Tetraalkylammonium Trihydridocyanoborates. Versatile, Selective Reagents for Reductive Aminations in Nonpolar Media

Summary: Tetrabutylammonium cyanoborohydride or the combination of sodium cyanoborohydride with Aliquat 336 provides useful, convenient reagents for reductive amination of aldehydes and ketones in aprotic or protic media.

Sir: Trihydridocyanoborate (cyanoborohydride)[1] is well established as a mild, selective, acid-stable reducing agent for a variety of conversions including aldehydes and ketones to alcohols,[2] tosylhydrazones,[3] polar alkenes,[4] and alkyl halides[5] to hydrocarbons, and numerous carbon–nitrogen π-bond derivatives (imines, oximes, enamines) to amines.[2] This latter transformation has been particularly exploited as an excellent procedure for the reductive amination of aldehydes and ketones.[1,2,6] However, the commercially available sodium derivative suffers the limitation that solubility is restricted to a few polar protic (H_2O, low molecular weight alcohols), aprotic (Me_2SO, HMPA), or ether (THF, diglyme) solvents.[8] The reagent is almost totally insoluble and unreactive in most other useful solvents including CH_2Cl_2, $CHCl_3$, aromatic and aliphatic

(1) For reviews of cyanoborohydride chemistry, see (a) Hutchins, R. O.; Natale, N. R. *Org. Prep. Proced. Int.* **1979**, *11*, 201; (b) Lane, C. F. *Synthesis* **1975**, *135*; Lane, C. F. *Aldrichemica Acta* **1975**, *8*, 3.

(2) Borch, R. F.; Bernstein, M. D.; Durst, H. D. *J. Am. Chem. Soc.* **1971**, *93*, 2897. Recently, the intermediacy of iminium ions in certain reductive aminations has been questioned: Tadanier, J.; Hallas, R.; Martin, J. R.; Stanaszek, R. S. *Tetrahedron* **1981**, *37*, 1309; Kapnang, H.; Charles, G.; Sondengam, B. L.; Hemo, J. H. *Tetrahedron Lett.* **1977**, 3469.

(3) Hutchins, R. O.; Maryanoff, B. E.; Milewski, C. A. *J. Am. Chem. Soc.* **1975**, *40*, 923.

(4) Hutchins, R. O.; Rotstein, D.; Natale, N. R.; Fanelli, J.; Dimmel, D. *J. Org. Chem.* **1976**, *41*, 3328.

(5) Hutchins, R. O.; Kandasamy, D.; Maryanoff, C. A.; Masilamani, D.; Maryanoff, B. E. *J. Org. Chem.* **1977**, *42*, 82.

(6) Other reagent systems recently introduced for reductive aminations include: (a) potassium hydridotetracarbonylferrate, Bodrini, G. P.; Panunzio, M.; Umani-Ronchi, A. *Synthesis* **1974**, *261*; (b) $NaBH_4/H_2SO_4$, Giumanini, A. G.; Chiavari, G.; Musiani, M. M.; Rossi, P. *Synthesis* **1980**, *743*; (c) the Leukart reaction; see, for example, Baeh, R. D. *J. Org. Chem.* **1968**, *33*, 1647; (d) $NaBH_4$ in carboxylic solvents, Schellenberg, K. A. *J. Org. Chem.* **1963**, *28*, 3259; Gribble, G. W.; Lord, P. D.; Skotnicki, J.; Dietz, S. E.; Eaton, J. T.; Jonson, J. L. *J. Am. Chem. Soc.* **1974**, *96*, 7812; Marchini, P.; Liso, G.; Reho, A.; Liboratore, F.; Moracci, F. M., *J. Org. Chem.* **1975**, *40*, 3453; (e) ion-exchange resin supported BH_3CN^-, Hutchins, R. O.; Natale, N. R.; Taffer, I. M. *J. Chem. Soc., Chem. Commun.* **1978**, 1088.

(7) From Alfa or Aldrich Chemical.

(8) Wade, R. C.; Sullivan, E. A.; Berschied, J. R.; Purcell, K. F. *Inorg. Chem.* **1970**, *9*, 2146.

