

Synthesis of Carboxamides by LDA-Catalyzed Haller–Bauer and Cannizzaro Reactions

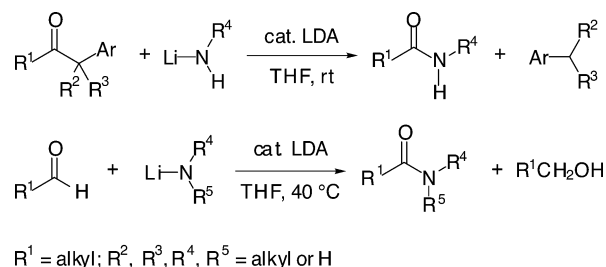
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ABSTRACT



The first direct synthesis of *N*-alkylcarboxamides and *N,N*-dialkylcarboxamides by Haller–Bauer (HB) and Cannizzaro-type reactions has been realized. Lithium *N,N*-diisopropylamide (LDA) catalyst was successfully used in not only the HB reaction of benzylic ketones with lithium *N*-alkylamides to give the corresponding carboxamides and hydrocarbons but also in the Cannizzaro-type reaction of aldehydes with lithium *N*-alkylamides or lithium *N,N*-dialkylamides to give the corresponding carboxamides and alcohols.

The base-induced cleavage of nonenolizable ketones leading to a carboxylic acid derivative and a neutral fragment in which the carbonyl group is replaced by a hydrogen is referred to as the Haller–Bauer (HB) reaction.¹ This reaction is traditionally carried out with excess amounts of sodium or potassium amide in boiling benzene.

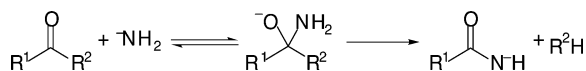
The generally accepted mechanism for this reaction involves nucleophilic addition of the amide to furnish a tetrahedral intermediate, which cleaves to a carboxamide and a carbanion. Intermolecular proton transfer leads to a hydrocarbon product and an amide salt (Scheme 1).¹ The

for certain classes of these compounds. It is one of the few general methods for the synthesis of tertiary carboxamides, which are useful intermediates for tertiary carboxylic acids or tertiary carbinamines. However, the suitable substrates for the HB reaction are limited to nonenolizable ketones and the group 1A metal amides (MNH₂ where M = Li, Na, K).

To extend the scope and utility of this reaction, we investigated the base-induced cleavage reactions of ketones and aldehydes with *N*-alkylamines and *N,N*-dialkylamines. We describe here the first example of the direct synthesis of *N*-alkylcarboxamides and *N,N*-dialkylcarboxamides from the corresponding ketones and aldehydes by HB and Cannizzaro reactions, catalyzed by lithium *N,N*-diisopropylamide (LDA).

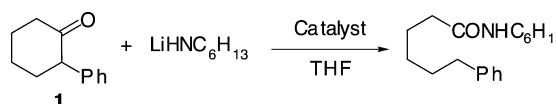
Our studies began with the HB reaction of enolizable 2-phenylcyclohexanone (**1**) with lithium *N*-hexylamide in THF (Table 1). Almost no *N*-hexyl-6-phenylhexanoamide was obtained from an equimolar mixture of **1** and lithium *N*-hexylamide in the absence of catalysts under the conditions

Scheme 1. Generally Accepted Mechanism for the HB Reaction



reaction has been applied on many nonenolizable ketones with sodium amide and is of considerable synthetic utility

(1) For reviews, see: (a) Hamlin, K. E.; Weston, A. W. *Org. React.* **1957**, 9, 1. (b) Paquette, L. A.; Gilday, J. P. *Org. Prep. Proceed. Int.* **1990**, 22, 167. (c) Mehta, G.; Venkateswaran, R. V. *Tetrahedron* **2000**, 56, 1399.

