A Mild, Pyridine–Borane-Based Reductive Amination Protocol

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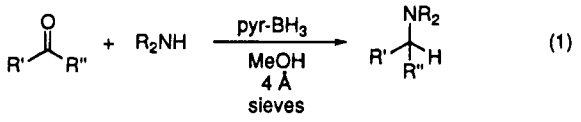
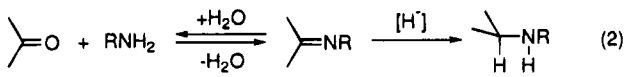
The in situ reductive amination of ketones or aldehydes has been an important part of the synthetic chemist's repertoire since the introduction of a procedure based on cyanoborohydride,[1] yet the toxicity and disposal problems associated with this material has led to a continuing search for alternative reductants.[2,3] We would like to report a simple and mild in situ reductive amination protocol using methanolic pyridine–borane and 4 Å molecular sieves.



(1)

A successful reductive amination procedure for ketones and aldehydes hinges on rapid imine formation and imine selective reductants. As imine formation is usually rate-determining for in situ reductive aminations, catalyzing this reaction is desirable.[4] Typical catalysts are harsh, for example, PCl_5,[5] $BF_3{\cdot}OEt_2$,[6] and $ZnCl_2$,[7] with at least one exception—molecular sieves. The in situ application of molecular sieves to imine synthesis is logical given the equivalent of water generated during imine formation.[8] Westheimer, however, recognized that molecular sieves also play a catalytic role,[9] although the origin of this effect has been contested.[10] To our knowledge, molecular sieves have been applied to reductive amination in only two examples reported in passing by Borch.[1b]



(2)

A member of the amine–borane family of reducing agents,[11] pyridine–borane has the selectivity necessary for reductive aminations. It will only reduce ketones and aldehydes activated by a Lewis acid. Also, it is available in bulk and is convenient to handle due to its relative air stability. Two applications of pyridine–borane to in situ reductive amination have appeared. The recent study of Moormann was limited to reductive amination of piperidines with aldehydes.[12] The older and broader study of Pelter exploited an unusual two-phase reaction medium of acetic acid, presumably a catalyst for imine formation, and petroleum ether (2:7).[13]

The yields (single experiments unless noted otherwise) of desired reductive amination product derived from several pairings of amine and carbonyl compounds are shown in Tables 1 and 2 using the following general reduction conditions: amine (6.0 mmol), carbonyl compound (6.0 mmol), pyridine–borane (5.0 mmol), powdered and activated 4 Å molecular sieves (0.53 g), MeOH (24 mL), 20 °C, 16 h. Several comments are appropriate. Reactions run in methanol were significantly faster than reactions run in CH_2Cl_2, THF, $CHCl_3$, Et_2O, and DMF, but all can be used to good effect. The amount of 4 Å molecular sieves added (0.53 g) limited zeolite loading to no more than 20% by weight water if the theoretical amount of water was generated (6 mmol, 0.108 g). Although higher amine and carbonyl compound concentrations would be expected to accelerate imine formation, their concentrations were deliberately kept low (0.25 M) to test reaction effectiveness. Finally, the ratio of amine to carbonyl compound was kept at 1:1 despite higher ratios generally being acknowledged to provide higher yields.[1]

The reductive amination yields for benzaldehyde and *n*-hexanal pairings with amines are shown in Table 1. When isolated yields of secondary amine were low, analysis of the reaction mixture showed significant quantities of tertiary amine, which resulted from further reaction of the desired secondary amine with aldehyde. For example, with the pairing of *n*-hexanal and isobutylamine, the major product isolated was *N,N*-diisobutylhexylamine (45%). Doubling the concentration of isobutylamine used in the preceding experiment changed the ratio of secondary to tertiary amine product from 1:4 to 3.3:1 (determined from ^1H NMR spectra of unpurified reaction mixtures). The 16-h reaction time used in generating Table 1 was longer than necessary. Reactions with aldehydes run for 1–3 h provided comparable or slightly better yields. For example, benzaldehyde and benzylamine gave 96 and 87% isolated yields of dibenzylamine after 3- and 16-h reaction times, respectively. Similarly, *n*-hexanal and aniline gave 91 and 84% isolated yields of *N*-hexylaniline after 3- and 16-h reaction times, respectively. With apparently rapid imine formation, the added 4 Å molecular sieves might appear superfluous for aldehydes; however, the reaction of benzaldehyde and benzylamine for 3 h in the presence and absence of sieves afforded 96 and 80% isolated yields (average of two experiments) of dibenzylamine, respectively.