0022-3263/81/1946-3571$01.25/0

Table I. Reductive Aminations with Tetraalkylammonium Trihydridocyanoborates

carbonyl	amine	hydride	solvent (time, h)	product (picrate mp, °C)[a]	% yield[b]
C_6H_5CHO	pyrrolidine	$NaBH_3CN$	CH_3OH (72)	*N*-benzylpyrrolidine (123–24)	70
		TBACB	CH_2Cl_2 (2.5)		76
		TBACB	THF (2.5)		75
		TBACB	hexane (2.5)		66
		TBACB	C_6H_6 (2.5)		64
		TBACB	CH_3CN (2.5)		58
		$NaBH_3CN$ Aliquat 336	CH_2Cl_2 (48)		84
	morpholine	$NaBH_3CN$ Aliquat 336	CH_2Cl_2 (48)	*N*-benzylmorpholine (185–86)	41
	$(CH_3CH_2)_2NH$[c] + $(CH_3CH_2)_2NH_2^+Cl^-$	$NaBH_3CN$ Aliquat 336	CH_2Cl_2 (42)	$C_6H_5CH_2N(CH_2CH_3)_2$ (116–17)	53
	$CH_3CH_2CH_2NH_2$	TBACB	CH_2Cl_2 (2)	$C_6H_5CH_2NHCH_2CH_2CH_3$	79
		$NaBH_3CN$ Aliquat 336	CH_2Cl_2 (48)		60
	$(CH_3)_2CHNH_2$	TBACB	CH_2Cl_2 (2.5)	$C_6H_5CH_2NHCH(CH_3)_2$	58
p-BrC_6H_4CHO	pyrrolidine	TBACB	CH_2Cl_2 (23)	*N*-(*p*-bromobenzyl)pyrrolidine (140–41)	83
m-ClC_6H_4CHO		TBACB	CH_2Cl_2 (21)	*N*-(*m*-chlorobenzyl)pyrrolidine (153–54)	89
2,6-$Cl_2C_6H_3CHO$		TBACB	CH_2Cl_2 (2.5)	*N*-(2,6-dichlorobenzyl)pyrrolidine (180–81)	57
		$NaBH_3CN$ Aliquat 336	CH_2Cl_2 (48)		79
p-NCC_6H_4CHO	pyrrolidine	TBACB	CH_2Cl_2 (17)	*N*-(*p*-cyanobenzyl)pyrrolidine (166–67)	58
$CH_3(CH_2)_8CHO$		$NaBH_3CN$	CH_3OH (46)	*N*-decylpyrrolidine (73–74)	67
		TBACB	CH_2Cl_2 (2.5)		64
	$(CH_3)_2CHNH_2$	TBACB	CH_2Cl_2 (42)	$CH_3(CH_2)_8CH_2NHCH(CH_3)_2$	52
$C_6H_5COCH_3$	pyrrolidine	$NaBH_3CN$	CH_3OH (70)	*N*-(α-methylbenzyl)pyrrolidine (125–26)	82
		TBACB	CH_2Cl_2 (72)		89
		TBACB	hexane (72)		69
		TBACB	C_6H_6 (72)		61
		$NaBH_3CN$ Aliquat 336	CH_2Cl_2 (48)		74
		$NaBH_3CN$ Aliquat 336	C_6H_6 (48)		70
	$CH_3NH_3^+Cl^-$	TBACB	CH_3OH (90)	$C_6H_5CH(CH_3)NHCH_3$ (182–83)	71
		TBACB	CH_2Cl_2 (90)		<5
	NH_4OAc	TBACB	CH_3OH (45)	$C_6H_5CH(CH_3)NH_2$	49
	$CH_3CH_2CH_2NH_2$	$NaBH_3CN$ Aliquat 336	CH_2Cl_2 (48)	$C_6H_5CH(CH_3)NHCH_2CH_2CH_3$	36
p-BrC_6H_4CHO	pyrrolidine	TBACB	CH_2Cl_2 (48)	*N*-(*p*-bromo-α-methylbenzyl)pyrrolidine (164–65)	82
cyclohexanone	pyrrolidine	$NaBH_3CN$	CH_3OH (72)	*N*-cyclohexylpyrrolidine (163–64)	71
		TBACB	CH_2Cl_2 (47)		90
cyclohexanone	pyrrolidine	$NaBH_3CN$ Aliquat 336	CH_2Cl_2 (48)	*N*-cyclohexylpyrrolidine	94
		$NaBH_3CN$ Adogen 464	CH_2Cl_2 (48)		78
		$NaBH_3CN$ Aliquat 336	$(C_2H_5)_2O$ (42)		73

