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Sodium Diisopropylamide in *N,N*-Dimethylethylamine: Reactivity, Selectivity, and Synthetic Utility

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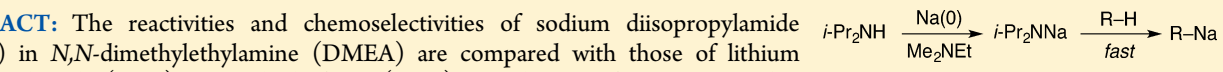
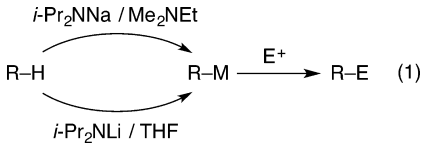
ABSTRACT: The reactivities and chemoselectivities of sodium diisopropylamide (NaDA) in *N,N*-dimethylethylamine (DMEA) are compared with those of lithium diisopropylamide (LDA) in tetrahydrofuran (THF). Metalations of arenes, epoxides, ketones, hydrazones, dienes, and alkyl and vinyl halides are represented. The positive attributes of NaDA–DMEA include high solubility, stability, resistance to solvent decomposition, and ease of preparation. The high reactivities and chemoselectivities often complement those of LDA–THF.



INTRODUCTION

This paper is the first in a series describing illustrative metalations by sodium diisopropylamine (NaDA) dissolved in *N,N*-dimethylethylamine (DMEA). The key insight is that NaDA is highly soluble and stable in trialkylamines (eq 1) and



(1)

can be prepared in 15 min. The utility of NaDA–DMEA is illustrated by showing that its metalations have rates that far exceed those of LDA–THF but give comparable yields and selectivities that are often complementary. To our surprise, we have witnessed no solubility problems with NaDA dissolved in several trialkylamines or with the resulting metalated intermediates. From these results, we argue that synthetic chemists should revisit NaDA.

BACKGROUND

The preparation of lithium diisopropylamide (LDA) by Levine and co-workers[1] in 1949 introduced soluble, highly reactive amide bases to the repertoire of synthetic organic chemists. Metalations with LDA began to flourish in the 1960s,[2] and LDA became one of the most prominent reagents in organic synthesis.[3] Levine[4] first synthesized NaDA in 1959 by reacting phenylsodium and diisopropylamine. Improved preparations include those of Lochmann[6] (using LDA–*t*-BuONa[5] or *n*-BuNa–diisopropylamine prepared from *n*-BuLi–*t*-BuONa) and Wakefield[7] (using a sodium metal–isoprene-based reduction). More recently, Mulvey and co-workers[8] have drawn attention to the merits of sodium chemistry by developing new reagents for synthesis and providing an excellent review of these heavy-alkali-metal bases. Most reports of NaDA focus on exploration for its own sake,[9] however, and only a few appear to be consumer-driven applications of NaDA to solve specific problems.[10,11]

Why has NaDA languished in relative obscurity? Ambiguities about composition—sodium bases versus mixed-metal "super-bases"—have been largely resolved,[6a] and such details certainly would not have deterred synthetic chemists pursuing reactivity and selectivity. The reported thermal instability of solid NaDA[7]—resolved by refrigeration—also seems insufficient to curb the interest of the synthetic organic community. We suspect the major obstacle to be the scarcity of solvents that afford both high solubility and resistance to base-mediated decomposition.[9b,12] This presumption prompted us to examine DMEA and related trialkylamines.

RESULTS

NaDA was prepared by modifying Wakefield's procedure[7] using sodium dispersion in toluene, isoprene, and diisopropylamine, all in DMEA. The sodium dispersion served as both a drying agent for all reagents and a reductant, allowing millimolar-scale synthesis without specialized glassware in 15 min and multiples of that scale in 30 min. (The longer reaction time stems from an exotherm demanding slower addition.) The resulting amide solution can be used directly, stored for later use at −20 °C, or recrystallized to give a white solid. Upgrading purity via recrystallization had a negligible influence on reactivity.

