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SYNTHESIS OF 1,3,8,8a-TETRAHYDRO-3,8-EPOXYAZIRINO[1,2-*b*]ISOQUINOLINES AND THEIR REACTIONS WITH OXYGEN NUCLEOPHILES

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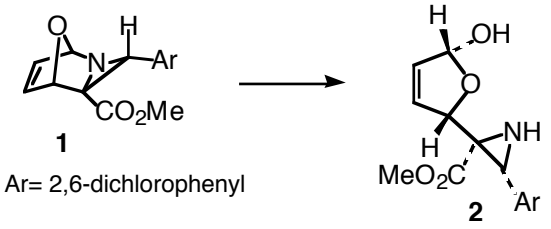
Abstract - Cycloadditions of 2*H*-azirines to isobenzofurans is described. The *endo* and *exo* products were obtained and were reacted with oxygen nucleophiles. Tetrahydroquinolines or benzofuranols were obtained, usually in excellent yields. Cycloaddition of the less electrophilic azirine (**14**) was performed at room temperature in the presence of $ZnCl_2$. The cycloadduct was hydrolysed in the reaction conditions, but dehydration to give back the original cycloadduct was obtained in the presence of 4Å molecular sieves. The structure assigned in the literature to the product of hydrolysis of the cycloadduct (**10**) was rectified.

INTRODUCTION

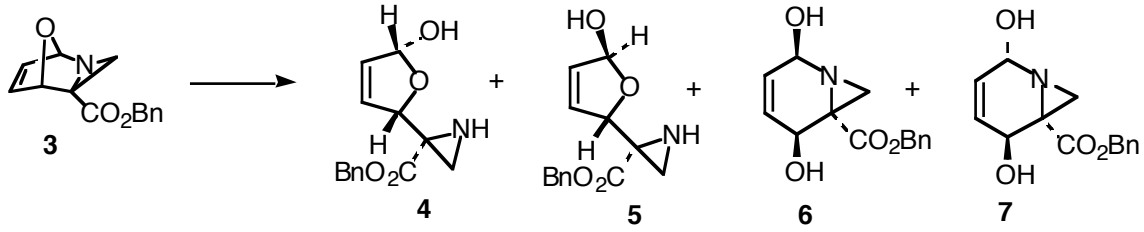
We studied earlier the reaction of alkyl 2*H*-azirine-3-carboxylates with furan and furan derivatives.[1] Methyl 2,6-dichlorophenyl-2*H*-azirine-3-carboxylate reacts with furan forming the *exo* cycloadduct (**1**) quantitatively and so does the benzyl 2*H*-azirine-3-carboxylate giving the cycloadduct (**3**). Hydrolysis product obtained from **1** gives a single adduct (**2**) (Scheme 1). In contrast, a much more complex reactivity is shown in hydrolysis of adduct (**3**), giving four products: the *cis* (**4**) and *trans* (**5**) 1,3-dihydrofurans and *cis* (**6**) and *trans* (**7**) azabicycloheptenediols (Scheme 2).[1] Hassner and Anderson[2] reported that several adducts could be obtained with total stereo-control from cycloadducts of 1,3-diphenylisobenzofuran with alkyl- and aryl 2*H*-azirines depending on the hydrolysis conditions. Scheme 3 shows conditions for exclusive formation of the *cis* (**8**) or *trans* (**9**) tetrahydroisoquinolines, according to the authors. As either the oxygen bridge or the C-N bond are prone to break in these reactions we decided to take a further look at the reactivity of cycloadducts of 2*H*-azirines with 1,3-diphenylisobenzofuran and isobenzofuran. To broaden the interest of such reactions we tried a less reactive 2*H*-azirine, the ethyl 2*H*-azirine-2-carboxylate. This would open up the possibility of forming chirally enriched products after reacting known chiral alkyl 2*H*-azirine-2-carboxylates[3] and 2*H*-azirine-2-phosphonates[4] with isobenzofurans. The hydrolysis and methanolysis products obtained were new

tetrahydroisoquinolines fused to an aziridine ring formed with total stereo-control or 1,3-dihydroisobenzofurans attached to aziridine that either formed a 1:1 mixture of *cis* and *trans* isomers or a single product. The methanolysis product of the cycloadduct (**10**) was proved to be the furanol (**27**), rather than the tetrahydroquinoline (**28**), proposed before.[2]



