Pergamon

Tetrahedron Letters, Vol. 37, No. 45, pp. 8133-8136, 1996

0040-4039/96 $15.00 + 0.00

PII: S0040-4039(96)01891-6

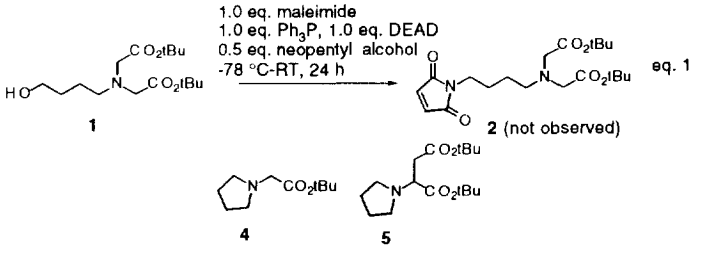
An Unusual Tandem Cyclization-Stevens Rearrangement Mediated by Ph3P/DEAD or Bu3P/ADDP

Michael A. Walker

Bristol-Myers Squibb Pharmaceutical Research Institute, 5 Research Parkway Wallingford, CT 06492

Abstract: Alcohols **1** and **10c** when treated with Ph3P/DEAD or Bu3P/ADDP[1] yield products resulting from intramolecular cyclization to form five- and six-membered, cyclic quaternary ammonium salts (respectively) which undergo a Stevens rearrangement in the same pot. Copyright © 1996 Elsevier Science Ltd

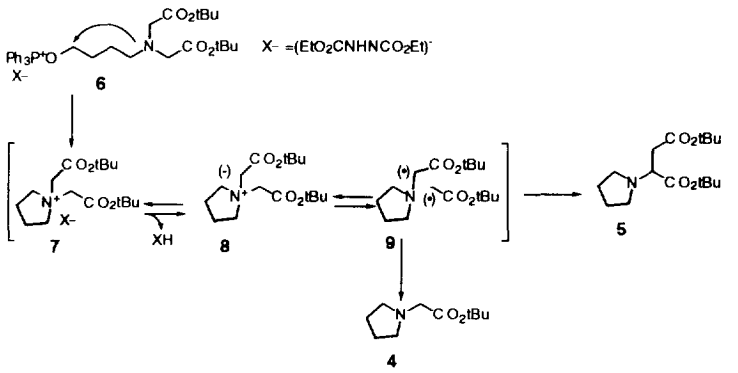
Since its discovery almost 20 years ago the Mitsunobu reaction has played an important part in synthetic chemistry.[2] A number of mechanistic studies have appeared in the literature[3] suggesting that the efficiency of this multi-step process is sometimes lowered by competing side reactions such as elimination or nucleophilic attack at the wrong position (ie. S_N2' vs S_N2) or by the wrong nucleophile.[4] Additionally, Ph3P or Ph3P•DEAD (betaine) can react with certain nucleophiles independently of the main reaction course.[5] Therefore, we are currently examining the Mitsunobu reaction in an attempt to increase the efficiency of the process. As part of this effort this letter reports an unusual side reaction observed when a Mitsunobu reaction was attempted on **1**.[6]



When compound **1** was subjected to our modified-Mitsunobu reaction conditions[7] we were unable to detect any of the desired product **2** (eq. 1). Our curiosity was aroused by the fact that the starting material had been completely consumed but none of the typical by-products (vide supra) were observed. Instead, the reaction produced pyrrolidines **4** and **5**, in low yield (13% and 16% respectively).

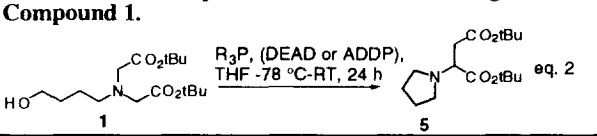
A proposed mechanism leading to both products is shown in the scheme below. The intermediate alkoxyphosphonium salt (**6**) undergoes a rapid cyclization reaction to form a 5- membered ring[8] (**7**) Although the imino nitrogen is a weak nucleophile[9] due to steric hindrance and the presence of two electron

withdrawing substituents the driving force for this reaction is the formation of a five membered ring.[10] This is followed by deprotonation with the mono-anion of H•DEAD (cf. X- in the scheme) perhaps, acting as the base. This sets the stage for a Stevens rearrangement[11] to give **5**. The same mechanism delivers **4** via separation and hydrogen abstraction of the putative radical pair **9** before the rearrangement can be completed.