	$NaBH_3CN$	hexane (42)			67
	Aliquat 336				
morpholine	TBACB	CH_2Cl_2 (2.5)	*N*-cyclohexylmorpholine (169–70)		58
	$NaBH_3CN$	CH_2Cl_2 (48)			52
	Aliquat 336				
$CH_3CH_2CH_2NH_2$	TBACB	CH_2Cl_2 (2.5)	cyclohexylpropylamine		55
$(CH_3)_2CHNH_2$	$NaBH_3CN$	CH_2Cl_2 (48)	cyclohexylisopropylamine		48
	Aliquat 336				
$(C_2H_5)_2NH$[c] +	$NaBH_3CN$	CH_2Cl_2 (48)	*N,N*-diethylcyclohexylamine		36
$(C_2H_5)_2NH_2^+Cl^-$	Aliquat 336				
4-*tert*-butylcyclohexanone	TBACB	CH_3OH (45)	4-*tert*-butylcyclohexanol (~145, mixture)		73 (67t, 33c)
$CH_3(CH_2)_5COCH_3$	$NaBH_3CN$	CH_2Cl_2	2-pyrrolidinyloctane (86–87)		73
	Aliquat 336				
$C_6H_5NH_2$	TBACB	CH_2Cl_2	$CH_3(CH_2)_5CH(CH_3)NHC_6H_5$		31
	$NaBH_3CN$	CH_3CN (48)	$C_6H_5N(CH_3)_2$		66
	$NaBH_3CN$	CH_2Cl_2			61
	Aliquat 336				

[a] All known products were identified by comparisons with authentic samples. New compounds showed IR, NMR, and elemental analysis consistent with the assigned structures. [b] Isolated and purified by distillation. [c] No added acid.

hydrocarbons, and diethyl ether.

To circumvent the solubility problem and hence augment the utility of cyanoborohydride, we have explored the use of the tetrabutylammonium derivative[9] and other phase-transfer techniques[10] for typical cyanoborohydride reductions in nonpolar media.[5,9,11] This communication reports the successful application of phase transfer to reductive amination, which extends the useful media for these conversions to include most common organic solvents, including CH_2Cl_2, hexane, benzene, and diethyl ether.

Tetrabutylammonium cyanoborohydride (TBACB), prepared as previously described,[9,11] is an air- and moisture-stable crystalline solid (mp 144–45 °C) which, in contrast to the sodium counterpart, is not hygroscopic. Phase transfer was also used to solubilize $NaBH_3CN$ by employing Aliquat 336, an inexpensive liquid reagent composed of methyltrialkylammonium chlorides with C_8–C_{10} chains. Successful reductive aminations were obtained under a variety of conditions, but the most convenient consisted of simply dissolving the aldehyde or ketone (10 mmol), amine (60 mmol), and TBACB (7 mmol) or $NaBH_3CN$ (7 mmol) plus Aliquat 336 (7 mmol) in 21 mL of solvent followed by addition of HCl (20 mmol), conveniently added as a 2.5–5.0 N solution in methanol or other solvent. Approximately 1 g of 4A molecular sieves was added (to absorb H_2O formed), and the mixture was stirred at ambient temperature. Progress of the reactions could be followed by monitoring the disappearance of the carbonyl by IR. Upon completion, isolations were accomplished in standard fashion (experimental), the products purified by short-path distillation, and identified by comparison (IR and/or NMR) with authentic samples.

The results for a range of carbonyls and amines are presented in Table I. Examples using the standard method ($NaBH_3CN$, CH_3OH, 2–3 days)[2] are included for comparisons. As illustrated, aromatic and aliphatic aldehydes and ketones react readily with unhindered primary and secondary amines to afford respectable to excellent isolated yields of amines in reasonable times, usually 2.5–24 h for aldehydes and 24–48 h for ketones. Two limitations were encountered. Relatively hindered secondary amines (i.e., diethylamine) reacted only reluctantly with ketones and gave inferior yields (<40%) of amine products. Also ammonium salts ($NH_4^+X^-$, $RNH_3^+X^-$) generally failed to react in aprotic solvents in which solubility is a problem. In such cases, methanol solvent is clearly superior.[2]

The general reaction procedure is illustrated for the preparation of *N*-cyclohexylpyrrolidine. To a solution containing pyrrolidine (4.26 g, 60 mmol) in 21 mL of CH_2Cl_2 was added HCl (20 mmol, 8 mL of a 2.5 N solution in CH_3OH) followed by cyclohexanone (0.98 g, 10 mmol), $NaBH_3CN$ (0.44 g, 7 mmol), and Aliquat 336 (2.93 g, 7 mmol). Approximately 1 g of 4A molecular sieves was added, and the mixture was stirred at room temperature for 48 h. The mixture was filtered, the filtrate acidified (methyl orange indicator), and the solvent removed on a rotary evaporator. The residue was taken up with 10 mL of H_2O and extracted with three 20-mL portions of ether

(9) Hutchins, R. O.; Kandasamy, D. *J. Am. Chem. Soc.* **1973**, *95*, 6131; a number of other tetraalkylammonium cyanoborohydrides are also readily available: Reparsky, J. E.; Weidig, C.; Kelly, H. C. *Syn. React. Inorg. Met.-Org. Chem.* **1975**, *5*, 337.