Reductive aminations with cyclohexanone, 2-pentanone, and 4-methyl-2-pentanone are shown in Table 2. Cyclohexanone is quite reactive and can be compared to benzaldehyde and *n*-hexanal. Its reactions with

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Table 1. Reductive Amination Yields for Aldehyde and Amine Pairings[a]

aldehyde	amine	isolated yield,[b] %
benzaldehyde	benzylamine	87 (96)
benzaldehyde	aniline	55
benzaldehyde	di-*n*-butylamine	50
benzaldehyde	isobutylamine	87
n-hexanal	benzylamine	58
n-hexanal	aniline	84 (91)
n-hexanal	di-*n*-butylamine	89 (91)
n-hexanal	isobutylamine	10 (45[d])

[a] See general procedure in Experimental Section. [b] Purified by distillation. Single experiments unless noted in text. Values in parantheses are for 3-h reaction time. [c] Estimated yield of secondary amine. [d] Isolated yield of tertiary amine.

Table 2. Reductive Amination Yields for Ketone and Amine Pairings[a]

ketone	amine	isolated yield,[b] %
cyclohexanone	benzylamine	96
cyclohexanone	aniline	71
cyclohexanone	di-*n*-butylamine	31
cyclohexanone	isobutylamine	63 (76)
2-pentanone	benzylamine	80
2-pentanone	aniline	27
2-pentanone	di-*n*-butylamine	22
2-pentanone	isobutylamine	35
4-methyl-2-pentanone	benzylamine	67 (15)
4-methyl-2-pentanone	aniline	4
4-methyl-2-pentanone	di-*n*-butylamine	14
4-methyl-2-pentanone	isobutylamine	45

[a] See general procedure in Experimental Section. [b] Purified by distillation. Single experiments unless noted in text. Values in parentheses are for 3-h reaction time.

primary amines are complete within 1 h, and a decreased 3-h reaction time improved the isolated yield. Reactions of isobutylamine and cyclohexanone, though, suggested an increased importance for added molecular sieves with ketones. Holding other variables constant, multiples of the normal amount of molecular sieves were used and an isolated yield obtained for each (3-h reaction time): 3.0, 80%; 2.0, 76%; 1.0, 76%; 0.5, 78%; 0.25, 66%; 0.125, 53%; 0.0, 25%. The acyclic ketones 2-pentanone and 4-methyl-2-pentanone were markedly less reactive than cyclohexanone, requiring the full 16-h reaction period. The yield from pairing 4-methyl-2-pentanone and benzylamine decreased 52% on reducing the reaction time to 3 h. The poorer yields observed with 4-methyl-2-pentanone relative to 2-pentanone are presumably the result of the increased β-branching, which is known to slow imine formation.[4b]

Acetophenone was a poor substrate. Of the four amines surveyed in Tables 1 and 2, only benzylamine (10% isolated yield) gave any of the desired reductive amination product. Similarly, di-*n*-butylamine gave consistently low yields with ketones. These results are consistent with the increased difficulty of forming imines from aromatic ketones and secondary amines.

Following the reaction of cyclohexanone, benzylamine, and pyridine–borane by ^{1}H NMR in methanol-d_4 provided further information about the reductive amination protocol. Alcohols resulting from carbonyl reduction were observed sometimes in isolated but unpurified reaction mixtures. NMR monitoring showed that only trace amounts of alcohols were formed during the reaction itself. Presumably, the acid added during workup catalyzed carbonyl reduction.[11] Also, intermediate imine concentration was revealed to decrease with time while product amine concentration increased. Therefore, intermediate imines are reduced during the reaction and not during the acidic workup. Finally, in three separate experiments, ethyl acetate, acetonitrile, and cyclohexene were shown to be inert during the reaction. The more mild of the two workups described is not expected to effect these compounds (see Experimental Section).

In conclusion, in situ reductive aminations of aldehydes and ketones with methanolic pyridine–borane in the presence of 4 Å molecular sieves offer a mild, convenient, and effective alternative to cyanoborohydride-based procedures.

Experimental Section

Reactions were conducted in oven-dried (150 °C) glassware under a dry nitrogen atmosphere. Pyridine–borane was used as supplied from Boulder Scientific Co. All other reagents were commercially available and fractionally distilled before use. Molecular sieves were activated by heating (150 °C) for at least 12 h. All reductive amination products possessed physical characteristics that matched previously reported values.

General Reductive Amination Procedure. To MeOH (24 mL) containing 0.53 g of powdered and activated 4 Å molecular sieves was added sequentially the carbonyl compound (6.0 mmol), amine (6.0 mmol), and pyridine–borane (0.507 mL, 5.0 mmol). After 16 h, the resulting mixture was treated with 10 mL of 6 N HCl for 1 h and then the pH adjusted to 14 using 8 N NaOH.[14] Three extractions were performed with Et_2O, and the combined organic extracts were washed with brine, dried over anhyd Na_2SO_4, and concentrated in vacuo. Kugelrohr distillation of the resulting residue afforded material that was ≥95% pure by ^{1}H NMR and matched previously reported bp data.

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(14) Substituting 1 N HCl for 6 N HCl and decreasing the acid contact time to 5 min had no effect on the isolated yields.