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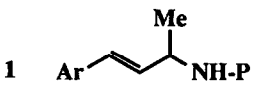
WITTIG OLEFINATION IN THE ABSENCE OF AN EXOGENOUS BASE: A NEW SYNTHESIS OF α-SUBSTITUTED PRIMARY ALLYLIC AMINES.

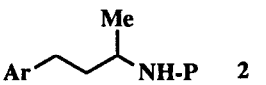
Joseph F. Dellaria, Jr.*and Kevin J. Sallin

Immunosciences Research Area, Department 47K,
Abbott Laboratories, Abbott Park, Illinois 60064

Abstract: A new synthesis of α–substituted primary allylic amines through the *in situ* generation and trapping of an ylide from the reaction of an N-acyl aziridine, triphenylphosphine, and an aldehyde in refluxing isopropanol is reported. These compounds can be prepared enantioselectively (>94.6% ee) by employing a chiral nonracemic N-acyl aziridine.

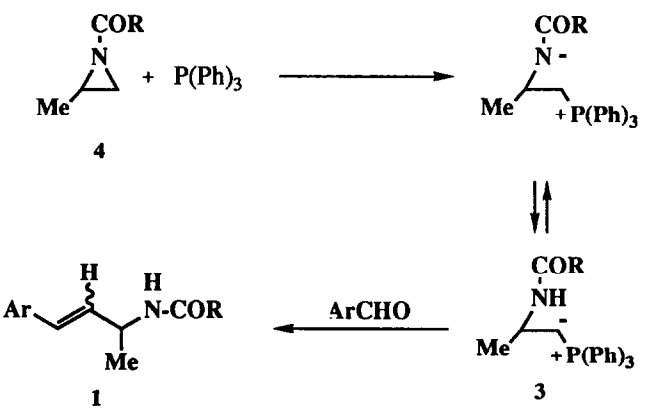
Recently we required a rapid and efficient synthesis of α-substituted primary allylic amines of the general formula **1**, and the corresponding hydrogenated congeners **2**, for a wide range of aryl substituents. In addition, it





was necessary for the methodology to provide the flexibility of preparing these compounds in the chiral nonracemic form. There are a variety of methods available to prepare primary allylic amines lacking an α-substituent.[1,2] However, there are a limited number of options for the preparation of α–substituted primary allylic amines;[3] none of which fulfilled our needs.[4] Since we wished to vary the aryl moiety, a Wittig reaction between **3** and an aromatic aldehyde would take advantage of the ready, commercial availability of aromatic aldehydes and obviate the handling of the sometimes capricious α–amino aldehydes.[5] This created the need to generate **3** or an appropriate equivalent. We were intrigued with the possibility that triphenylphosphine would add to an N-acyl aziridine (**4**), undergo proton transfer to generate **3**, and undergo a subsequent Wittig reaction with the desired aldehyde (Scheme I). *This approach has the added advantage of circumventing the need to add an exogenous base.* It is

Scheme I



well established that N-acyl aziridines (**4**) are susceptible to ring-opening by nucleophiles;[6] in particular, trialkylphosphites have been shown to undergo the Michaelis-Arbuzov reaction with N-acyl aziridines.[7] Moreover, other α–unsubstituted analogues of **3** have been generated by the addition of nitrogen nucleophiles to vinyltriphenylphosphonium salts.[8] In a conceptually related reaction it has been shown that triphenylphosphine, an α,β–unsaturated ester, and an aryl aldehyde sequentially undergo Michael-addition, proton transfer, and Wittig condensation to generate a β,γ–unsaturated ester.[9] We now wish to report our preliminary results which demonstrate that compounds **1** may indeed be prepared in a one-pot reaction through the *in situ* formation and Wittig reaction of **3** by heating an N-acyl aziridine, triphenylphosphine, and an aromatic aldehyde in a polar protic solvent.

