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Tetrahedron Letters
Tetrahedron Letters 46 (2005) 4535–4538

Tandem Hass–Bender/Henry reaction for the synthesis of dimethylnitro alcohols from benzylic halides

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Received 4 May 2005; accepted 6 May 2005
Available online 24 May 2005

Abstract—Dimethylnitro alcohols are constructed in a one-pot process from benzylic halides and 2-nitropropane. The use of tetrabutylammonium fluoride (TBAF) as the promoter is essential for this tandem Hass–Bender/Henry reaction to proceed.

Nitro alcohols exemplified by structure **3** (Scheme 1) constitute an important class of intermediates for the preparation of a number of biologically relevant organic molecules. For example, they are an ideal source of amino alcohols, amino ketones, aziridines and amines.[1]

Molecules of this type can be synthesized from aldehydes and nitronate anions, a conversion termed the Henry or nitroaldol reaction.[2] We wish to report the convenient synthesis of molecules of this general structure, not from benzaldehydes, but from benzylic halides and the anion of 2-nitropropane. The overall transformation consists of a one-pot Hass–Bender oxidation followed by a Henry reaction.

The Hass–Bender oxidation consists of the reaction of a substituted nitronate anion with an activated halide to produce a carbonyl compound.[3] The mechanism for this reaction is believed to be the displacement of the halide or leaving group by the nitronate oxygen to afford the *O*-alkylated nitronate. The carbonyl compound is then produced by expulsion of acetoneoxime from the intermediate *O*-alkylated nitronate (Scheme 1).

The Hass–Bender oxidation and the Henry reaction can both share 2-nitropropane as a common component. In addition, the product of the Hass–Bender oxidation and the starting material for the Henry reaction (i.e., aldehyde) are equivalent. Therefore, we reasoned that coupling these two processes would produce the desired hydroxynitro compounds directly from benzylic halides. Since both reactions are dependent on a base to proceed, we anticipated that choosing the appropriate base to promote both the Hass–Bender oxidation and the Henry reaction would be the crucial factor in the overall success of this transformation.

Table 1 shows the outcome of screening various promoters (1.5 equiv) with 2-chlorobenzyl bromide in the presence of excess 2-nitropropane. The bases NH_4OAc, LiF and CsF (entries 1-3) afforded little, if any reaction. However, the tertiary amine bases, DBU, Hunig's base and HMPP[4] (entries 4, 5, and 6) afforded, in addition to unchanged 2-chlorobenzyl bromide, a mixture of aldehyde and desired nitroalcohol but with the aldehyde intermediate predominating. Fortunately, we found that the use of tetrabutylammonium fluoride (TBAF) (entry 7) promoted both the Hass–Bender oxidation as well as the Henry reaction to provide the desired product in 93% yield after chromatography.[5] The reaction did not proceed under slightly acidic conditions or without the aid of a promoter as shown in entries 10 and 11. Only the starting benzylic bromide was isolated in these cases. Stronger bases such as sodium hydride or sodium ethoxide promoted the Hass–Bender oxidation, however, under these conditions the Henry product was not observed (entries 8 and 9).

A possible explanation for the essential role of TBAF resides in the observation that nitro-alcohols with structure **3** revert to the aldehyde **1** when exposed to strong bases such as sodium hydride or sodium ethoxide.[6] It

Keywords: Hass–Bender reaction; Henry reaction; Tandem reaction; TBAF.
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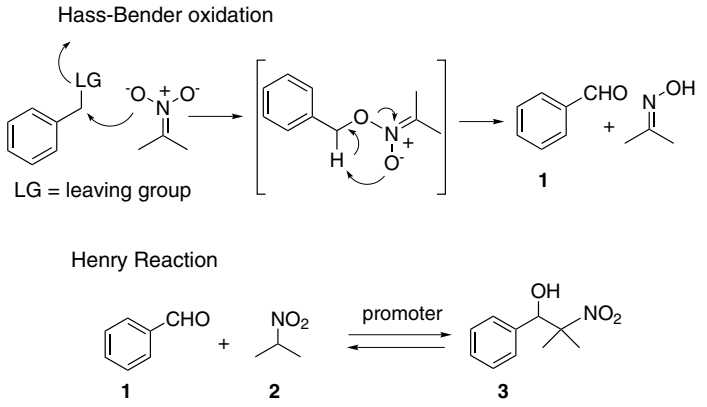
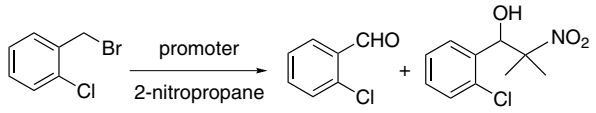
doi:10.1016/j.tetlet.2005.05.021



Scheme 1. Tandem Hass–Bender/Henry reaction.