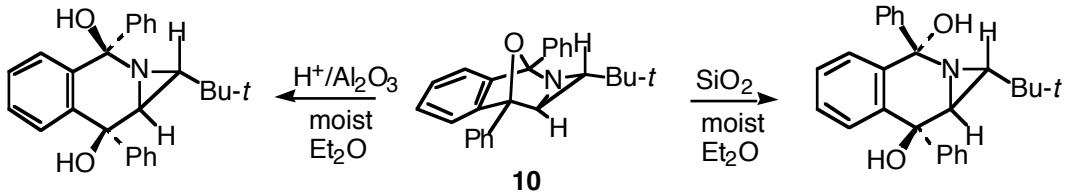
1 **2**

Scheme 1. Hydrolysis of adduct (**1**)



3 **4** **5** **6** **7**

Scheme 2. Hydrolysis of adduct (**3**)



8 **10** **9**

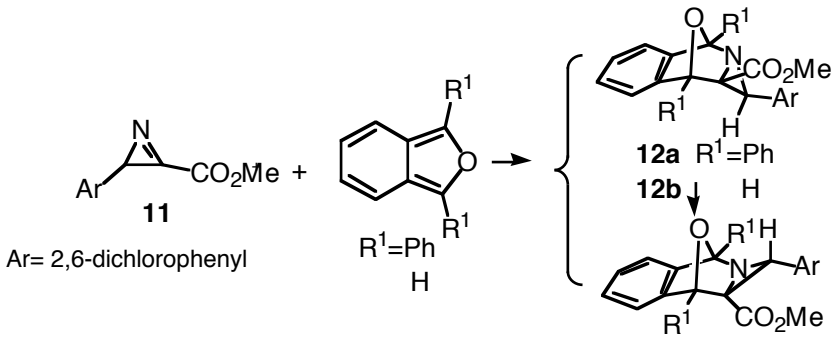
Scheme 3. Cycloadduct (**10**) and the lit.[2] proposed structures for its hydrolysis (**8** and **9**)

RESULTS AND DISCUSSION

Cycloadditions of 2*H*-azirines to 1,3-diphenylisobenzofuran and isobenzofuran

The only literature on cycloadditions of azirines to 1,3-diphenylisobenzofuran are reports in the early seventies by Nair[5] and Hassner and Anderson.[2] Recently, we have reacted methyl 2-(2,6-dichlorophenyl)-2*H*-azirine-3-carboxylate (**11**) with 1,3-diphenylisobenzofuran. The *endo* kinetic product (**12a**) was obtained if strict reaction conditions were observed. If the reaction temperature was allowed to rise to refluxing THF the *exo* thermodynamic product (**13a**) was formed exclusively. A pure specimen of the *endo* adduct could be fully converted into the *exo* isomer by refuxing it in THF and also a slow conversion could be observed by ^{1}H NMR spectrum at room temperature. It is likely that the *endo* product suffers a retro Diels-Alder reaction giving back the reagents that will equilibrate to the

thermodynamically more stable *exo* adduct. This suggestion was first made by Nair in his work on cycloadditions of azirines to 1,3-diphenylisobenzofuran.[5] The cycloaddition of azirine (**11**) with isobenzofuran occurs at room temperature and is complete after 16 h. A mixture of the *endo* and the *exo* products was formed [1.3 (*exo*):1 (*endo*) ratio]. Curiously reflux of the *endo*/*exo* mixture of adducts (**12b**) and (**13b**) gave a mixture of *exo* adduct (**13b**) and the hydrolysis product of the *endo* adduct (**12b**), compound (**22**). Reflux of a clean sample of the *endo* adduct in dry ether showed exclusive formation of compound (**22**). This result shows the greater sensitivity of the *endo* cycloadduct to hydrolysis than that of the *exo* cycloadduct. The same product (**22**) was obtained by treatment of a solution of **12b** in DCM with silica. The main difference between the *endo* and *exo* cycloadducts in their ^{1}H NMR spectra is the chemical shift of the aziridine proton. This is at 2.42 ppm lower field in the *exo* adduct than in the *endo* product. This effect can be explained by opposite effects in both compounds: the influence of the bridge oxygen on the aziridine proton that lies close to it in the *exo* adduct structure, shifting the aziridine proton to lower field (δ_H = 4.15 ppm), and to the aromatic ring at the back of the *endo* structure, that shifts the aziridine proton to higher field (δ_H = 1.86 ppm), (see structures (**12**) and (**13**) in Scheme 4)