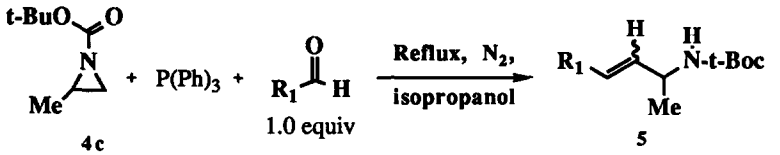
Attempts to preform **3** by heating N-methoxycarbonyl-2-methylaziridine (**4a**) and triphenylphosphine in dimethylformamide (DMF) led to the consumption of starting materials within one hour; addition of benzaldehyde at that point provided no detectable amounts of the desired product. However, when **4a**, triphenylphosphine, and benzaldehyde were heated at 80 °C in dry DMF for three hours, a 17% yield of the desired allylic amine **5a** was obtained as a 1:2 mixture of E:Z isomers. A survey of various N-protecting groups failed to improve the yield. We then turned our attention to investigating the influence of the solvent and discovered that when isopropanol was employed as the solvent a dramatic improvement in the yield was observed.[10] In DMF at 80 °C, with N-benzoyl 2-methylaziridine (**4b**), benzaldehyde, and triphenylphosphine a 28% yield of the N-benzoyl allylic amine, **5b**, was obtained; while, in refluxing isopropanol a 71% yield of **5b** was realized. Interestingly the E:Z ratio was reversed from 1:2 in DMF to 3:1 in isopropanol. The t-butyloxycarbonyl (Boc) group was selected as the preferred activating group for the aziridine in the anticipated ease of deprotecting the allylic amines.

The Table summarizes the unoptimized results from a survey of a variety of aldehydes using the standard conditions of refluxing an isopropanol solution (0.25M based on the aldehyde) of triphenylphosphine (1.5 equiv), N-t-Boc-2-methylaziridine (**4c**, 1.2 equiv), and the desired aldehyde (1.0 equiv) under nitrogen for the noted time. The yields[11,12] for aryl aldehydes vary from good to excellent and appear to be independent of the electronic character of the aryl moiety. The reaction is somewhat tolerant of steric factors as demonstrated by the yield obtained with 2-methylbenzaldehyde (85%, **5f**), but has its definite limitations when the aldehyde bears two *ortho*-substituents (e.g. **5j**, 8%). The geometrical isomers are produced in E:Z ratios varying from 1:1 to 3.4:1. The reaction can be used to prepare dienes from the corresponding α,β-unsaturated aldehydes; however, superior results are obtained when a γ–hydrogen is not present (e.g. **5k** versus **5l**). Aliphatic aldehydes give poor results as represented by the reaction with cyclohexylcarboxaldehyde which provided **5m** in a 9% yield; aromatic and aliphatic ketones do not give any of the desired products.

As previously mentioned, we were also interested in the enantioselective synthesis of these compounds. This could be achieved by employing a chiral nonracemic N-acyl aziridine. Towards that end D-(-)-alaninol was converted to R-(-)-N-t-Boc-2-methylaziridine [(-)-**4c**; $[\alpha]_{25}^{D}$ -27.1 (c 0.965, CH_2Cl_2); 65% overall yield] as summarized in Scheme II. This route proved to be a modification of the methodology Saito[13] and co-workers employed to convert L-threonine to the corresponding N-Boc aziridine. Utilizing standard reaction conditions, (-)-**4c** was reacted with benzaldehyde to provide a 2:1 E:Z ratio of **5c** in a 73% yield. Conversion of chiral nonracemic **5c** to the corresponding Mosher amide,[14] and analysis by analytical capillary gas chromatography, in comparison to the Mosher amide of racemic **5c**, indicated a 97.3:2.7 ratio of diastereomers [we have not eliminated the possibility

that the racemization was introduced during the preparation of the aminoalcohol[15]. Thus demonstrating that the methodology is capable of delivering the products in a chiral nonracemic form.