(10) For excellent, general reviews of phase-transfer reactions, including reductions, see Weber, W. P.; Gokel, G. W. "Phase Transfer Catalysis in Organic Synthesis"; Springer-Verlag: New York, 1977; Keller, W. E. "Compendium of Phase-Transfer Reactions and Related Synthetic Methods"; Fluka AG, Ch-9470 Buchs, Switzerland, 1979.

(11) Hutchins, R. O.; Kandasamy, D. *J. Org. Chem.* **1975**, *40*, 2530.

(discarded). The aqueous phase was basified (solid KOH, phenolphthalein indicator), 20 mL of brine was added, and the mixture was extracted exhaustively with ether. These combined extracts were dried ($MgSO_4$), concentrated, and distilled in a Kugelrohr apparatus to yield 1.43 g (94%) of *N*-cyclohexylpyrrolidine, identified by comparison (IR) with an authentic sample. GLC analysis indicated >98% purity.

In conclusion, phase-transfer techniques greatly augment the utility of cyanoborohydride for reductive aminations of carbonyls and complement analogous conversions in protic media.

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Registry No. Cyclohexanone, 108-94-1; 4-*tert*-butylcyclohexanone, 98-53-3; pyrrolidine, 123-75-1; morpholine, 110-91-8; *N*-benzylpyrrolidine picrate, 78064-90-1; *N*-benzylmorpholine picrate, 58531-53-6; *N*-(*p*-bromobenzyl)pyrrolidine picrate, 78064-91-2; *N*-(*m*-chlorobenzyl)pyrrolidine picrate, 78064-93-4; *N*-(2,6-dichlorobenzyl)pyrrolidine picrate, 78064-95-6; *N*-(*p*-cyanobenzyl)pyrrolidine picrate, 78064-97-8; *N*-decylpyrrolidine picrate, 78064-98-9; *N*-(α-methylbenzyl)pyrrolidine picrate, 78064-99-0; *N*-(*p*-bromo-α-methylbenzyl)pyrrolidine picrate, 78065-00-6; *N*-cyclohexylpyrrolidine picrate, 33109-41-0; *N*-cyclohexylmorpholine picrate, 33109-39-6; cyclohexylpropylamine picrate, 78065-01-7; cyclohexylisopropylamine picrate, 2499-05-0; *N*,*N*-diethylcyclohexylamine picrate, 78065-02-8; *N*-(4-*tert*-butylcyclohexyl)pyrrolidine picrate, 78065-03-9; 2-pyrrolidinyloctane picrate, 42367-34-0; TBACB, 43064-96-6; $NaBH_3CN$, 25895-60-7; C_6H_5CHO, 100-52-7; *p*-BrC_6H_4CHO, 1122-91-4; *m*-ClC_6H_4CHO, 104-88-1; 2,6-$Cl_2C_6H_3CHO$, 83-38-5; *p*-NCC_6H_4CHO, 105-07-7; $CH_3(CH_2)_6CHO$, 112-31-2; $C_6H_5COCH_3$, 98-86-2; $CH_3(CH_2)_5COCH_3$, 111-13-7; CH_2O, 50-00-0; $(CH_3CH_2)_2NH$, 109-89-7; $(CH_3CH_2)_2NH{\cdot}HCl$, 660-68-4; $CH_3CH_2CH_2NH_2$, 107-10-8; $(CH_3)_2CHNH_2$, 75-31-0; $CH_3NH_2{\cdot}HCl$, 593-51-1; NH_4OAc, 631-61-8; $C_6H_5NH_2$, 62-53-3; $C_6H_5CH_2NHCH_2CH_2CH_3$ Picrate, 78065-04-0; $C_6H_5CH_2NHCH(CH_3)_2$ Picrate, 68723-39-7; $CH_3(CH_2)_8CH_2NHCH(CH_3)_2$ Picrate, 78065-06-2; $C_6H_5CH(CH_3)NHCH_3$ Picrate, 78065-07-3; $C_6H_5CH(CH_3)NH_2$ Picrate, 78065-08-4; $C_6H_5CH(CH_3)NHCH_2CH_2CH_3$ Picrate, 78065-09-5; $CH_3(CH_2)_5CH(CH_3)NHC_6H_5$ Picrate, 78065-10-8; $C_6H_5N(CH_3)_2$ Picrate, 7510-42-1; $C_6H_5CH_2N(CH_2CH_3)_2$ Picrate, 78065-11-9.

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