STEREOSELECTIVE SYNTHESIS OF N-SUBSTITUTED 2-BENZYLIDENEPYRROLIDIN-5-ONES VIA THE WITTIG REACTION OF BENZYLIDENETRIPHENYLPHOSPHORANE ON SUCCINIMIDES

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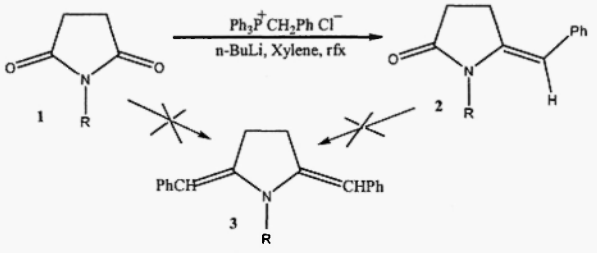
Abstract: The stereoselective synthesis of N-substituted 2-benzylidenepyrro-lidin-5-ones, (E-configuration), in good yields, by the Wittig reaction of benzylidenetriphenylphosphorane, (prepared *in situ*, from benzyltriphenyl-phosphonium chloride using n-butyllithium in refluxing xylene), on N-substituted succinimides, is described here.

The Wittig reaction as a synthetic process is the most important method for the olefination[1] of simple carbonyl compounds e.g. ketones and aldehydes. It constitutes the classical form of the reaction, compared with that, called "non classical" Wittig reaction, of carboxylic acid derivatives, such as esters, lactones, amides, imides etc. leading to the formation of heterosubstituted alkenes including enol ethers, enamines etc. The selective formation of E-alkenes in the case of reactive ylides is possible using the Schlosser methodology.[2] For stabilized ylides the selective formation of E-alkenes is achieved using phosphorous ylides.[3] Despite these traditional and well established methods for the selective formation of alkenes using reactive and stabilized ylides, there is still a considerable lack of efficient methods for the selective formation of alkenes in the case of moderate or semistabilized ylides, as arylidenetriphenyphosphoranes, (Ph_3P=CHAr).

The Wittig reaction of imides has been known for some time and many examples[4,5] are known in organic synthesis. Cyclic imides are particularly applicable to this reaction as reported in a detailed study of the Wittig reaction on maleimides[6] and was found that steric and electronic effects play a considerable role in the product outcome of the reaction. Other examples including Wittig reaction with imide carbonyl of heterocycles as piperazindiones,[7] phthalimides and succinimides with Ph_3P=CHCOOEt[8,9] and $(EtO)_2OP$=CHCN on succinimides[10] (Homer reaction), were reported.

Wittig reactions on succinimides with arylidenetriphenylphosphoranes, ylides which belong to the semistabilized class, have to date not been reported.

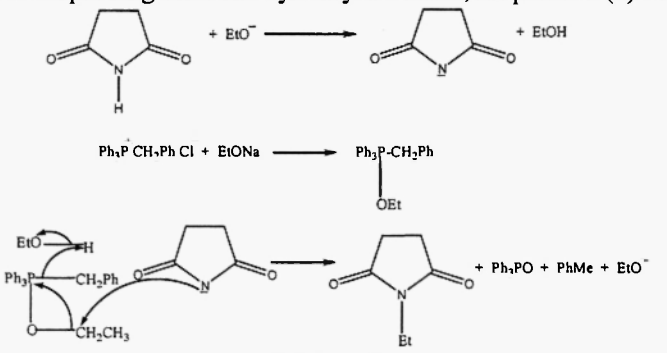
Here we want to report some reactions of benzylidenetriphenylphosphorane on succinimides, (Scheme-1), in connection with a recent work,[11] refered to the synthesis of the same benzylidenepyrrolidinones (**2a-e**) by utilization of the reaction of the γ-benzylidene-γ-butyrolactone with different amines. We experimented with this Wittig reaction using the Ph_3P=CHPh, (prepared *in situ* from benzyltriphenylphosphonium chloride[12] and n-butyllithium in hexane, as base, in xylene as reaction solvent), on succinimides in order to compare the results recieved from the above mentioned work (efficiency, reaction conditions, yields and selectivity). The more forcing reaction conditions required in comparison with those in the case of ketones and aldehydes were rather due to the less reactive imide carbonyl and increased steric hindrance present.