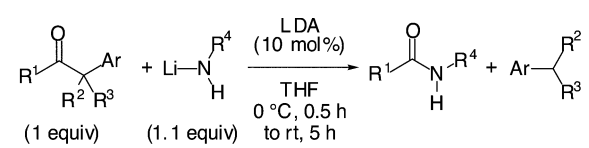
Table 1. HB Reaction of **1** with Lithium *N*-Hexylamide^a


entry	catalyst (mol %)	conditions (°C, h)	yield ^b (%)
1	<i>c</i>	0, 5	<10
2	LiHNC ₆ H ₁₃ , 10	0, 5	11
3	LiHNC ₆ H ₁₃ , 100	0, 5	79
4	BuLi, 10	0, 5	46
5	LDA, 10	0, 5	54
6	LDA, 10	0, 0.5 to rt, 5	86
7	LTMP, 10	0, 0.5 to rt, 5	85

^a LiHNC₆H₁₃ (2 mmol) and **1** (2 mmol) as substrates were used in THF (2 mL). ^b Isolated yield. ^c No catalyst was added.

in entry 1. However, the desired carboxamide was obtained in 79% yield upon the addition of a second equivalent of lithium *N*-hexylamide under the same conditions (entry 3). These experimental results suggest that lithium amides may serve as catalysts. Therefore, we examined several lithium amides as catalysts for the HB reaction and found that sterically hindered lithium amides such as LDA were much more effective as catalysts (entry 2 vs entry 5). Indeed, the reaction proceeded smoothly in the presence of 10 mol % of LDA or lithium 2,2,6,6-tetramethylpiperidide (LTMP) at room temperature (entries 6 and 7). The reaction was, however, quite slow in less polar solvents such as Et₂O or toluene.

To explore the generality and scope of the LDA-catalyzed HB reaction, we examined the reactions of various structurally diverse ketones with the lithium amides (R₄NHLi) in Table 2. In most cases, the HB reaction of benzylic ketones

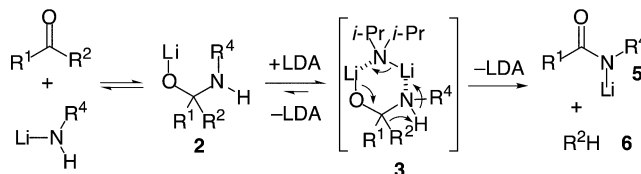
Table 2. HB Reaction of Benzylic Ketones with Lithium *N*-Alkylamides


ketone	R ⁴ NHLi	<i>N</i> -alkylcarboxamide	yield (%) ^a
1	C ₆ H ₁₃ NHLi	Ph(CH ₂) ₅ CONHC ₆ H ₁₃	89
1	<i>i</i> -PrNHLi	Ph(CH ₂) ₅ CONH <i>i</i> -Pr	92
1	BnNHLi	Ph(CH ₂) ₅ CONHBn	84
Bn ₂ C=O	C ₆ H ₁₃ NHLi	BnCONHC ₆ H ₁₃	52 (73) ^b
Et-C(=O)-Bn	C ₆ H ₁₃ NHLi	Et-C(=O)-NHC ₆ H ₁₃	84
CH ₃ -C(=O)-CHPh ₂	C ₆ H ₁₃ NHLi	MeCONHC ₆ H ₁₃	74 ^c

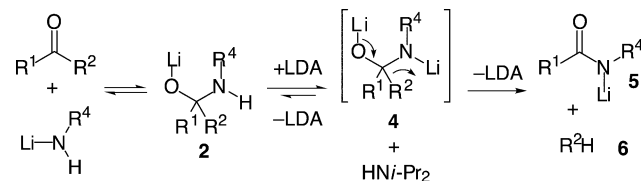
^a Isolated yields of carboxamides are shown. ^b C₆H₁₃NHLi (100 mol %) was used in place of LDA. ^c Diphenylmethane was isolated in 65% yield.

with lithium *N*-alkylamides was complete at room temperature within 5 h and gave the desired *N*-alkylcarboxamides in good yield. HB-cleaved products were obtained in good yield from enolizable and nonenolizable ketones. However, strong bases such as sodium *N*-alkylamides and lithium *N,N*-dialkylamides were not suitable as nucleophiles because they predominantly abstracted α-protons from the ketones.

