**	DME	- 23	40 min	80	2	7
20	CH$_2$=CH-CH$_2$Br	none	DME	- 23	40 min	2	~0	93
21	CH$_2$=CH-CH$_2$Br	**12**	DME	- 23	40 min	60	1	34
22	n-BuI	none	DME	25	2 hr	12	1	77
23	n-BuI	**12**	DME	25	2 hr	39	6[b]	45

[a] A typical procedure is described in the text.

[b] Formation of C,O-dibutylated poduct (2-butyl-1-butoxy-3,4-dihydro-naphtahlene) (1%) was observed.

decreases the ratio of **8a**/**9a**. The effect of **12** on the rate of the reaction is superior to that of HMPA (run 9 vs run 3).

Evaluating that **12** is the most effective to enhance the rate of the reaction, benzylation reaction of **3** was then examined in THF, ether, and toluene (runs 12–17). It is shown that chemical yields of the products are very low in the absence of any additives (runs 12, 14, 16), but they increase in the presence of **12** also in these solvents (runs 13, 15, 17). Judging from the chemical yield of **8a** and the ratio of **8a**/**9a**, it is concluded that DME is the solvent of choice for this reaction.

Using DME as a solvent, reactions of **3** with other alkyl halides were examined in the absence and in the presence of **12**. It is again shown that methyl iodide, allyl bromide and butyl iodide gave the corresponding monoalkylated products in reasonably higher chemical yields in the presence of **12** (runs 18–23).

A typical experimental procedure (run 9 in Table 1) is as follows. Under argon atmosphere, a solution of **3** (155 mg, 1.06 mmol) in DME (2 mL) was added to a solution of LDA (prepared from butyllithium in hexane (1.52 *N*, 0.77 mL, 1.17 mmol) and diisopropylamine (0.18 mL, 1.28 mmol) as usual) in DME (6 mL) at −45°C. A solution of **12** (730 mg, 3.17 mmol) in DME (1 mL) was added, and the whole was stirred for 50 min. A solution of benzyl bromide (0.63 mL, 5.30 mmol) in DME (1.5 mL) was added at −78°C, and the whole was stirred at −23°C for 40 min. After addition of 40% aqueous citric acid (10 mL), the whole was allowed to warm to room temperature under stirring, and was extracted with AcOEt (40 mL×3). The organic extracts were combined, washed with saturated aqueous sodium bicarbonate (30 mL) and brine (30 mL), dried over $MgSO_4$ and filtered. The filtrate was mixed with 2-acetonaphthone (59.3 mg) as an internal standard, and was subjected to HPLC analysis (μ PORASIL, hexane:AcOEt (100:1)). It is shown that the solution contains **8a**, **9a**, and **3** in 72%, 1% and 24% yields, respectively, based on **3** used.

It is known that lithium enolates are aggregated in solution, and the reactivity of the lithium enolates can be dramatically modified by formation of mixed aggregates with amines.[3,4] In the present case, it is conceivable that the rates of alkylation reactions are enhanced due to the formation of the complex(es) between the lithium enolate of **3** and **12** in solution. Studies on the structure(s) are a matter of future investigation.

In conclusion, it is shown that the rates of the reactions of the lithium enolates of **3** with alkyl halides are enhanced in the presence of a tetradentate amine (**12**). It is also shown that the ratio of the monoalkylated product to the dialkylated product (**8/9**) increased under a shorter reaction time. Since **12** is commercially available, the results shown here should be widely useful in synthesis.

Acknowledgements

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5. In the presence of 1.0, 2.0 and 6.0 equivalents of **12**, **8a** was obtained in 47, 63 and 66% yields, respectively, after 40 min.