R: a = Me-; b = Et-; c = $PhCH_2$-; d = Ph-; e = 3-$O_2NC_6H_4$-

Scheme-1

Efforts to prepare the corresponding 2,5-bis-olefinated pyrrolidines (**3**) were unsuccessful either starting from succinimides (**1**) or from the 2-benzylidene-pyrrolidin-5-ones (**2**), using a large excess of the ylide. Instead and contrary to the refered[9] result from the reaction on 1-methylsuccinimide with the stabilized ylide, Ph_3P=CHCOOEt, resulting- though in small yield- to the corresponding dicarbethoxymethylene-imine, the products (**2**) were received.

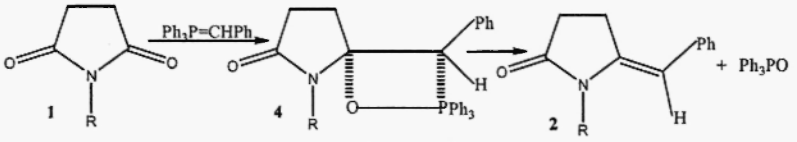


Scheme-2

It must be pointed out that attempts to apply the method on succinimide itself were unsuccessful, unlike the reaction with the stabilized ylide Ph_3P=CHCOOEt.[8,9] But the unpredictable result from the reaction of succinimide with benzylidenetriphenylphosphorane, prepared from benzyl-triphenylphosphonium chloride using sodium ethoxide in ethanol, instead of n-butyllithium in xylene for other succinimides used, resulting in the formation of 1-ethyl-2-benzylidenepyrrolidin-5-one (**2b**), instead of 2-benzylidene-pyrrolidin-5-one, could be explained through a process proposed in Scheme 2, which includes the formation of the N-ethylsuccinimide.

The configuration of all prepared 2-benzylidenepyrrolidin-5-ones (**2**) was assigned as E-diastereomers corresponding to the more stable configuration, in accordance to a general observation[10,13] on reactions of resonance stabilized ylides with relatively no reactive carbonyl compounds which drive almost exclusively to the more stable configurations. Additionally, the coupling constant of vinylic protons of all these derivatives agrees[14] with the statement that a transoid allylic coupling constant, is about ~2Hz, compared to the corresponding cissoid of about ~1.5Hz. The yields of all these derivatives from this process of analytical grade products are good, (63-77%), and exclusively of E-configuration, as above mentioned.

The stereoselectivity of this reaction could be explained by the Wittig reaction mechanism according to a betaine intermediate (**4**) formation, (Scheme 3), which appears to favor the less sterically hindered E-diastereomer than the corresponding Z-.



Scheme-3

The observed stereoselectivity of this reaction may also be due to a shift of an equilibrium of two possible products to the more thermodynamically stable, in the strong basic environment of the reaction.[10,13]

In conclusion, the accomplishment of the Wittig reaction on N-substituted succinimides with benzylidenetriphenylphosphorane, a semistabilized ylide, (prepared from benzyltriphenylphosphonium chloride and n-butyllithium in refluxing xylene), was successful stereoselectively affording the E-diastereomers in good yields. The non applicability of the method on succinimide and the use of sodium ethoxide/ethanol, instead of n-butyl-lithium/xylene, drived, unexpectedly, to the 1-ethyl-2-benzylidenepyrrolidin-5-one. Further utilization of the method using heteroaromatic-phosphoranes on non- or C-substituted succinimides is in our immediate plan.

Experimental

Melting points were determined in capillary tubes and are uncorrected. Microanalyses were performed by microanalytical laboratory of CNRS (France). UV-VIS spectra were recorded at a Perkin Elmer spectrophoto-meter. IR spectra were obtained at a Nicolet Magna 560 spectrometer as nujol mulls and were calibrated against the polystyrene 1601 cm^{-1} band, and given in reciprocal centimeters. ^1H NMR spectra were recorded at ambient temperature using a Varian EM-360 60 MHz spectrometer. The data are reported as follows: chemical shifts are quoted in ppm on the δ scale downfield from TMS (internal standard), multiplicity (br=broad, s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet), coupling constants are given in (Hz). The N-substituted succinimides were prepared according to a standard method,[15] or[16] except if otherwise stated.