On the basis of the above results, two possible catalytic cycles for LDA in the HB reaction can be proposed (Schemes 2 and 3). In path A, **2** becomes associated with the LDA to

Scheme 2. One Possible Catalytic Cycle for LDA in the HB Reaction (Path A)

furnish a more stable six-membered intermediate **3**, which irreversibly cleaves to a carboxamide salt **5** and a hydrocarbon product **6** (Scheme 2). In path B, **2** is further deprotonated by LDA to yield a dianionic species **4** with an enhanced proclivity toward C–C bond cleavage (Scheme 3).² The HB reaction promoted by lithium *N*-hexylamide in place of LDA (entries 2 and 3 in Table 1) should proceed by a mechanism analogous to path A, since lithium *N*-hexylamide cannot abstract the *N*-proton of **2**. On the other hand, when much stronger bases such as BuLi are used as catalysts, these reactions can also follow path B (entry 4 in Table 1). It is difficult to determine whether the catalytic cycles for LDA and LTMP follow path A or B.

Scheme 3. Another Possible Catalytic Cycle for LDA in the HB Reaction (Path B)

Kinetic resolution of racemic **1** was observed when HB cleavage was effected with the dilithium amide **7** derived from (1*R*,2*R*)-(–)-1,2-diphenylethylenediamine (Table 3). Here, the HB reaction furnished the carboxamide **8** in 40% yield. The (*R*)-**1** remaining was isolated in 35% yield and 66% ee (entry 1). Judging from the HB reactions of each enantiomer of **1** (entries 2 and 3), the enantioselectivity observed in entry 1 was likely due to kinetic resolution by

(2) For the mechanism of the HB reaction of ketones with H₂O via dianionic species in the presence of KO-*t*-Bu, see: Gassman, P. G.; Lumb, J. T.; Zalar, F. V. *J. Am. Chem. Soc.* **1967**, 89, 946.

Table 3. Kinetic Resolution of (\pm)-**1** by HB Cleavage with (1*R*,2*R*)-Dilithium Amide **7**^a

entry	ee (%) of reactant 1	yield ^b (%) of 8	yield ^a (%) and ee ^b (%) of 1 recovered
1	0	40	35, 66 (<i>R</i>) ^c
2	91 (<i>R</i>) ^{c,d}	<11	71, 83 (<i>R</i>) ^c
3	92 (<i>S</i>) ^{c,d}	69	10, 11 (<i>S</i>) ^c

^a Isolated yield. ^b Determined by HPLC (Daicel OD-H column). ^c Absolute configuration of **1** is shown in parentheses. ^d For the preparation of optically active **1**, see: Ishihara, K.; Kaneeda, M.; Yamamoto, H. *J. Am. Chem. Soc.* **1994**, *116*, 11179.

HB cleavage and the partial epimerization of **1**. This reaction did not proceed at all with the corresponding monolithium amide under the same conditions. These results were mechanistically interesting.

The observed kinetic resolution can be understood in terms of the difference in the differing stereoelectronic effect operating in bicyclic intermediates **9** and **10**, as shown in Figure 1. These intermediates are expected to be furnished

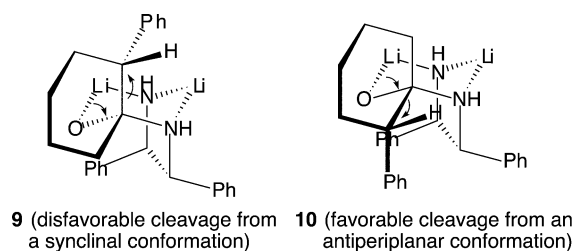
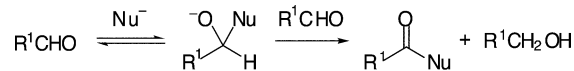


Figure 1. Bicyclic intermediates **9** and **10** via path A.

by the preferential equatorial attack³ of **7** with (*R*)- and (*S*)-**1**, respectively, through path A. The Li–O bond in **10** can adopt an antiperiplanar position to a C–C bond to be cleaved, while the Li–O bond in **9** is conformationally restricted to be in a synclinal position. Therefore, the reaction rate of (*S*)-**1** would be much faster than that of its (*R*)-enantiomer. In contrast, there do not appear to be any striking differences between the steric stabilities of intermediates **9** and **10**.