Scheme 4. Cycloadditions of azirine (**11**) to 1,3-diphenylisobensofuran and isobenzofuran

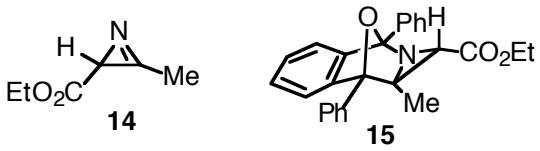


Figure 1. 2*H*-azirine (**14**) and its cycloadduct (**15**)

Cycloaddition reactions of less electrophilic azirine (**14**) to 1,3-diphenylisobenzofuran were attempted both in refluxing toluene and in presence of $ZnCl_2$ at room temperature. In the first case the cycloadduct (**15**) was obtained after 22 h (Figure 1). In the presence of the Lewis acid catalyst the reaction occurs at room temperature in 1.5 days but the cycloadduct suffers hydrolysis, compound (**25**) being isolated in 67% yield after flash chromatography. Lewis acid catalysis was employed recently by Somfai *et al.*[6] in cycloadditions of 2*H*-azirines to several dienes, but this is the first case where such catalysis was used in a

reaction of 2*H*-azirine with a furan. The extreme sensitivity to acid of the aminal function in the cycloadduct promotes the hydrolysis process. Even so, as described below, the reaction can be turned to advantage from a synthetic point of view.

The reaction of 2-*tert*-butyl-2*H*-azirine with 1,3-diphenylisobenzofuran described by Hassner and Anderson was repeated with the aim of re-examining the structure proposed for the methanolysis product of the cycloadduct (**10**). All the analytical data for cycloadduct (**10**) is coincident with the literature results.

Reaction of the cycloadducts with oxygen nucleophiles

Furanol (**16**) was obtained before by treatment of the *exo* cycloadduct (**13a**) with silica in DCM.[1] We now treated a solution of the *endo* adduct (**12a**) with silica and observed the formation of the furanol (**17**) in 94% yield as a single isomer (Figure 2). The stereochemistry at C-3 is unkown. When **12a** was treated with methanol for 24 h at room temperature a 1:1 mixture of the *cis* isomer (**18**) and *trans* isomer (**19**) was obtained. The mixture could not be separated by chromatography: the same ratio of isomers was obtained in each one of the column fractions.

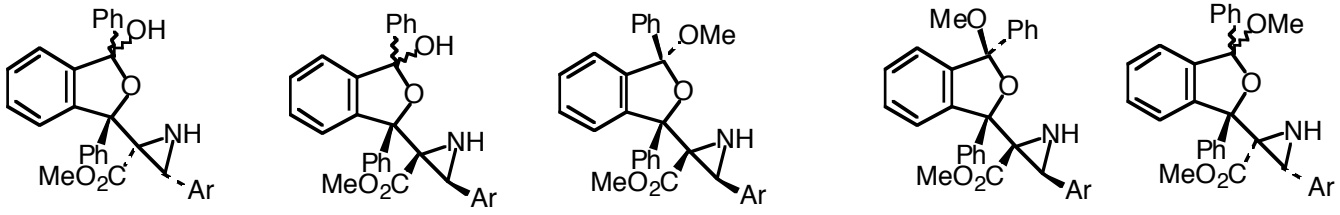


Figure 2. Hydrolysis and methanolysis products obtained from *endo* and *exo* adducts (**12a**) and (**13a**)