Table 1. The effect of various promoters on the ratio of products **7** and **8**



6 **7** **8**

Entry	Promoter	Ratio of **7**:**8**
1	NH_4OAc	No reaction
2	LiF	No reaction
3	CsF	No reaction
4	Hünig's base	3:1
5	DBU	2:1
6	HMPP	1.5:1
7	**TBAF**	**1:15**
8	NaH	>100:1
9	NaOEt	>100:1
10	Acetic acid	No reaction
11	None	No reaction

DBU = 1,8-diazabicyclo[5.4.0]undec-7ene; HMPP = 1,3,4,6,7,8-hexahydro-1-methyl-2H-pyrimido[1,2-A]pyrimidine; TBAF = tetrabutylammonium fluoride.

seems that the stronger bases promote the Hass–Bender oxidation but not the Henry reaction, in fact they seem to favor the retro-Henry. The tertiary amine bases, on the other hand, allow for the Hass–Bender reaction to proceed but are not basic enough to drive the Henry reaction to completion. Apparently, the TBAF solution is unique in that it possesses an intermediate basicity that is strong enough to promote the Hass–Bender oxidation but moderate enough so that the retro-Henry is not favored.[7]

To define the scope of this transformation we examined the reactions of a variety of benzyl halides (1.0 equiv) with 2-nitropropane (3.0 equiv) in the presence of TBAF (1.5 equiv). The results of these experiments are summarized in Table 2.

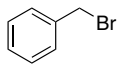
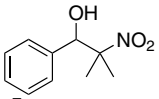
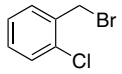
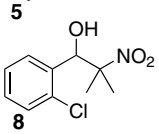
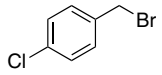
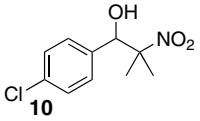
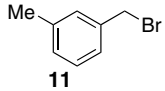
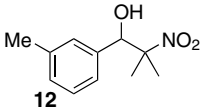
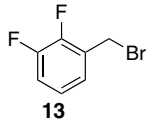
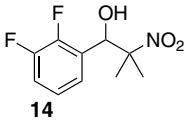
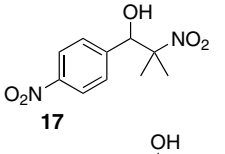
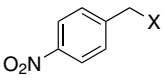
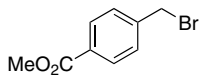
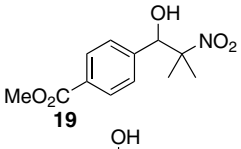
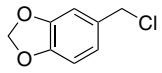
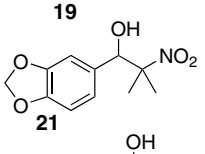
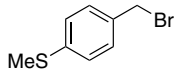
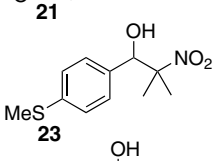
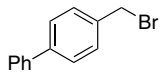
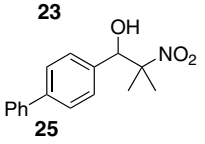
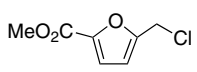
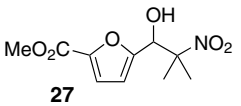
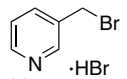
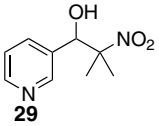
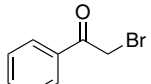
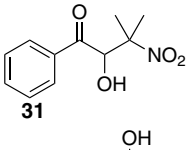
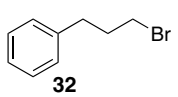
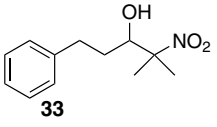
The reaction of benzyl bromide with 2-nitropropane and 1.5 equiv of TBAF afforded the dimethyl nitro product **5** in 69% yield. *o*-Chloro benzyl bromide provided the desired product **8** in 76% isolated yield while the use of *p*-chloro benzyl bromide gave compound **10** in essentially the same yield (77%) illustrating that the steric environment associated with ortho-substitution is tolerated. 3-Methyl benzylbromide **11** produced the dimethylnitro compound **12** in 85% yield while the 2,3-difluoro benzyl bromide **13** gave **14** in 89% yield. Benzylic chlorides **20** and **26** also proved to be viable in the transformation supplying **21** and **27** in 46% and 91% yield, respectively. A number of different functional groups were well tolerated, including the nitro substituent (entry 6), the ether functionality (entry 9), the readily oxidized thioether (entry 10), aromatic halides (entries 2, 3, and 5) as well as the ester functional group (entries 8 and 12).

