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Synthesis of 3-Amino 3-Phenyl Azetidine

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SYNTHESIS OF 3-AMINO 3-PHENYL AZETIDINE

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Abstract : We report a convenient preparation of 3-amino 3-phenyl azetidine from N-benzhydryl 3-azetidinone. Our strategy involves a modified Strecker reaction using dibenzylamine as an amino equivalent followed by the displacement of the cyano group by phenyl magnesium bromide and a final catalytic hydrogenation.

During the course of our antibacterial program, we had need for 3-amino 3-phenyl azetidine. Though the interest in 3-substituted, 3-amino azetidines has been recently rekindled, this residue being considered as a promising substituant at the C-7 position of antibacterial quinolones[1] , no hint of the desired azetidine could be found in the literature. In this paper, we report our synthetic efforts toward the preparation of this compound.

Our first move was to recognise N-benzhydryl 3-azetidinone[2] (1) as a valuable starting material owing to its protected nitrogen atom and its versatile carbonyl group . From this point, in order to gain access to the target molecule, an obvious strategy relied upon the immediate introduction of the phenyl group through addition to the carbonyl, followed by the displacement of the generated hydroxy group (*or of a derivative of the latter*) by a masked amino group and subsequent deprotection (see scheme I).

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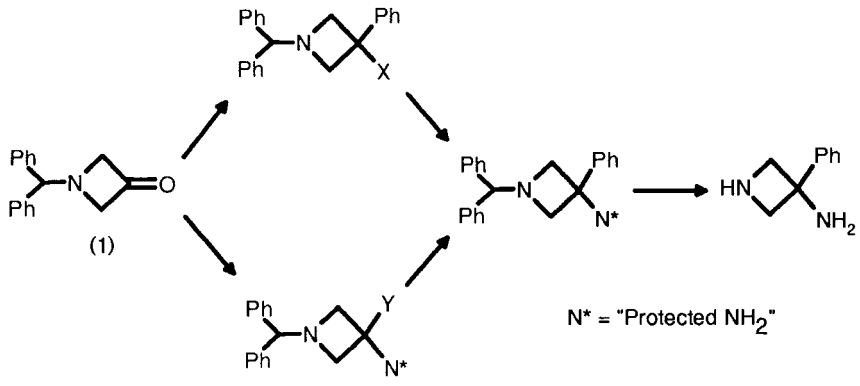

Scheme I

An alternative but less trivial strategy seemed also possible : in this approach, the phenyl group was to be attached later in the synthetic sequence, after initial introduction of the amino equivalent on azetidinone (1) (see scheme I).

In the first approach (see Scheme II), azetidinone (1) was readily converted into alcohol (2) upon reaction with phenyl lithium in ether[2]. Reaction of (2) with sodium azide under various acidic conditions (H_2SO_4 in ether, chloroform or acetic acid [3], CF_3CO_2H in ether) or preformed HN_3 in chloroform[4] invariably returned starting material as did reaction of O-benzyl hydroxylamine in CF_3CO_2H[5]. This lack of reactivity was ascribed to the insolubility of the protonated azetidine under the reactions conditions.

We then discovered that mesylation of alcohol (2) using standard conditions (exc. MsCl / TEA; CH_2Cl_2; RT or reflux) afforded the corresponding chloro derivative (3) instead of the expected sulphonate. Compound (3) was generally pure enough to be used as such, provided that the reaction scale remained below 10 g : isolation by chromatography afforded indeed (3) in 69 % yield (scale 3 g) or in 31 % yield (scale 80 g) due to the degradation of the reaction mixture in the latter case.

Direct aminolysis of (3) with ethanolic ammonia at atmospheric pressure and under reflux turned out to be of no interest for large scale synthesis : after one week, the conversion rate was indeed less than 10% starting from 25 g of (3)[6].