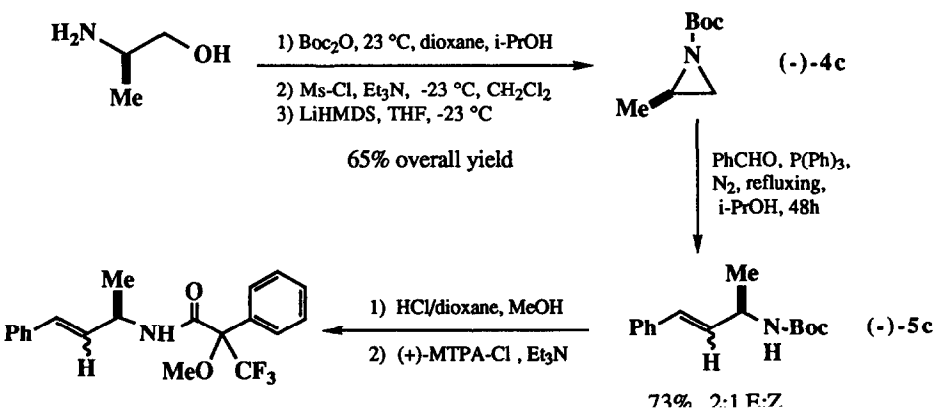
Olefination With Triphenylphosphine, N-t-Boc-2-methylaziridine(4c), and Various Aldehydes.



4c 5

R_1	CMPD	Time(h)	Olefin % Yield	E:Z Ratio
Ph	**5c**	48	71	2:1
4-MeO-Ph	**5d**	72	53	1.1:1
3-MeO-Ph	**5e**	48	77	3:1
2-Me-Ph	**5f**	48	86	1:1
4-CN-Ph	**5g**	26	90	2:1
4-Br-Ph	**5h**	32	85	2:1
3-Cl-Ph	**5i**	25	60	1:1
2,4,6-Me_3-Ph	**5j**	51	8	3.4:1
PhCH=CH	**5k**	26	71	1:1
Me(Me)C=CH	**5l**	21	22	1:1
C_6H_{11}	**5m**	9	9	2:1

Scheme II



Deprotection to the corresponding amines under standard conditions (10 equiv of HCl, 23 °C, 0.5-1.0 h) worked well (84-96% yields) for allylic amines bearing non-electron rich aryl groups (e.g. **5c**, **5g**,and **5i**). However, when the aryl moiety was more electron rich than unsubstituted phenyl, the allylic amines proved to be extremely labile under the standard conditions and provided intractable tars.[16] After extensive investigations, it was found that the conditions of Ohfune[17] successfully removed the t-Boc group in good to excellent yields. Thus exposure of **5d**, **5f**,and **5h** to trimethylsilyl trifluoromethanesulfonate (TMSOTf, 1.5 equiv), 2,6-lutidine (2.0 equiv) in dry dichloromethane at -23 to 0 °C provided 66, 98, and 84% yields of the corresponding amines after chromatography.

Acknowledgements. Preliminary experiments carried out by Shari L. DeNinno and Robert G. Maki are gratefully acknowledged. The expert assistance of David Stroz in obtaining the analytical capillary gas chromatographic results is gratefully acknowledged. The spectroscopic and analytical support from Department 417 is also acknowledged.

