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A Regioselective Entry to Azirino[1,2-*a*]indole Derivatives by Epoxidation/Staudinger Reaction of *o*-Allylphenyl Azides

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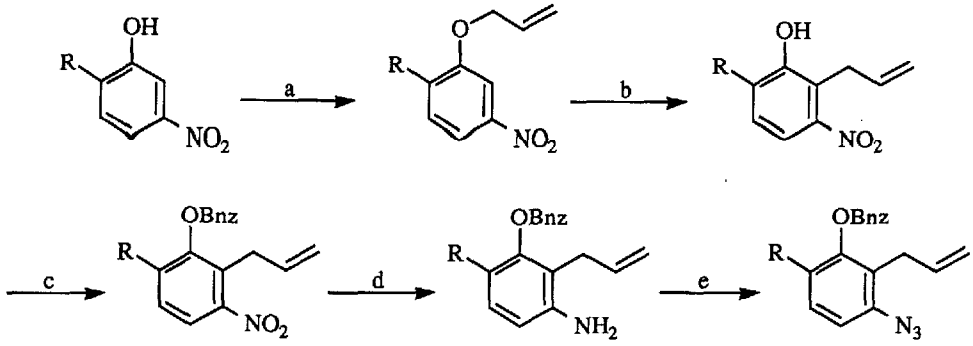
Abstract: On treatment with triphenylphosphine epoxy-azides 2 form azirino[1,2-a]indoles 6 via Staudinger type aminocyclization reaction.

The thermal intramolecular azide-olefin cycloaddition (IAOC) has some interesting precedent in synthetic applications. Because the unsaturated azides are disposed to undergo a variety of mechanistically diverse transformations, the application of such reactions has been limited to special cases[1]. Some of the more serious side reactions reported to occur during the IAOC include the formation of several types of compounds. Thus, olefinic azides undergo thermal decomposition to give triazolines which open up to give cyclic imines and 1-azabicyclo[3.1.0]hexanes[2]. Similarly, thermolysis of allyl α-azidoalkyl ethers provides either 2,5-dihydrooxazoles or bicyclic aziridines[3], and *o*-(allyloxy)phenyl azides at 120°C lead to benzoxazines, dihydroazirinobenzoxazines or 3-alkenylbenzomorpholines through fragmentation of intermediate triazolines[4]. Faced with such a diversity of options, we tested several simple *o*-allylphenyl azides for their regioselective conversion into 1-azabicyclo[3.1.0]hexane derivatives. This ring system is found as an important structural fragment in complex natural products with antitumor activity[5]; in addition it is an interesting synthetic intermediate: ring-opening of the three-membered ring by acids leads to pyrrolidines under kinetically and piperidines under thermodinamically controlled conditions[6].

Our approach for the preparation of the almost unknown azirino[1,2-*a*] indole ring system[7] from *o*-allylphenyl azides is based on the initial protection by epoxidation of the double bond of the side-chain followed by Staudinger reaction with triphenylphosphine to give iminophosphoranes. It is known that iminophosphoranes react intermolecularly with epoxides to form aziridines[8]. The starting azide **1a** was prepared as described in the literature[4] whereas the previously unreported azides **1b** and **1c** were prepared by standard chemistry as depicted in Scheme 1.

Epoxidation of azides **1** with *m*-chloroperbenzoic acid in dry dichloromethane at room temperature led to the corresponding epoxy-azides **2**[9] in good yields (45-87 %). Compounds **2** can be stored at 0°C for weeks without any sign of decomposition. Reaction of epoxy-azides **2** with triphenylphosphine in dry chloroform at room temperature