The *exo* adduct (**13a**) needed acid or base catalysis to react with water at room temperature. But reaction of **13a** with methanol progress cleanly in reflux giving a single isomer. An equilibrium between the starting cycloadduct (**13a**) and the methanol adduct (**20**) prevents reaction to achive completion. The best yield of product (**20**) is 31% after crystallization. A solution of **20** in $CDCl_3$ contained in an NMR tube and left at room temperature for 15 days gave a mixture of the cycloadduct (**13a**) and the adduct (**20**) in a 2:1 ratio. Major features in the ^{1}H NMR spectra of furanols (**16–20**) (**23**, **24** and **27**) are the coupling constant of the CH aziridine proton to its neighbouring NH and their respective chemical shifts. The CH appears around 3.0–3.6 ppm as well as the NH. In each compound the NH is always upper field compared to the CH. The coupling constant between the CH and the NH proton is *ca*. 10 Hz.

The cycloadducts of 2*H*-azirines with isobenzofuran have as a start the advantage of having hydrogens at position 1 and 3 instead of phenyl groups, which should allow the stereochemistry of the hydrolysis and

methanolysis adducts to be assigned by ^{1}H NMR spectrum. Adducts formed in the reaction of the azirine (**11**) with isobenzofuran proved to behave differently from the adduct of the same azirine with 1,3-diphenylisobenzofuran in the presence of oxygen nucleophiles; in some cases tetrahydroisoquinolines were obtained rather than furanols. The *exo* adduct (**13b**) after refluxing in methanol furnishes 92% yield of the *cis*-tetrahydroisoquinoline (**21**). The *cis* structure was confirmed by X-Ray crystallography (Figure 3).

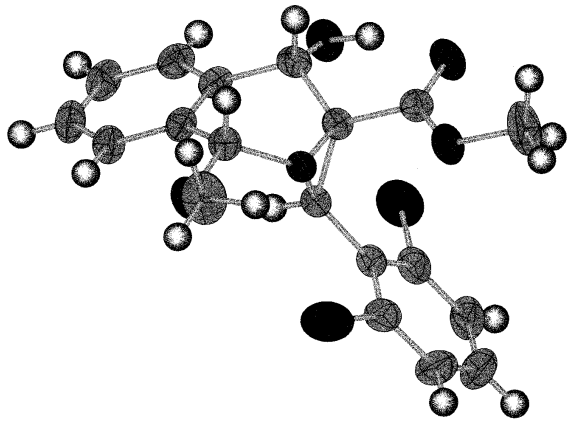


Figure 3. The molecular structure of compound (**21**)

Treatment of the *endo* adduct (**12b**) with silica in DCM gave the tetrahydroisoquinoline (**22**), in 93% yield, after stirring the solution 24 h. The sterochemistry of compound (**22**) was assigned on the basis of a NOESY experiment that showed that 3-H and 8-H are close to 1-H (Figure 4). Major feaures of these tetrahydroquinolines in ^{1}H NMR spectra are the coupling of 3-H and 8-H with the hydrogen of the geminal OH group whenever it exists. ^{13}C NMR spectra are significantly different from those of the furanols. Chemical shifts of the tetrahedral carbon atoms attached to the oxygens are 25–30 ppm lower than the carbons attached to the oxygen in the five membered ring of furanols. This change is possibly due to the difference in strain of the two ring systems: the six memered ring in the tetrahydroquinoline and the five membered ring in the furanols.

