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Stereospecific synthesis of Z olefins bearing an ω-azido group.

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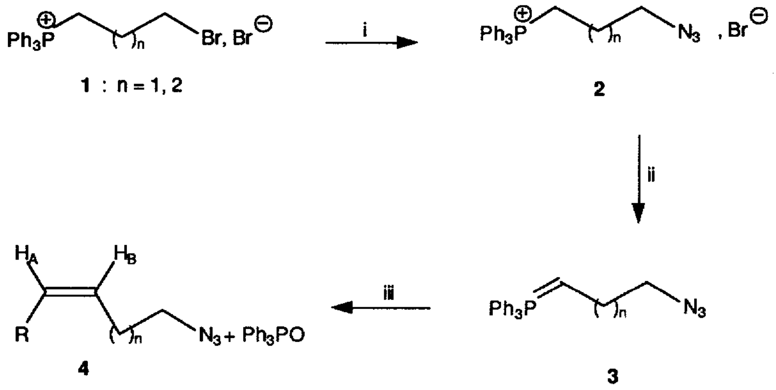
Summary : Ylides derived from ω-azidoalkyltriphenylphosphonium salts were generated at low temperature. They are stable at -80°C for several hours and react smoothly and stereospecifically with typical aldehydes to form Z-ω-azido olefins which are the precursors of ω-unsaturated primary and secondary amines.

In connection with research devoted to the synthesis and study of the reactivity of ω-azido and ω-aminoepoxides, we faced the problem of lenghty acetylenic routes to the olefinic precursors [1]. We describe now a simpler synthesis of the Z derivatives based on the use of phosphorus ylids. Phosphorus reagents have been scarcely used for the synthesis of ω-amino alkenes. Most of the work in this area concerns a direct access to allylic amines [2], a combination of the Wittig reaction and the Gabriel synthesis to prepare a number of cis-4-aryl-3-butenylamine hydrochlorides [3] and the use of 3-dimethylaminopropyltriphenylphosphoranes as highly reactive equivalents of allylidenetriphenylphosphoranes[4].

Although it is known from the literature that α-carbonyl phosphorus ylids [5] and organometallics [6] react with azides, the relatively good stability of the azido group in the presence of carbanions [7] and the availability of chemoselective reduction methods, either to primary [8] or secondary amines [9], led us to envision the sequence depicted in scheme I.

Scheme I



Reagents and conditions : i NaN_3 (1.5 eq.), H_2O, EtOH (1/1), reflux, 12 hrs. ii $[Me_3Si]_2NK$, (1 eq.), THF, -80°C. iii RCHO (1 eq.), -80°C, 1 hr.

The azidophosphonium bromide **2** were synthetized readily by the sequence : (1) reaction of triphenylphosphine with excess 1,3-dibromopropane or 1,4-dibromobutane in benzene at 80°C to give 3- or 4-bromoalkyltriphenylphosphonium bromides as colorless cristalline solids in good yields [10] and (2) subsequent reaction with excess sodium azide in a refluxing 1/1 mixture of EtOH/H_2O (12 hrs) to give, after workup, the bromides **2** in good yields (**2** (n = 1) : 91 %, m.p. = 180-181°C, IR (Nujol) : $^{\nu}N_3$ = 2100 cm^{-1} ; **2** (n = 2) : 90 %, m.p. = 163-164°C, IR (Nujol) : νN_3 = 2100 cm^{-1}). The conversion of the phosphonium salts **2** to a yellow to orange solution of the ylides 3 was effected by reaction with potassium hexamethyldisilazide in THF at -80°C for one hour. Wittig coupling of **3** with aldehydes under the concentration conditions stipulated by Maryanoff et al [11] occured smoothly at -80°C for one hour and then warming up to room temperature. Usual workup followed by column chromatography (silica gel, 1/1 mixture of petroleum ether/ether) led to the isolation of the pure ω-azido olefins **4** in good yield (table).