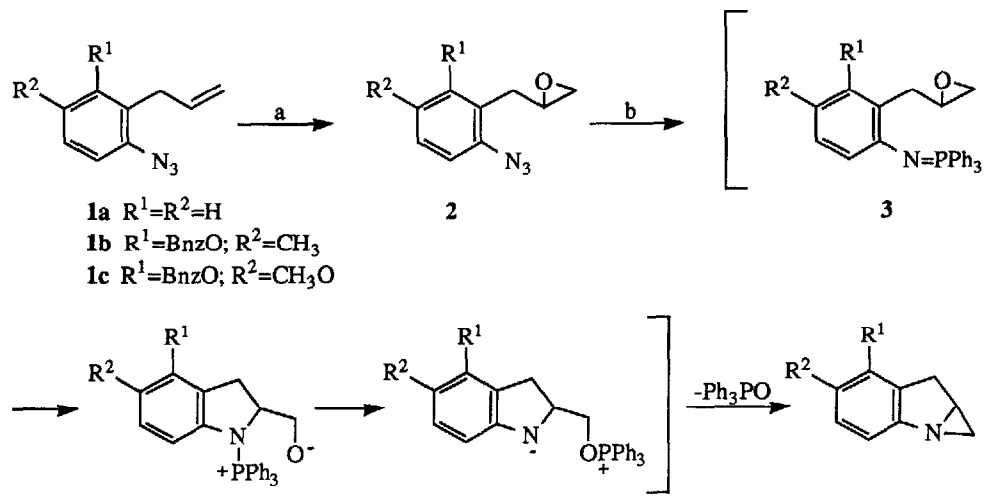
1b R=CH_3
1c R=CH_3O

Reagents: a) CH_2=CH-CH_2Br, K_2CO_3 (83-92 %); b) 190° C, under N_2 (25-42 %); c) BnzBr, K_2CO_3 (95-97 %); d) Pd/C, $NaBH_4$ (75-81 %); e) $NaNO_2$, HCl, 0° C, then NaN_3 (77-88 %).

Scheme 1

led directly to the corresponding azirino[1,2-*a*]indoles **6**[10] in good yields (45-90 %). Efforts to improve the yields of **6** by using tributylphosphine were unsuccessful.

A reasonable mechanism for the conversion **2**→**6** involves as first step the formation of the iminophosphorane **3** via Staudinger reaction[11]. The strongly nucleophilic nitrogen atom opens the epoxide in a 5-exo fashion[12] to generate the betaine **4** which undergoes a N-O migration of the phosphorus to give **5**. Triphenylphosphine oxide is eliminated from **5** and the 1-azabicyclo[3.1.0]hexane ring system is formed via a S_N2-type cyclization (Scheme 2).



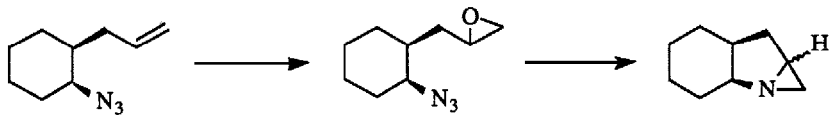
1a R^1=R^2=H
1b R^1=BnzO; R^2=CH_3
1c R^1=BnzO; R^2=CH_3O

2 **3** **4** **5** **6**

Reagents: a) *m*-CPBA, r.t. (45-87 %); b) PPh_3, $CHCl_3$, r.t. (45-95 %)

Scheme 2

This procedure is also applicable to the preparation of the fully saturated ring octahydroazirino[1,2-*a*] indole **9**. Thus, the readily available trans-2-allylcyclohexanol[13] undergoes stereoespecific azidation by the action of diphenylphosphoryl azide / triphenylphosphine / diethyl azodicarboxylate[14] to give the cis-2-allylazidocyclohexane **7** in 33 % yield, which by treatment with *m*-chloroperbenzoic acid is converted into the epoxy-azide **8** in 63 % yield. Reaction of **8** with triphenylphosphine in dry chloroform at room temperature leads to **9** in moderate yield (38 %) (Scheme 3).



7 **8** **9**

Scheme 3

A final word about the selectivity of this procedure is relevant. Thermal decomposition of azide **1c** in toluene at reflux temperature for 4 h led to a mixture of 6-benzyloxy-5-methoxy-7,7a-dihydroazirino[1,2-*a*]indole (8 %) and 4-benzyloxy-5-methoxyindole (17 %), whereas using this protocol the azide **1c** was converted into the corresponding azirino[1,2-*a*]indole in 35 % overall yield.