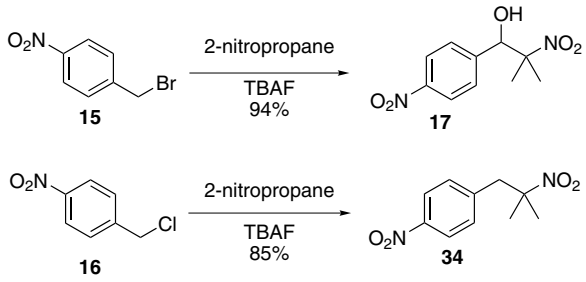
Entries 12 and 13 illustrate the methodology is applicable to heteroaromatic substrates. Thus methyl 5-(chloromethyl)-2-furoate **26** and 3-(bromomethyl)pyridine hydrobromide **28** furnished the desired products in excellent yields. However, the pyridine hydrobromide (entry 13) required the use of an extra equivalent of TBAF for the reaction to proceed, presumably to generate the free base in situ.[8] In general, the yields for the benzylic halides substituted with electron withdrawing substituents tended to be higher than those containing electron donating groups (compare entries 6 and 8 with 9, 10, and 11). This is probably a reflection of the nitroaldol (Henry) portion of the reaction sequence since in all cases the benzylic halide was consumed and the only isolated by-product was the corresponding aldehyde ensuing from the Hass–Bender oxidation. Attempts to drive the reaction to completion in these cases by manipulating the stoichiometry of the nitro-propane and/or TBAF had little or no effect.

The non-benzylic, but nonetheless activated halide, acetophenone methylbromide (entry 14) produced the desired product **31** in moderate 40% yield. Entry 15 demonstrates that a non-activated halide is a feasible substrate for this transformation, producing the expected dimethylnitro alcohol in 73% yield.

The reactions involving *p*-nitrobenzylbromide and *p*-nitrobenzylchloride deserve further comment. Reacting *p*-nitrobenzylchloride with 2-nitropropane in the pres-

Table 2. Scope of the TBAF promoted Hass–Bender/Henry reaction

Entry	Alkyl halide	Product	Yield (%)
1	 **2**	 **5**	69
2	 **6**	 **8**	76
3	 **9**	 **10**	77
4	 **11**	 **12**	85
5	 **13**	 **14**	89
6	X=Br **15**	 **17**	94
7	X=Cl **16** 		8
8	 **18**	 **19**	84
9	 **20**	 **21**	46
10	 **22**	 **23**	57
11	 **24**	 **25**	63
12	 **26**	 **27**	91
13	 **28** ·HBr	 **29**	84
14	 **30**	 **31**	40
15	 **32**	 **33**	73



Scheme 2. Hass–Bender/Henry versus formal S_N2 reaction.

ence of strong bases such as sodium hydride or sodium ethoxide is reported to afford the product of formal direct S_N2 displacement **34** without prior oxidation to the aldehyde in the Hass–Bender sense (Scheme 2). An SR_N1 mechanism has been invoked to account for this transformation.[9]

When *p*-nitrobenzylbromide **15** was reacted with 2-nitropropane in the presence of TBAF the Hass–Bender/Henry reaction product **17** was isolated in very high yield (see entry 6).[10] However, we found that when *p*-nitrobenzylchloride was subjected to our reaction conditions compound **34** was indeed produced in 85% with only 8% of the desired compound **17** being formed (entry 7).