Footnotes and References

1. For a review on the synthesis of allylic amines refer to: Cheikh, R. B. ; Chaabouni, R. ; Laurent, A.; Mison, P. ;Nafti, A. *Synthesis*, **1983**, 685.
2. For more recent leading references, refer to: **a)** Deleris, G. ; Dunogues, J. ; Gadras, A. *Tetrahedron*, **1988**, 44, 4243. **b)** Bargar, T. M. ; McCowan, J. R. ; McCarthy, J. R. ; Wagner, E. R. *J. Org. Chem.*, **1987**, 52, 678. **c)** Connell, R. D.; Rein, T. ; Akermark, B. ; Helquist, P. *J. Org Chem.*, **1988**, 53, 3845. **d)** Connell, R. D.; Helquist, P. *J. Org. Chem.*, **1989**, 54, 3359.
3. **a)** Morgan, B.A.; Singh, J.; Ward, S.J. in *Peptides: Structure and Function, Proc. Am. Pept. Symp., 9th*; Deber, C. M.; Hruby, V. J.; Kopple, K. D., Eds.; Pierce Chem. Co.: Rockford Ill., **1985**, 515-519. **b)** Morgan, B. A. *U.S. Pat.* 4,533,657, **1985**. **c)**: Breipohl, G.; Knolle, J.; Wegmann, H.; Ruppert, D. ***Eur. Pat.*** DE 3601248, **1987**. **d)** Czarnocki, Z.; MacLean, D. B.; Szarek, W. A. *J. Chem. Soc., Chem. Commun.*, **1987**, 493. **e)** For two elegant synthetic methods which deliver the 1,3-transposed allylic amines refer to: Buchwald, S. L. ; Watson, B. T.; Wannamaker, M. W.; Dewan J. C. *J. Am Chem. Soc* , **1989**, 111, 4486 and Jensen, M. ; Livinghouse, T. L. *J. Am Chem. Soc* , **1989**, 111, 4495.
4. Developing a more predictable method was undertaken because references 3a-c reported preparing similar compounds utilizing the Wittig reaction between an N-protected α-amino aldehyde and a benzylidenetriphenylphosphonium ylide. The results were variable where in one case the products were obtained as a single geometrical isomer and, as judged by optical rotation, in an enantiomerically pure form (ref. 3a); while in another case, the products were obtained as geometrical mixtures and no comment of the optical purity was made (ref. 3c).
5. **a)** Moriwake, T. ; Hamano, S. -i. ; Saito, S. ;Tori, S. *Chem. Lett.*, **1987**, 2085. **b)** Luly, J. R. ; Dellaria, J. F. ; Plattner, J. J. ;Soderquist, J. L. ; Yi, N. *J. Org. Chem.*, **1987**, 52, 1487 and references cited within each of these references. **c)** Dellaria, J. F.; Maki, R. G.; Stein, H. H.; Cohen, J. ;Whittern, D. ; Marsh, K. ; Hoffman, D. J. ; Plattner, J. J. ; Perun, T. J. *J. Med. Chem.*, **1990**, 33, 534, especially footnote 11.
6. Dermer, O. C. ; Ham, G. E. *Ethylenimine and Other Aziridines*; Academic Press: New York, **1969**; p 205-303.
7. Stamm, H. ; Gerster, G. *Tetrahedron Lett.*, **1980**, 21, 1623.
8. For a recent example refer to: Linderman, R. J. , Meyers, A. I. *Tetrahedron Lett.*, **1983**, 24, 3043 and references cited therein.
9. The first report was: **a)** Oda, R.; Kawabata, T.; Tanimoto, S. *Tetrahedron Lett.* **1964**, 1653. For more recent examples refer to: **b)** Kozikowski, A. P.; Jung, S. H. *J. Org. Chem.*, **1986**, 51, 3402. **c)** Kim, S.; Lee, P. H. *Tetrahedron Lett.*, **1988**, 29, 5413. **d)** Bertenshaw, S.; Kahn, M. *Tetrahedron Lett.*, **1989**, 30, 2731.
10. In the work from references 7, 9a, and 9d, polar protic solvents were also demonstrated to provide superior results in comparison to aprotic solvents.
11. All yields refer to chromatographically purified substances unless stated otherwise.
12. Satisfactory combustion analyses and spectral data (NMR, MS) were obtained for all new compounds reported herein.
13. Saito, K. ;Saijo, S. ; Kotera, K. ; Date, T. *Chem. Pharm. Bull.* **1985**, 33, 1342.
14. Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, 34, 2543.
15. The starting D-(-)-aminoalcohol was purchased from the Aldrich Chem. Co.
16. The acid lability in the deprotection of the N-t-Boc protected allylic amines was reported in ref. 3a.
17. Yamonoi, K.; Ohfune, Y. ***Tetrahedron Lett.*** **1988**, 29, 11.

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