While studying the HB reaction, we found that *N*-alkyl carboxamides and *N,N*-dialkyl carboxamides were directly obtained in good yield from 2 equiv of aldehyde and 1 equiv of the corresponding lithium amide by a C–H bond cleavage reaction (Scheme 4). In this reaction, alcohols were also

Scheme 4. Cannizzaro-Type Reaction (Nu = OH, OR, NR²R⁵)



produced by hydride transfer to aldehydes. To our knowledge, this is the first example of a Cannizzaro-type reaction⁴ to give carboxamides and alcohols.

The effects of bases were investigated for the Cannizzaro-type reaction of a nonenolizable benzaldehyde with metal *N*-hexylamide in THF (Table 4). Sodium *N*-hexylamide was

Table 4. Cannizzaro-Type Reaction of Benzaldehyde with Metal *N*-Hexylamide

entry	MNHC ₆ H ₁₃	catalyst (mol %)	conditions (°C, h)	yield ^{a,b} (%)
1	NaNHC ₆ H ₁₃		0, 0.5 to rt, 5	82 (76)
2	LiNHC ₆ H ₁₃		0, 0.5 to rt, 5	64 (70)
3	LiNHC ₆ H ₁₃	LDA, 10	0, 0.5 to rt, 5	71 (75)
4	LiNHC ₆ H ₁₃	NaH, 10	0, 0.5 to rt, 5	73 (73)
5	LiNHC ₆ H ₁₃	LDA, 10	0, 0.5 to 40, 5	80 (75)

^a Isolated yield of *N*-hexylbenzamide. ^b Isolated yield of benzyl alcohol is shown in parentheses.

reactive enough at room temperature for the Cannizzaro reaction, and *N*-hexylbenzamide and benzyl alcohol were obtained in respective yields of 82% and 76% yields (method A; entry 1). On the other hand, lithium *N*-hexylamide, which was less reactive than sodium *N*-hexylamide, gave *N*-hexylbenzamide in 64% yield (entry 2). Although LDA and NaH slightly accelerated the reaction with lithium *N*-hexylamide (entries 3 and 4), sodium *N*-hexylamide was still more reactive than lithium *N*-hexylamide–LDA. The reactivity of lithium *N*-hexylamide was further improved under heating at 40 °C in the presence of 10 mol % of LDA (method B; entry 5).

To explore the generality and scope of the above reaction, the Cannizzaro-type reaction was examined with various aldehydes and amines using method A or B (Table 5). Most aromatic aldehydes exhibited good reactivity, while aliphatic aldehydes were less reactive. Notably, carboxamides were obtained from not only lithium *N*-alkylamides but also from relatively less hindered lithium *N,N*-dialkylamides. Dilithium anilide was also a useful nucleophile.⁵

The present methods A and B were successfully applied to the Cannizzaro reaction of anhydrous phenylglyoxal⁶ with

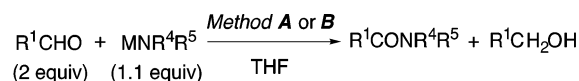
(3) Several examples of the preferential equatorial attack of alkyllithium to 2-substituted cyclohexanones have been reported: (a) Maruoka, K.; Itoh, T.; Yamamoto, H. *J. Am. Chem. Soc.* **1985**, *107*, 4573. (b) Maruoka, K.; Itoh, T.; Sakurai, M.; Nonoshita, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1988**, *110*, 3588.




(4) Cannizzaro, S. *Justus Liebigs Ann. Chem.* **1853**, *88*, 129.

(5) Ooi, T.; Tayama, E.; Yamada, M.; Maruoka, K. *Synlett* **1999**, 729.

(6) An anhydrous solution of phenylglyoxal in toluene was used. For its preparation, see the Supporting Information.