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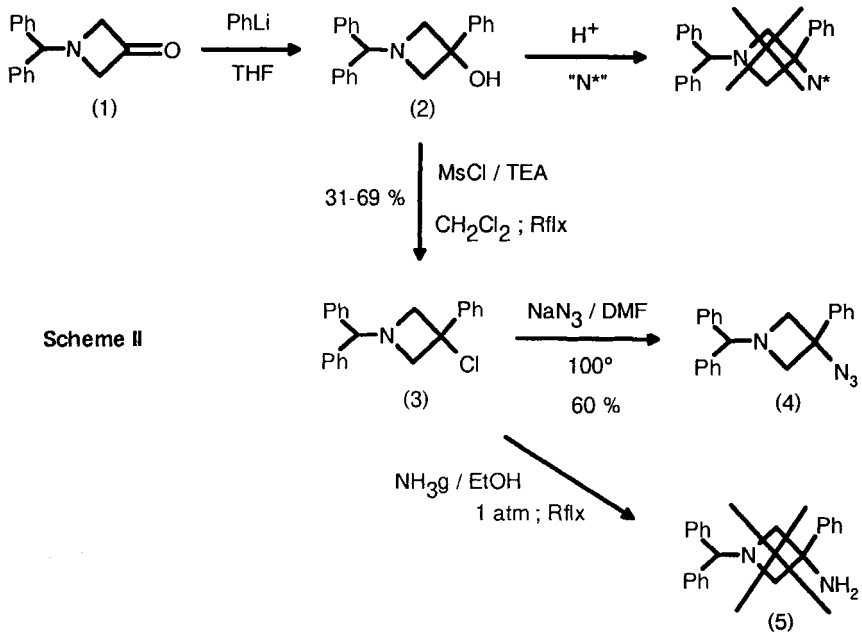

Scheme II

Likewise, reaction of (3) with NaN_3 in DMF (100°C) was briefly investigated : whereas azide (4) could be isolated in 60 % yield starting from 1 g of chromatographed (3) (42 % overall yield from alcohol (2)), purification of (4) was more difficult and overall yield dropped to 33% when the same reaction was carried out on 15 g of crude (3). Furthermore, the reaction temperature was also of importance in this substitution : on the one hand no reaction took place at 60°C and on the other hand, running the reaction in refluxing DMF resulted in extensive degradation of the reaction mixture (overall yield : 14 % ; scale : 10 g).

With these disappointing results in hand, we decided to abandon this approach owing to poor yields and lack of efficient large scale procedures for most of the steps of this synthetic sequence. We therefore turned our attention toward the second strategy summarised in scheme I. It appeared to us that an alpha-amino nitrile, prepared from (1) by the Strecker reaction (Y = CN in Scheme I), could be the pivotal intermediate of this approach. The Bruylants reaction[7] would then allow the exchange of the cyano group for the necessary phenyle and final hydrogenolysis would deprotect both

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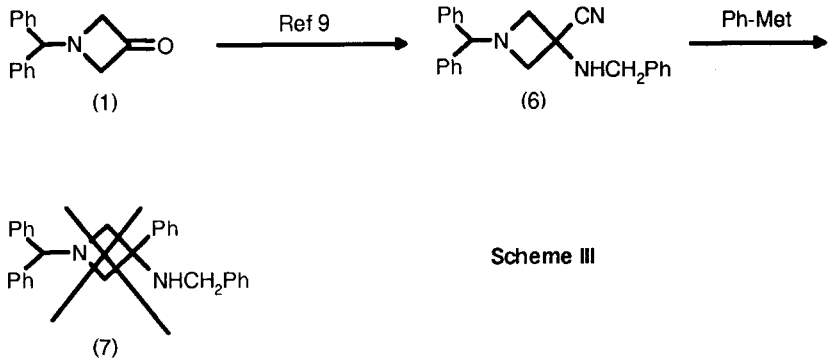

Scheme III

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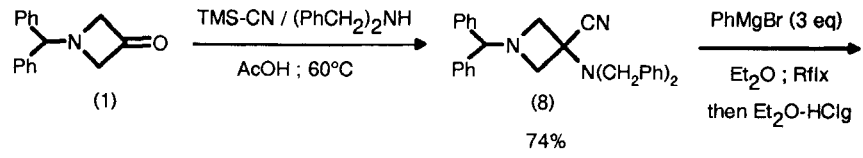
nitrogens of the molecule, provided that N* could generate the amino group under these conditions.