Synthesis of N-substituted succinimides.

1-Methylsuccinimide (**1a**): was prepared in an analogous manner described by method[15] or[16] from equimolar amounts, of succinic anhydride and aqueous methylamine (41%) by stirring at room temperature for 1 hour and then condensation of the solution to the solid N-methylsuccinamic acid. Distillation of this crude solid gave a product bp 227-228 ^{0}C/760 torr, mp 70-71 ^{0}C, lit.[15] 71 ^{0}C. 1-Ethylsuccinimide (**1b**): was prepared analogously to the method for 1-methylsuccinimide, using aqueous ethylamine (70%). After distillation of the corresponding succinamic acid, the distillate bp 119-121 ^{0}C /15 torr may be solidify to a product mp 26 ^{0}C, lit.[17] bp 108-11 ^{0}C/11 torr, mp 26 ^{0}C. This product has been prepared[17] by reaction of succinimide with tetraethylorthocarbonate. 1-Benzylsuccinimide (**1c**): was prepared according to the preparation method[18] of 1-benzylphthalimide, from succinimide and benzyl chloride in the presence of potassium carbonate. Mp 104-105 ^{0}C, lit.[19] mp 103 ^{0}C. 1-Phenylsuccinimide (**1d**): was prepared according to a described method[20] from equimolar amounts of succinic acid and and fresh distilled aniline. Mp 156-158 ^{0}C, lit.[20] mp 156-158 ^{0}C. 1-(3-Nitrophenyl)succinimide (**1e**): was prepared according to the above method for 1-phenylsuccinimide, this imide has been prepared[21] from the corresponding maleimide with a reduction reaction using triphenylphosphine in refluxing methanol. Mp 142-143 ^{0}C, lit.[21] mp 140-142 ^{0}C.

Benzyltriphenylphosphonium chloride: was prepared from triphenylphos-phine and benzyl chloride according to the procedure described[12] by Friedrich e. al.

General procedure for the preparation of 2-benzylidenepyrrolidin-5-ones (**2**): in a solution of the succinimide (**1**) 4 mmol in 30 ml of dry xylenes (mixture of o-, m-, p-), under nitrogen atmosphere, 4.68 g (12 mmol) of benzyltriphenyl- phosphonium chloride were added and then 3.90 ml of a solution of n-butyllithium 20% in hexane, (12 mmol). The orange-yellow mixture was stirred at room temperature for 10 minutes and then to reflux for 24-48 hours. To the mixture after cooling to room temperature, petrol ether (bp.30-50 ^{0}C) was added and the precipitate formed (mainly triphenylphosphine oxide), was filtered. From the filtrate after cooling in a refrigerator the crystalline solid was collected and recrystallized from ethanol to give an analytical sample of the product (**2**), in yields 63-77%, should be noted that the crude product proved, ^1H NMR, to be a clean product (**2**). 2-Benzylidene-1-methylpyrrolidin-5-one, (**2a**): yield 68%, mp 98-99 ^{0}C, lit[11]. mp 98-99^{0}C, lit.[22] mp. 98 ^{0}C. Anal. Calcd % for $C_{12}H_{13}NO$: C, 77.00; H, 6.95; N, 7.48. Found: C, 77.21; H, 7.19; N, 7.36. UV (EtOH), λ_{max}nm ($\log\varepsilon_{max}$): 218 (4.00), 276 (4.33). IR (Nujol mull, cm^{-1}): 1704, 1629, 1590. ^1H NMR (60 MHz, $CDCl_3$): δ 2.20-3.33 (m, 7H, $-CH_2CH_2-$ and >NMe as a s, at 3.08), 5.71 (t, J = 2 Hz, 1H, =CH-), 7.23 (s, 5H, arom). 2-Benzylidene-1-ethylpyrrolidin-5-one, (**2b**): yield 63%, mp 105-107 ^{0}C. Anal. Calcd.% for $C_{13}H_{15}NO$: C, 77.60; H, 7.52; N, 6.96. Found: C, 77.54; H, 7.49; N, 7.20. UV (EtOH), $\lambda_{max}(\log\varepsilon_{max})$: 206 (4.13), 218 (4.04), 276.5 (4.39). IR (Nujol mull): 1718, 1639, 1600. ^1H NMR (60 MHz, $CDCl_3$): δ 1.22 (t, J=7 Hz, 3H, CH_3), 2.20-3.17 (m, 4H, $-CH_2CH_2-$), 3.63 (q, J=7Hz, 2H, $>N-CH_2$), 5.68 (t, J=2 Hz, 1H, =CH-), 7.26 (s, 5H, arom.). 1-Benzyl-2-benzylidene-pyrrolidin-5-one, (**2c**): yield 77%, mp 114-116 ^{0}C, lit.[11] 115-116 ^{0}C. Anal. Calcd % for $C_{18}H_{17}NO$: C,