Metalations of representative organic substrates are summarized in Table 1. The yields are of isolated, purified products unless noted otherwise.[13] The relative reactivities of NaDA–DMEA and LDA–THF were assessed with either IR or NMR spectroscopy by measuring pseudo-first-order rate constants or initial rates for 0.10 M solutions of base. The relative rate constants (k_{rel}) for NaDA–DMEA versus LDA–THF are often lower limits because LDA is too unreactive or NaDA is too reactive to measure. Large temperature differences demanded by the two reagents prompt us to crudely (but conservatively) use a 2-fold correction for every 10 °C.[14]

DISCUSSION

The substrates in Table 1 were chosen to enable a broadly based comparison of NaDA–DMEA and LDA–THF. The dehydrohalogenations in entries 1–3 of Table 1 offer striking

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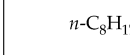
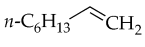
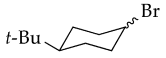
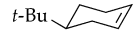
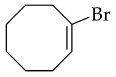
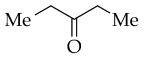
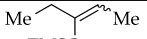
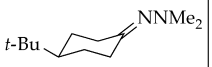
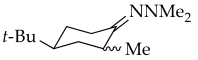
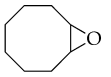
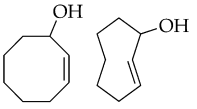
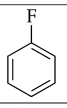
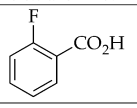
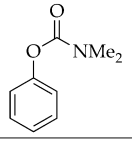
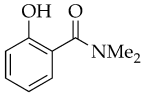
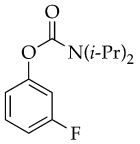
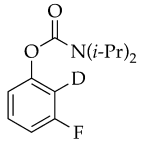
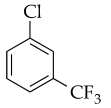
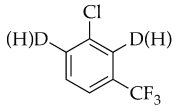
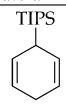
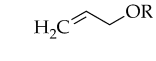
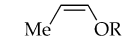
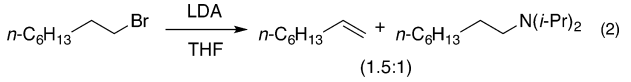
Table 1. Reactions of Substrates with NaDA[a]

	Substrate	Conditions	E+	Product	k_{rel}	Yield
1		1.2 equiv NaDA 0 °C	—		5	87%
2		1.2 equiv NaDA 0 °C	—		>500	80%
3		1.2 equiv NaDA 0 °C	—		5	87%
4		1.1 equiv NaDA −78 °C	TMSCl	 *E*:*Z* = 1:4	N/A	61%
5		1.2 equiv NaDA −78 °C	CH_3I		>300	78%
6		1.3 equiv NaDA rt	H_2O	 cis:trans = 10:1	>500	80%
7		1.1 equiv NaDA −78 °C	CO_2		N/A	60%
8		1.2 equiv NaDA −78 °C	H_2O		>200	92%
9		1.2 equiv NaDA −78 °C	CH_3OD		>500	94%
10		1.2 equiv NaDA −78 °C	CH_3OD	 2-*d*:6-*d* = 6:1	1000	92%
11		1.1 equiv NaDA 0 °C	TIPSCl		>100	82%
12	 R = Me, Ph, $SiMe_3$	1.1 equiv NaDA 0 °C	—	 *Z*:*E* > 50:1	>1000	83% R = Ph

[a]Abbreviations: k_{rel}, relative rate constant; NaDA, sodium diisopropylamide; rt, room temperature; TIPSCl, triisopropylchlorosilane.

contrasts. Whereas *n*-octyl bromide (entry 1) undergoes clean NaDA-mediated elimination (>100:1), LDA−THF elicits elimination and S_N2-like substitution (eq 2).[15] Competing