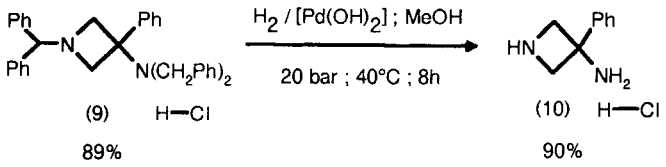
In a first endeavour (see Scheme III), we chose the benzyl amino group as the masked NH_2 group. The preparation of the necessary amino-nitrile (6) had been recently reported using the Strecker reaction[9]. However, this approach was no longer considered when reaction of (6) with Ph-Met[10] was found to yield no trace of the desired phenyl azetidine (7), owing to degradation (Met = Li) or lack of reactivity (Met = MgBr).

We were more fortunate with dibenzylamine as demonstrated by the following results (Scheme IV) : upon reaction with TMS-CN at 60 °C - a known non-aqueous modification of the Strecker reaction[8] - dibenzylamine and (1) afforded amino-nitrile (7) as a precipitate. Filtration of the reaction mixture gave pure (7) in 74% yield. . This reaction could be scaled up to 30 g without event.

Moreover, (8) underwent the expected cyano displacement[11] in good yield (89 % chromatographed yield; isolated as the mono hydrochloride (9); scale : up to 10g) when reacted with 3 equivalents of phenyl magnesium bromide in refluxing ether : under these conditions, the reaction was slow but rather clean[12].

Finally, we examined the hydrogenolysis of (9) in methanol using palladium hydroxide as the catalyst (scale : 5 g). At 40°C and under atmospheric pressure, the





Scheme IV

deprotection was incomplete and diamine (10) was obtained as a mixture with diamine (5); rising the pressure to 20 bar totally consumed diamine (5) but led, along with diamine (10), to a small amount (*up to 10 % in some instances*) of a non-identified impurity, arising from the opening of the azetidine ring. Complete purification of this material was prevented by its low solubility in common organic solvents, its high polarity and the slight unstability of the azetidine ring under ion-exchange resin procedure (*with NH_4OH as the eluent*). However, crude (10) could be used in subsequent reactions as such without any problem. Estimated yield for the above transformation was typically close to 90%.

In conclusion, we have developed a short and efficient access (3 steps from ketone (1) with a minimum of purification; 59% overall yield) to 3-amino 3-phenyl azetidine featuring a modified Strecker reaction with TMS-CN and dibenzylamine followed by a Bruylants substitution of the cyano group for a phenyle and a final deprotection step by hydrogenolysis. Furthermore, this sequence was shown to be amenable to large scale synthesis.

EXPERIMENTAL

General : Melting point (Kofler apparatus) are uncorrected. ^{1}H-NMR spectra were recorded on Brucker AC 200, 300, and WM 250 spectrometers. Chemical shifts are

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given in ppm relative to an internal tetramethylsilane standard. IR spectra were recorded on Nicolet 510 or 60 SXR spectrophotometers. Mass spectra were obtained from a Finnigan 3300 (EI, 70 ev). Purification by column chromatography were carried out on silica gel (Merck; 0.04-0.063 mm). Solvents and reagents were used as received from suppliers.

N-Benzhydryl 3-chloro 3-phenyl azetidine (3) :