In conclusion the results reported herein reveal that the combination of epoxidation/Staudinger reaction on *o*-allylphenylazides provides a selective entry for the preparation of azirino[1,2-*a*]indole derivatives under mild conditions and compares favourably with other synthetic methods.

Acknowledgements:

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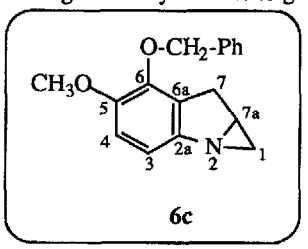
9. Compound **2b** (R^1=Bnz; R^2=CH_3).^{1}H n.m.r. (200 NHz, $CDCl_3$) δ 2.31 (s, 3H, CH_3), 2.53 (dd, 1H, J=2.6, 5.0 Hz, CH_aH_bO), 2.71 (dd, 1H, J=4.7, 5.0 Hz, CH_aH_bO), 2.75 (dd, 1H, J=5.8, 13.5 Hz, CH_aH_bAr), 3.02 (dd, 1H, J=5.0, 13.5 Hz, CH_aH_bAr), 3.19 (dddd, 1H, J=2.6, 4.7, 5.0, 5.8 Hz, >CH-O), 4.82 (d, 1H, J=11.2 Hz, $PhCH_aH_bO$), 4.87 (d, 1H, J=11.2 Hz, $Ph-CH_aH_bO$), 6.89 (d, 1H, J=8.2 Hz, H-5), 7.14 (d, 1H, J=8.2 Hz, H-6), 7.33-7.48 (m, 5H, aromatics); ^{13}C n.m.r. (50 MHz, $CDCl_3$) δ 16.46 (CH_3), 28.49 (Ar-CH_2), 47.55 (-CH_2O), 51.44 (>CH-O), 75.02 (Ph-CH_2O), 114.02 (C-6), 122.55 (C-2), 127.70 (PhC_o), 127.89 (C-4), 128.16 (PhC_m), 130.40 (C-5), 137.27 (PhC_i), 137.61 (C-1), 157.07 (C-3); I.r. (net) 2118 (N_3) cm^{-1}.
10. Typical Procedure: To a solution of epoxy-azide **2c** (0.77 g, 2.5 mmol) in dry dichloromethane (20 ml) was added triphenylphosphine (0.65 g, 2.5 mmol). The mixture was stirred at room temperature for 15 h, then the solvent was removed off under reduced pressure and the residue was chromatographed on a silica gel column eluting with ethyl acetate to give **6c** (R^1=BnzO; R^2=CH_3O) (45 %, oil). ^{1}H n.m.r. (300 MHz, $CDCl_3$) δ 1.13 (d, 1H, J=3.9 Hz, H_aH_bC-1), 2.27 (d, 1H, J=5.3 Hz, H_aH_bC-1), 2.88 (dddd, 1H, J=1.5, 3.9, 5.3, 6.5 Hz, HC-7a), 3.03 (dd, 1H, J=6.5, 17.1 Hz, H_aH_bC-7), 3.11 (dd, 1H, J=1.5, 17.1 Hz, H_aH_bC-7), 3.84 (s, 3H, CH_3O), 5.03 (s, 2H, $PhCH_2O$), 6.70 (d, 1H, J=8.3 Hz, H-3), 6.93 (d, 1H, J=8.3 Hz, H-4), 7.37-7.32 (m, 5H, aromatics); ^{13}C n.m.r. (75 MHz, $CDCl_3$) δ 30.99 (C-7), 39.59 (C-7a), 40.03 (C-1), 56.49 (CH_3O), 74.42 ($PhCH_2O$), 111.63 (C-3), 114.24 (C-4), 128.12 (PhC_o), 128.40 (PhC_p), 128.51 (PhC_m), 129.75 (C-6a), 137.82 (PhC_i), 145.09 (C-5), 150.13 (C-2a), 151.69 (C-6).



6c

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