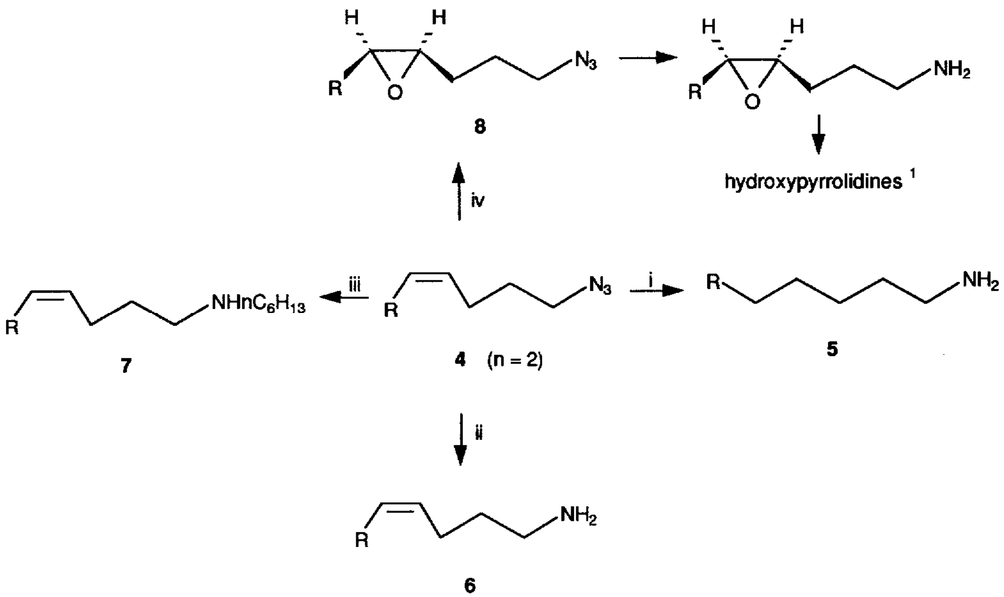
Table - Synthesis of the ω-azido olefins **4** [12]

N°	n	R	$^3J_{H_AH_B}$ (Hz)	Yield (%)[a]
4a	1	Et	10.8	78
4b	1	Ph	11.2	64
4c	1	CH_2=CH-	10.7	60
4d	1	PhCH=CH- (trans)[b]	10.6	74
4e	2	Et	10.9	71
4f	2	Ph	11.6	78
4g	2	CH_2=CH-	10.8	59
4h	2	PhCH=CH- (trans)[c]	10.8	75

[a] Yields are of isolated pure products. [b] J_{trans} = 15.6 Hz. [c] J_{trans} = 15.5 Hz.

None of the E isomer of **4** could be detected by ^{1}H NMR analysis at 300 MHz in agreement with the litterature data [11]. The Z stereochemistry of the newly formed double bond manifested itself in $^{3}J_{H_AH_B}$ values ranging from 10.6 to 11.6 Hz. This sequence gave equally good results with alkyl, aryl and α,β-insaturated aldehydes leading in the later case to E,Z ω-azido dienes. Some selected transformations of the azides **4** (n = 2) are reported in scheme II.

Scheme II



Reagents and conditions : i H_2, Pd/C, EtOH. ii LiAlH$_4$, Et$_2$O. iii nC$_6$H$_{13}$BCl$_2$, CH$_2$Cl$_2$ then NaOH (9). iv mCPBA, CH$_2$Cl$_2$ [1].

The simultaneous reduction of the double bond(s) of the olefins or the dienes **4** gave the alkylamines **5** (**5a** : 87 % ; **5b** : 86 % ; **5c** : 90 % ; **5d** : 88 %) while the reaction with LiAlH$_4$ led to the ω-insaturated primary amines **6** (**6a** : 90 % ; **6b** : 90 % ; **6c** : 92 % ; **6d** : 91 %). A slow addition of n-hexyldichloroborane to a solution of **4** in dichloromethane followed by an aqueous sodium hydroxyde workup produced the ω-insaturated secondary amines **7** in good yields (**7b** : 75 % ; **7c** : 72 % ; **7d** : 65 %). Finally, the mCpBA oxydation of the olefins **4** led to the cis azido epoxydes **8** (**8a** : 71 % ; **8b** : 81 %) which could be selectively reduced to the corresponding primary amines which, in turn, gave hydroxypyrrolidines by an intramolecular regio and stereoselective epoxyde ring opening [1].

In conclusion, the numerous possibilities offered by the selective transformations of the azido group of the olefins **4** into primary or secondary amines in the presence of the double bond (s) or conversely of the double bond (s) in the presence of the azido group enhance the interest of this simple sequence for the direct introduction of an azidoalkyl chain in a substrate containing an aldehyde fonctionnality.

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