To a solution of alcohol (2)[2] (2.9 g ; 9.2 mmoles), Et_3N (5.4 mL ; 38 mmoles) and chloroform (20 mL) stirred in a 100-mL flask equipped with a magnetic bar and a condenser connected to a bubbler, was added rapidly at room temperature MsCl (ml ; 38 mmoles). The resulting brown mixture was then refluxed for 4 hours before cooling and quenching by 20 mL of water. The layers were separated and the aqueous layer extracted by CH_2Cl_2 (2x20 mL). The combined organic layers were dried and then concentrated . The brown oily residue (5.7 g) was chromatographed on silica gel (95/5 Cyclohexane/AcOEt) to afford 2.1 g of a yellow oil (69 % yield; R_f = 0.43; 0.78 for 70/30 Cyclohexane/AcOEt). ^{1}H-NMR : (200 MHz, $CDCl_3$) δ : 3.85 , 3.95 (d, 2H each, J = 7 Hz; $C\underline{H}_2NC\underline{H}_2$), 4.55 (s, 1H, C<u>H</u>Cl), 7.2-7.6 (m, 15H, $C_6\underline{H}_5$); IR (CH_2Cl_2) : 3100-3000, 3000-2750, 2110, 1600, 1490, 1450 cm^{-1}; MS (EI) m/z : 333 ($M^{+\cdot}$), 167, 152, 91.

Similarly, starting from 84 g of (2), 27.55 g of (3) were finally obtained (31 % yield).

N-Benzhydryl 3-azido 3-phenyl azetidine (4) :

In a 250-mL flask equipped with a condenser connected to a bubbler were introduced azetidine (3) (1.17 g, 3.5 mmoles), sodium azide (FLUKA; 0.91 g, 14 mmoles) and DMF (32 mL). The resulting solution was stirred at 100°C overnight and then

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partitioned between water (50 mL) and CH_2Cl_2 (50 mL). The aqueous layer was separated and extracted with CH_2Cl_2 (3x50 mL). The combined organic layers were washed with water (3x50 mL), dried over $MgSO_4$ and concentrated to afford a brown oil (1.3 g). Flash chromatography of this residue (95/5 Cyclohexane/AcOEt) afforded azide (4) as a pale yellow oil (0.72 g; R_f = 0.4; yield : 60.5 %). ^{1}H-NMR (200 MHz; $CDCl_3$) δ : 3.65 (q, 4H, $C\underline{H}_2NC\underline{H}_2$), 4.50 (s, 1H, NC$\underline{H}$Ph), 7.2-7.6 (m, 15H, $C_6\underline{H}_5$); IR (CH_2Cl_2) : 3100-3000, 3000-2750, 2110, 1600, 1490, 1450 cm^{-1}; MS : m/z (DCI) : 341 (MH^+), 183.

In a related run, 5 g of (4) were obtained after two chromatography starting from 15 g of crude (3) (overall yield from (2) : 33 %); likewise, reaction of 9.8 g of (3) under reflux for 2 h, lead to 1.46 g of (4) (overall yield : 14 %).

N-Benzhydryl 3-cyano 3-(dibenzylamino) azetidine (8) :

To a stirred solution of azetidinone (1) (3 g; 12.6 mmoles), dibenzylamine (6.1 mL; 31.6 mmoles) and acetic acid (20 mL) in a 50-mL flask equipped with a magnetic bar and a bubbler was added rapidly at room temperature, trimethylsilyl cyanide (FLUKA; 2 mL, 15.8 mmoles). After addition, the mixture was stirred at 60°C for 8 hours. During this period, a creamy precipitate was formed. The resulting suspension was left on standing at room temperature overnight and then cooled to 5°C before filtration. The insoluble solid was washed by a mixture Ether-Petroleum Ether and then dried to afford 4.15 g of pure (8) as a pale yellow solid (yield : 74 %). An analytical sample (R_f = 0.6 for 80/20 Cyclohexane/AcOEt, 0.34 for 90/10 Cyclohexane/AcOEt) was obtained by recrystallization from Cyclohexane (mp : 143°C). Calculated for $C_{31}H_{29}N_3$: C 83.94, H 6.59, N 9.47; Found : C 83.6, H 6.9, N 9.4; ^{1}H-NMR (300 MHz; $CDCl_3$) δ : 2.90, 3.50 (d, 2H each, J = 8 Hz, $C\underline{H}_2NC\underline{H}_2$),

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3.70 (s, 4H, $C\underline{H}_2Ph$), 4.40 (s, 1H, $NC\underline{H}Ph$), 7.2-7.6 (m, 20H, $C_6\underline{H}_5$); IR (KBr) : 3100-3000, 3000-2000, 1600, 1585, 1490, 1450, 750, 700 cm^{-1}; MS : m/z (DCI) : 445 (MH^+), 417.