It was found that Ph3P/DEAD,[12] without maleimide or neopentyl alcohol present, was able to deliver **5** in moderate yield (cf. entries 1-4 in the table).[13] Compound **4** was not observed when maleimide was absent. The yield was progressively increased as the amount of reagent was increased but leveled off at 57% using ≥1.5 equivalents of Ph3P/DEAD. Bu3P/ADDP (entries 5-7) was better at directing the cyclization-Stevens rearrangement reaction providing **5** in up to 77% yield.

Table. Tandem Cyclization-Stevens Rearrangement of Compound 1.

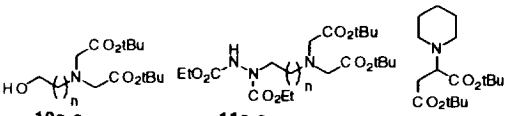


entry	R3P (equiv.)	DEAD/ADDP	(**5**) yield%[a]
1	Ph3P (1.0)	DEAD (1.0)	40[b]
2	Ph3P (1.0)	DEAD (1.0)	50
3	Ph3P (1.1)	DEAD (1.1)	57
4	Ph3P (1.5)	DEAD (1.5)	57
5	Bu3P (1.0)	ADDP (1.0)	60
6	Bu3P (1.5)	ADDP (1.5)	72
7	Bu3P (2.2)	ADDP (2.2)	77

[a]Isolated yield. [b]Benzene was used as solvent

The scope of this reaction is still under investigation. Substrates **10a-c** (n = 1, 2 and 4) have been examined using Ph3P/DEAD and Bu3P/ADDP. In brief, **11a-c** were produced when Ph3P/DEAD was used

while Bu3P/ADDP effected no reaction at all. The exception to this was that **12**[14] was obtained (from **10c**) in modest yield (27%) using Bu3P/ADDP. Evidently, the proximity of the hydroxyl group to the nitrogen in the starting material determines if the tandem cyclization Stevens rearrangement will occur. Thus, entry into the cascade appears to be correlated to the cyclization rate with 6-membered ring formation being the lower limit.[15,16] In the absence of this step, the reactive alkoxy-triphenylphosphonium salt is attacked by $EtCO_2NHN^{(-)}CO_2Et$ to give **11a-c**. The alkoxy-tributylphosphonium salt produced by Bu3P/ADDP is less reactive, which fortunately precludes reaction with the analogous monoanion of H•ADDP, but the cyclization reaction is inhibited for **10a** and **10b** (n =1 and 2 respectively). The conclusion, to date, is that Bu3P/ADDP is better suited than Ph3P/DEAD for this reaction sequence and is capable of forming both 5-membered and 6-membered rings without by-products.



In conclusion, we have presented a novel reaction mediated by Ph3P/DEAD and Bu3P/ADDP. In contrast to the Mitsunobu reaction, in which the hydrogen of a Brønsted acid is replaced with an alkyl group, the above reaction involves the exchange of alkyl groups on a tertiary nitrogen. The above Stevens rearrangement is interesting in that ammonium salt formation and rearrangement are carried out in one pot. More importantly, this rearrangement is accomplished under essentially neutral conditions, in contrast to the literature version which is carried out under basic conditions.[17]

References

1. Abbreviations: ADDP; 1,1'-(azodicarbonyl)dipiperidine, DEAD; diethyl azodicarboxylate.

2. Recent review; Hughes, D. L. *Org. Prep. Proc. Intl.* **1996**, *28*, 129

3. See references cited in ref 2

4. Wojciechowska, H.; Pawlowicz, R.; Andruszkiewicz, R.; Grzybowska *Tetrahedron Lett.* **1978**, *42*, 4063. Comins, D. L.; Jianhua, G. *Tetrahedron Lett.* **1994**, *35*, 2819. Charette, A. B.; Coté, B.; Moroc, S.; Prescott, S. *J. Org. Chem.* **1995**, *60*, 6888.

5. Hedaya, E.; Theodoropulus, S. *Tetrahedron* **1968**, *24*, 2241. Bittner, S.; Assaf, Y.; Krief, P.; Pomerantz, M.; Ziemnicka, B. T.; Smith, G. S. *J. Org. Chem.* **1985**, *50*, 1712. Castro, J. L.; Matassa, V. G.; Ball, R. G. *J. Org. Chem.* **1994**, *59*, 2289.

6. Compounds **1**, **10a-c** were prepared from the corresponding amino alcohols and 2.0 eq. of t-butyl bromo acetate (2.5 eq. $KHCO_3$, DMF).