82.10; H, 6.51; N, 5.31. Found: C, 82.21; H, 6.44; N, 5.23. UV (EtOH), λ_{max}nm ($\log\varepsilon_{max}$): 204 (4.40), 276 (4.41). IR (Nujol mull, cm^{-1}): 1704, 1634, 1587. ^{1}H NMR (60 MHz, $CDCl_3$): δ 2.33-3.16 (m, 4H, -CH_2CH_2-), 4.70 (s, 2H, -CH_2Ph), 5.60 (t, J = 2 Hz, 1H, =CH-), 7.07 and 7.21 (two s, 10H, arom.). 2-Benzylidene-1-phenylpyrrolidin-5-one, (**2d**): yield 67%, mp 145-146 ^{0}C, lit.[11] 145-146 ^{0}C. Anal. Calcd % for $C_{17}H_{13}NO$: C, 81.94; H, 6.07; N, 5.62. Found: C, 82.12; H, 6.13; N, 5.49. UV (EtOH), λ_{max}nm ($\log\varepsilon_{max}$): 220 (4.04), 276 (4.39). IR Nujol mull, cm^{-1}): 1721, 1639, 1590. ^{1}H NMR (60 MHz, $CDCl_3$): δ 2.60-3.44 (m, 4H, -CH_2CH_2-), 5.60 (t, J = 2Hz, 1H, =CH-), 7.07-7.70 (m, 10H, arom.). 2-Benzylidene-1-(3-nitrophenyl)pyrro- lidin-5-one, (**2e**): yellow solid, yield 65%, mp 157-158 ^{0}C, lit.[11] 156-158 ^{0}C. Anal. Calcd % for $C_{17}H_{14}N_2O_3$: C, 69.40; H, 4.78; N, 9.51. Found: C, 69.52; H, 4.56; N, 9.44. UV (EtOH), λ_{max}nm ($\log\varepsilon_{max}$): 270 (4.44). IR (Nujol mull, cm^{-1}): 1724, 1624, 1592. ^{1}H NMR (60 MHz, $CDCl_3$): δ 2.60-3.43 (m, 4H, -CH_2CH_2-), 5.60 (t, J = 2 Hz, 1H, =CH-), 7.10-8.40 (m, 9H, arom.).

Reaction of succinimide with benzyltriphenylphosphonium chloride in sodium ethoxide/ethanol: In a solution of sodium ethoxide (10 mmol) in ethanol, prepared from 0.23 g of sodium and 15 ml of absolute ethanol, under nitrogen atmosphere, 3.95 g (10 mmol) of benzyltriphenylphosphonium chloride were added. To the resulting orange colored mixture after 10 minutes of stirring 0.5 g (5 mmol) of succinimide was added and the mixture was refluxed for 72 hours. The hot mixture was filtered, from the produced sodium chloride, and the filtrate was concentrated under vacuum. After dissolution of the concentrated residue, in benzene/petrol ether and cooling, (in a refrigerator), the precipitate was filtered (mainly triphenylphosphine oxide), the filtrate was concentrated and the crude product was purified by column chromatography on silica gel (benzene/ethyl ether) to afford 0.38 g, yield 37.7 %, of the 1-ethyl-2-benzylidenepyrrolidin-5-one (**2b**), identical (mp, mp mixture and ^{1}H NMR) to the product obtained from the Wittig reaction on the 1-ethylsuccinimide.

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