N-Benzhydryl 3-(dibenzylamino) 3-phenyl azetidine, hydrochloride (9) :

In a 500-mL two necked flask equipped with a magnetic bar, a nitrogen inlet and a dropping funnel connected to a bubbler were introduced phenyl magnesium bromide (ALDRICH, 3M in ether; 15 mL, 45 mmoles) and anhydrous ether (50 mL). To this solution was added dropwise amino-nitrile (8) (10 g; 22,5 mmoles) in THF (50 mL). The reaction mixture was then stirred at room temperature for 20 hours. At that time, more PhMgBr was added (5.6 mL) and the resulting mixture refluxed for 4 hours to complete the reaction. The brownish suspension was then quenched by an aqueous solution saturated with NH_4Cl (120 mL). The organic layer was separated and the aqueous layer extracted with ether (2x100 mL). The combined organic layers were successively washed with the NH_4Cl solution (100 mL) and water (100 mL), before drying and concentration. Flash chromatography on silica gel (97/3 Cyclohexane/AcOEt) of the remaining orange, thick oil (16.4 g) gave (9) as a pale yellow oil (*major by-product isolated in this chromatography : biphenyl*). To this oil dissolved in ether (100 mL), was added 50 mL of 2N hydrochloric ether. The precipitated white solid was filtered, washed with ether and dried to afford 10.64 g of a material shown by combustion analysis to be the mono-hydrochloride of (9) (yield : 89 %). An analytical sample was obtained by recrystallization from toluene (mp : 230°C; R_f = 0.47 90/10 Cyclohexane/AcOEt). Calculated for $C_{36}H_{34}N_2$, HCl : C 81.42, H 6.64, Cl 6.67, N 5.27; Found : C 81.4, H 6.9, Cl 6.7, N 5.3; ^{1}H-NMR (200 MHz; $CDCl_3$) δ : 3.25, 3.40 (d, 2H each, J = 8 Hz, $C\underline{H}_2NC\underline{H}_2$), 3.90 (s, 4H, $C\underline{H}_2Ph$), 4.30

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(s, 1H, NCHPh), 7.0-7.5 (m, 20H, C_6H_5); IR (KBr) : 3100-3000, 3000-2000, 1600,1585,1490,1450,750,700 cm^{-1}; MS : m/z (DCI) : 495 (MH^+), 299;

3-Amino 3-phenyl azetidine, hydrochloride (10) :

A solution of hydrochloride (9) (5 g; 9.4 mmoles) in methanol (50 mL) was introduced in a 225-mL autoclave along with 20 % $Pd(OH)_2/C$ (JANSSEN; 0.5 g). The hydrogenolysis was carried out under pressure (20 bar) at 40°C for 8 hours and then overnight at room temperature. The resulting suspension was filtered on a pad of celite and the filtrate concentrated. The solid residue (3.1 g) was stirred with ether (50 mL) and then filtered to eliminate non-polar by-products. This sequence was repeated on the remaining solid with ether (2x50 mL) and CH_2Cl_2 (3x50 mL) to leave a grey powder (1.71 g). Purity of this solid was estimated to be close to 90 % by ^{1}H-NMR (estimated yield : 90 %; mp : 120°C).^{1}H-NMR (200 MHz; $CDCl_3$) δ : 4.35 (q, 4H, CH_2NCH_2), 7.1-7.5 (m, 5H, C_6H_5), 8.9 (br s, 4H, NH_2); IR (KBr) : 3250-2000, 1600, 1495, 1450, 765, 695 cm^{-1}; MS : m/z (DCI) : 149 (MH^+), 132 ($MH - NH_3)^+$. Attempted purification of this solid by ion-exchange resin chromatography (Dowex 50W (H^+) X-4 (200-400 mesh); elution with NH_4OH 1,5N) led to impure (10) (estimated purity 90-95 % according to ^{1}H-NMR).

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