(2)

substitution−elimination pathways have plagued analogous eliminations of *n*-alkyl halides.[16] Putative trans-diaxial elimination of conformationally anchored *cis*-4-*tert*-butylcyclohexyl bromide (entry 2) is highly effective with NaDA. Surprisingly, the equatorial form eliminates with nearly equal efficiency ($k_{axial}/k_{equatorial}$ = 5), contrasting with the absence of *any* equatorial elimination by LDA at 25 °C.[17] We suspect that a carbenoid mechanism may be involved.[18] The comparable rates of NaDA−DMEA and LDA−THF[17] for dehydrohalogenations in entries 1 and 3 are outliers in Table 1.

Enolization of 3-pentanone (entry 4) is too fast to monitor at standard temperatures. Although the selectivity for NaDA−DMEA is low, it is reversed relative to the 3:1 *E*:*Z* selectivity observed for LDA−THF.[19] In contrast to ketones, LDA-mediated hydrazone metalations are remarkably slow (Table 1, entry 5) but are markedly faster with NaDA−DMEA. Trapping the resulting sodium salt with MeI, however, shows a modest 5:1 axial selectivity in comparison with >15:1 for the lithium salt.[13e]

Cyclooctene oxide elimination (Table 1, entry 6) provided the most unexpected result by giving clean elimination to

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cyclooctenols in a 10:1 cis:trans selectivity (axial isomer[13f]). We can find no precedent for such a base-mediated elimination to give the trans isomer.[13f] LDA−THF, in contrast, is much slower (requiring reflux) and gives low yields of *cis*-2-cyclooctenol and bicyclo[3.3.0]octan-1-ol in >13:1 selectivity,[20] the latter presumably deriving from carbenoid chemistry.

Ortho metalation is the most obvious application of NaDA and has received some attention.[9,10] Metalation of fluorobenzene (Table 1, entry 7) is incomplete at equilibrium, as shown by partial carbonation and by monitoring the reaction with ^{19}F NMR spectroscopy. Precipitation of the arylsodium is observed at approximately 1.0 M at −78 °C. The appearance of benzyne products only above −30 °C is notable and surprising.

The rapid ortho metalation of the carbamate by NaDA−DMEA (in contrast to LDA−THF) in Table 1, entry 8, makes the arylsodium observable;[13h] the Snieckus−Fries rearrangement[21] served as an internal quench to illustrate the efficacy of the metalation. The facile haloarene metalations in entries 9 and 10 again underscore a surprising reluctance of the arylsodium to form benzyne at temperatures below −30 °C. In comparison with the ∼1:1 mixture observed for LDA, the regioselectivity in entry 10 that favors metalation at the 6-position rather than at the doubly activated 2-position is higher,[22] but facile equilibration[22,23] even at −78 °C affords the 2-sodiated intermediate as the exclusive form, as shown via quenching and ^{19}F NMR spectroscopy.

Metalations of 1,4-cyclohexadiene (Table 1, entry 11) with subsequent silylation can be carried out, albeit slowly, with LDA−THF, but literature reports all use alkyllithiums.[24] Especially notable here is the use of THF as an added ligand *after* metalation but *before* silylation; attempts to silylate without addition of THF suffered from a significant loss of yield owing to aromatization and protonation of the sodium salt. Although allyl methyl, phenyl, and trimethylsilyl ethers are not observably metalated by NaDA (entry 12), facile rearrangement to (*Z*)-1-propenyl ethers compares favorably to a method using *t*-BuOK−DMSO at >70 °C that gives (10−20):1 *Z* selectivity and is fast in comparison to a recently reported analogous procedure using LDA by Su and Williard.[25]