7. Walker, M. A. *J. Org. Chem.* **1995**, *60*, 5352.

8. Intramolecular cyclization of dialkyl amino groups to form quaternary ammoinum salts has been observed (or implied by product stereochemistry) previously under Mitsunobu conditions. Dow, R. L.;

Kelly, R. C.; Schletter, I.; Wierenga, W.*Syn. Comm.* **1981**, *11*, 43. Freedman, J.; Vaal, M. J.; Huber, E. W. *J. Org. Chem.* **1991**, *56*, 670.

9. Yamada, T.; Manabe, Y.; Miyazawa, T.; Kuwata, S.; Sera, A. *J. Chem. Soc. Chem. Comm.* **1984**, 1500. Tempé, J. in, "Chemistry and Biochemistry of Amino Acids, Peptides, and Proteins, Vol. 7" Boris Weinstein Ed., Marcel Dekker, New York, 1983.

10. The S_N2 step of the Mitsunobu reaction is only weakly dependent on nucleophile basicity. Hughes, D. L.; Reamer, R. A.; Bergan, J. J.; Grabowski, E. J. J. *J. Am. Chem. Soc.* **1988**, *110*, 6487.

11. Pine, S. H. *Org. React.* **1970**, *18*, 403.

12. It is known that the reaction of an alcohol with Ph_3P/DEAD will yield a dialkoxy phosphorane, $(RO)_2PPh_3$, which may be the actual activated intermediate under these conditions rather than alkoxyphosphonium salt **6**. Guthrie, R. D.; Jenkins, I. D. *Aust. J. Chem.* **1982**, *35*, 767. von Itzstein, M.; Jenkins, I. D. *ibid* **1983**, *36*, 557. Idem *J. Chem. Soc., Perkin Trans I*, **1986**, 437. Grochowski, E.; Hilton, B. D.; Kupper, R. J.; Michejda, C. J.; *J. Am. Chem. Soc.* **1982**, *104*, 6876.

13. Typical procedure: Amino alcohol **1** (1.0g, 3.15 mmole) was placed in a 100 mL shlenk flask and dissolved in 30 mL or THF under N_2. The solution was cooled to -78 °C. and Ph_3P (1.24g, 4.73 mmole) added followed by DEAD (0.75 mL, 4.73 mmole). After 5.0 min the cooling bath was removed and the reaction stirred overnight. The resulting clear solution was concentrated under vacuum and purified by flash chromatography (4.8x10 cm SiO_2, 5:1 Hex/EtOAc) to give **5** as an oil (540 mg, 57% isolated yield). ^1H NMR (300 MHz) δ 1.14 (s, 9), 1.18 (s, 9), 1.45 (m, 4), 2.2-2.5 (overlapping m, 6), 3.32 (dd, J = 6.1, 9.1). ^{13}C NMR (75 MHz) d 23.53, 27.83, 27.97, 37.23, 49.42, 61.58, 80.25, 80.82, 170.42. ESI-MS calcd for $C_{16}H_{29}NO_4$; (MH+) 300.2. Found; 300.4

14. Data for compound **12**: ^1H NMR (300 MHz) δ 1.41 (s, 9), 1.46 (s, 9), 1.25-1.56 (m, 6), 2.45 (m, 3), 2.69 (m, 3), 3.52 (dd, 1, J = 7.2, 8.2). ^{13}C NMR (75 MHz) δ 24.49, 26.47, 27.96, 28.21, 36.11, 50.77, 65.08, 80.18, 80.95, 170.05, 170.72. ESI-MS cald for $C_{17}H_{31}NO_4$: 314.2 (MH^+). Found: 314.2.

15. Based on the relative rates for cyclization of: 5>6>3>4. Carey, F. A.; Sundberg, R. J.; "Advanced Organic Chemistry, Part A: Structure and Mechanism" Plenum Press, New York, 1990.

16. Aziridination of amino-ethanol analogs under standard Mitsunobu conditions is difficult and is reported to result in by-products such as **11a** especially if the tether linking the amino and hydroxyl groups is unsubstituted. Pfister, J. R.; *Synthesis* **1984**, 969.

17. Marko, I. E. in "Comprehensive Organic Synthesis, Vol 3", Pattenden, G. Ed.; Pergammon Press, New York, 1991. Pine, S. H. *Org. React.*, **1970**, *18*, 403.

(*Received in USA* 12 *July* 1996; *accepted* 16 *September* 1996)