Table 5. Cannizzaro-Type Reaction of Aldehydes with Metal *N*-Alkylamides or *N,N*-Dialkylamides



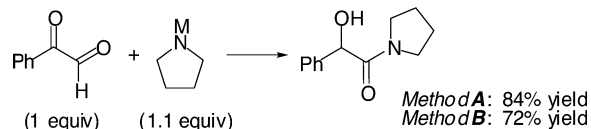
en-try	aldehyde	R ⁴ R ⁵ NM	met-hod ^a	yield ^{b,c} (%)
1	<i>p</i> -(MeO)C ₆ H ₄ CHO	C ₆ H ₁₃ NHNa	A	75 (70)
2	<i>p</i> -(MeO)C ₆ H ₄ CHO	C ₆ H ₁₃ NHLi	B	73 (70)
3	<i>p</i> -(CF ₃)C ₆ H ₄ CHO	C ₆ H ₁₃ NHLi	B	75 (71)
4	<i>i</i> -PrCHO	C ₆ H ₁₃ NHLi	B	49 (–) ^d
5 ^e	<i>t</i> -BuCHO	C ₆ H ₁₃ NHNa	A	45 (43)
6	<i>t</i> -BuCHO	C ₆ H ₁₃ NHLi	B	52 (–) ^c
7	PhCHO	 NLi	B	86 (83)
8	PhCHO	 NNa	A	82 (79)
9	PhCHO	 NLi	B	75 (68)
10	PhCHO	Et ₂ NLi	B	87 (83)
11 ^f	PhCHO	NH ₂ Li	B	62 (71)
12	PhCHO	PhNHLi	B	68 (75)
13	PhCHO	PhNLi ₂	B	81 (80)

^a Method A: the same conditions (no catalysts) with entry 1 in Table 4. Method B: the same conditions (10 mol % of LDA) with entry 5 in Table 4. ^b Isolated yield of carboxamides. ^c Isolated yields of alcohols are shown in parentheses. ^d Alcohols were not isolated. ^e The reaction was performed at 40 °C for 5 h. ^f The reaction was performed under reflux conditions in THF for 5 h.

metal pyrrolidinide (Scheme 5). This transformation resulted in the production of a synthetically useful α-hydroxy carboxamide. Commercially available phenylglyoxal hydrate was inert.

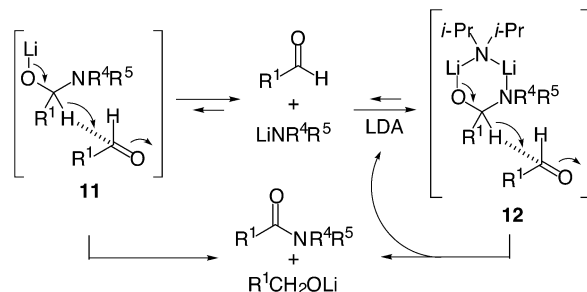
The most straightforward course for the Cannizzaro reaction is a rate-determining transfer of hydride via a linear or bent transition state to a second molecule of aldehyde. For the traditional reaction with NaOH, a linear transition state (TS) has been supported by MNDO–SCF calculations.⁷ For the present reaction with lithium amides, LDA may be

Scheme 5. Cannizzaro-Type Reaction of Anhydrous Phenylglyoxal with Metal Pyrrolidinide



associated with a linear TS **11** to furnish a more stable six-membered TS **12**, which irreversibly cleaves to a carboxamide and a lithium alkoxide (Scheme 6).

Scheme 6. Plausible Mechanistic Pathway for the LDA-Catalyzed Cannizzaro-Type Reaction



In conclusion, extension of the scope and utility of the traditional HB and Cannizzaro reactions provides a novel entry to the direct synthesis of carboxamides. The mechanistic details of the catalytic versions are now under investigation and will be reported elsewhere.

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Supporting Information Available: Experimental procedures and full characterization data of new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(7) Rzepa, H. S.; Miller, J. J. *Chem. Soc., Perkin Trans. 2* **1985**, 717.