CONCLUSION

Organosodium chemistry has witnessed brief periods of activity[26] followed by long periods of quiescence. We are hoping to regenerate interest. NaDA in DMEA can be prepared in only minutes, shows excellent solubility properties, and is stable as a concentrated stock solution for months with refrigeration. Metalations are breathtakingly fast in many instances, affording surprisingly soluble sodiated products. Importantly, ongoing studies show that DMEA and related trialkylamines are weakly bound to NaDA, which allows facile substitution with stoichiometric quantities of more conventional ligands such as THF, 1,2-dimethoxyethane, and *N,N,N′,N′*-tetramethylethylenediamine either *before or after the metalation*. Subsequent reports will show that these ligands often accelerate already rapid metalations by orders of magnitude. The merit of post-metalation ligand substitution is illustrated by the need for THF addition when trapping a dienyl anion with triisopropylchlorosilane. Applications and affiliated reaction mechanisms will be described in due course. Most importantly, we have yet to uncover any chronic limitations.

EXPERIMENTAL SECTION

Reagents and Solvents. DMEA, hexane, and THF were distilled from blue or purple solutions containing sodium benzophenone ketyl. All products in Table 1 have been prepared previously[13] or are commercially available.

Sodium Diisopropylamide. *N,N*-Dimethylethylamine (4.0 mL) and diisopropylamine (0.50 mL, 3.5 mmol) without pre-drying were placed in a 15 mL pear-shaped flask. To this mixture was added sodium dispersion in toluene (3.0 mL, 35 mmol), which produced effervescence for approximately 10 s. With stirring, isoprene (175 μL, 1.75 mmol) was added over the course of 1 min. Stirring was halted after 5 min, and insoluble materials were allowed to settle, which yielded a yellow supernatant. Variations in the quality (age) of the sodium dispersion can lengthen the reaction time. The resulting NaDA solution can be used directly or stored at −20 °C. The reaction was shown to be quantitative by monitoring NaDA formation (δ 3.2−3.3 ppm, septet) and the disappearance of diisopropylamine (δ 2.8−2.9 ppm, octet). Alternatively, the method of Kofron[27] was used to titrate the resulting NaDA solution. Diphenylacetic acid (20.0 mg, 0.094 mmol) and 1.0 mL of dry THF were placed in a vial. Then, the NaDA−DMEA solution was added dropwise at room temperature until the yellow coloration persisted, marking the end point of the titration. (The presumed sodium carboxylate can precipitate as a white solid that redissolves with a second equivalent of NaDA, suggesting that the enediolate is soluble.) The results of this titration provide a NaDA titer up to 1.2 times that anticipated owing to loss of highly volatile DMEA occurs *through the septum* during NaDA preparation.

IR Spectroscopic Analyses. IR spectra were recorded by using an in situ IR spectrometer fitted with a 30-bounce, silicon-tipped probe. The spectra were acquired in 16 scans at a gain of 1 and a resolution of 4 cm^{-1}. A representative reaction was carried out as follows: the IR probe was inserted through a nylon adapter and O-ring seal into an oven-dried, cylindrical flask fitted with a magnetic stir bar and a T-joint. The T-joint was capped with a septum for injections and a nitrogen line. After evacuation under full vacuum, heating, and flushing with nitrogen, the flask was charged with NaDA (62 mg, 0.50 mmol) in 4.9 mL of DMEA and cooled in a dry ice−acetone bath prepared with fresh acetone. After recording a background spectrum, we added substrate stock (100 μL, 0.50 mmol) with stirring. For the most rapid reactions, IR spectra were recorded every 6 s.

NMR Spectroscopic Analyses. NMR samples for monitoring reactions were prepared by using stock solutions and sealed with partial vacuum or under ambient argon pressure with two natural rubber septa. Standard ^{1}H and ^{19}F NMR spectra were recorded at 500 and 470 MHz, respectively. In the case of ^{1}H NMR spectroscopic analysis, the loss of NaDA and formation of diisopropylamine can be monitored (vide supra) in addition to characteristic changes corresponding to substrate.

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Notes

The authors declare no competing financial interest.

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