Kornblum has described the leaving group importance in partitioning between the Hass–Bender oxidation and an SR_N1 reaction.[9a,11] Thus under the conditions described here an SR_N1 mechanism can compete with, and even take precedence over the Hass–Bender oxidation/Henry reaction sequence to produce products such as **34** as long as the benzylic chloride is electron deficient enough to enter into the SR_N1 manifold.[12,13]

In summary, we have demonstrated a tandem Hass–Bender oxidation/Henry reaction sequence as a facile entry into dimethylnitro alcohols from a variety of benzylic halides and 2-nitropropane. The use of TBAF as the promoter is essential for the tandem sequence to proceed. Although not explored to its fullest extent, this methodology may also be applicable to non-benzylic halides based on the results in entries 14 and 15. Further exploration of nitroalkanes other than 2-nitropropane in this transformation is underway in our laboratory.

Acknowledgments

We acknowledge the members of Eli Lilly & Company's analytical laboratory for help in full characterization of the final dimethylnitro alcohols disclosed in this letter.

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4. HMPP has previously been used as a base in the Henry reaction; see: Simoni, D.; Invidiata, F. P.; Manfrenidi, S.; Ferroni, R.; Lampronti, I.; Roberti, M.; Pollini, G. P. *Tetrahedron Lett.* **1997**, *38*, 2749.
5. Procedure for the preparation of compound **8**: To a stirred solution of 2-chlorobenzylbromide (0.25 g, 1.22 mmol) in 2 mL of 2-nitropropane is added a 1.0 M solution of TBAF in THF (1.8 mL, 1.8 mmol, 1.5 equiv). The reaction mixture is stirred for 12 h and partitioned between ethyl acetate and saturated aqueous NH_4Cl. The layers are separated and the aqueous layer is extracted with ethyl acetate (2×25 mL). The combined organic layers are washed with water (2×25 mL), brine (25 mL) dried (Na_2SO_4), filtered and concentrated in vacuo. Silica gel chromatography (5–10% EtOAc/Hex) provided 0.26 g (93%) of the desired compound **8**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (d, $J = 7.6$ Hz, 1H), 7.22 (m, 3H), 5.82 (s, 1H), 2.72 (br s, 1H), 1.50 (s, 3H), 1.41 (s, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.3, 133.5, 129.8, 129.7, 129.3, 127.0, 93.1, 72.9, 24.4, 18.8 ppm. Anal. Calcd for $C_{10}H_{12}ClNO_3$: C 52.30, H 5.27, N 6.10; Found: C 52.16, H 5.22, N 6.05.
6. For example, attempts to silylate compound **8** using sodium hydride and TBSCl in CH_2Cl_2 provided a quantitative conversion to the corresponding aldehyde.
7. TBAF was purchased from Aldrich and used as received. No attempt was made to quantify or remove water in the TBAF solution.
8. For an example of an in situ generation of the free base of this compound see: Wittenberger, S. J.; Baker, W. R.; Donner, B. G. *Tetrahedron* **1993**, *49*, 1547–1556.
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10. For a report which describes the direct S_N2 displacement of benzylic bromides with an alkylnitroacetate to provide compounds related to **34** see: Gogte, V. N.; Natu, A. A.; Pore, V. S. *Synth. Commun.* **1987**, *17*, 1421–1429.
11. The subsequent Henry reaction was not observed under the conditions reported by Kornblum.
12. An excellent discussion describing the criteria for entering the SR_N1 reaction manifold is located in the following: (a) Kornblum, N. *Angew. Chem., Int. Ed. Engl.* **1975**, *14*, 734–744; (b) Beraud, V.; Perfetti, P.; Pfister, C.; Kaafarani, M.; Vanelle, P.; Crozet, M. P. *Tetrahedron* **1998**, *54*, 4923–4934; (c) Costentin, C.; Hapiot, P.; Medebielle, M.; Saveant, J.-M. *J. Am. Chem. Soc.* **2000**, *122*, 5623–5635.
13. The importance in the nature of the leaving group has been reported: (a) Kerber, R. C.; Urry, G. W.; Kornblum, N. *J. Am. Chem. Soc.* **1965**, *87*, 4520; (b) Kornblum, N.; Pink, P.; Yorka, K. *J. Am. Chem. Soc.* **1961**, *83*, 2779.