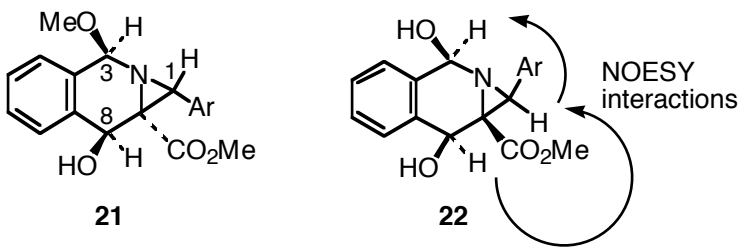
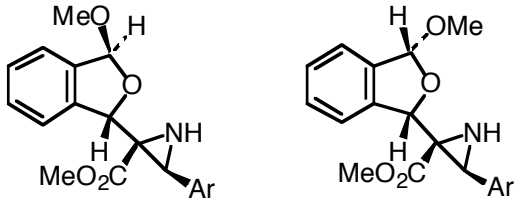


Figure 4. Hydrolysis product (**22**) obtained from cycloadduct (**12b**); methanolysis product (**21**) obtained from cycloadduct (**13b**)

Unexpectedly treatment of **12b** with methanol at room temperature gave again a 1:1 mixture of furanol isomers (**23**) and (**24**) (Figure 5). The *trans* isomer (**23**) is proposed on the basis of a small homoallylic coupling constant (1.2 Hz) between 1-H and 3-H that is well observable after D_2O exchange. Very sharp singlets were recorded for the corresponding protons in the other isomer (**24**). The two isomers were fully separated by flash chromatography, the *trans* isomer being obtained in 29% yield and the *cis* isomer in 38% yield.



23 **24**

Figure 5. Methanolysis products obtained from cycloadduct (**12b**)

Compound (**25**) is the hydrolysis product obtained directly from the mixture derived from the cycloaddition of the azirine (**14**) to 1,3-diphenylisobenzofuran in the presence of $ZnCl_2$. An X-Ray determination has shown the structure to be the *cis* furanol (Figure 6).

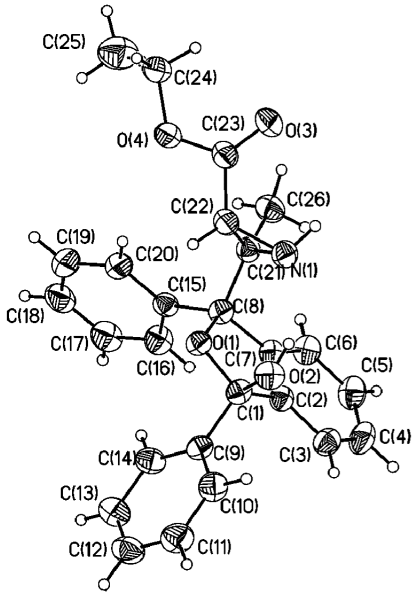
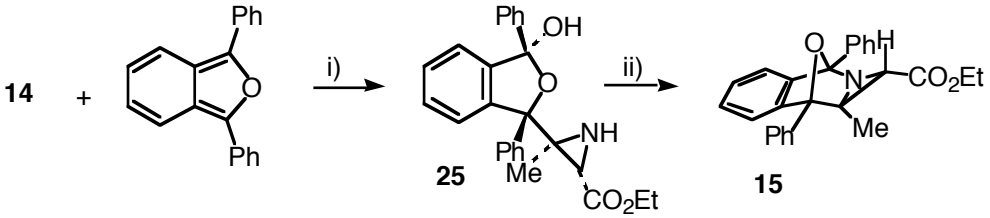


Figure 6. The molecular structure of compound (**25**)

We observed that compound (**25**) can eliminate 1 mol of water if it is refluxed in toluene in the presence of 4Å molecular sieves to give back the cycloadduct (**15**) (Scheme 5). So, the cycloadduct (**15**) that is very unstable in the presence of $ZnCl_2$ can be trapped as its adduct (**25**) and used later in its original form

just by heating **25** for some hours. The adduct (**15**) can also be obtained from azirine (**14**) and diphenylisobenzofuran after 22 h in refluxing toluene.

The cycloadduct (**10**) first obtained by Hassner and Anderson was treated with methanol under the conditions referred in their publication.[2] A solid was formed that was shown to be the furanol structure (**27**) and not a tetrahydroisoquinoline (**28**), as was stated before (Figure 7).



Scheme 5. Cycloaddition of azirine (**14**) to 1,3-diphenylisobensofuran.
i) $ZnCl_2$, rt, 1.5 days; ii) reflux in toluene, 16 h, 4Å molecular sieves

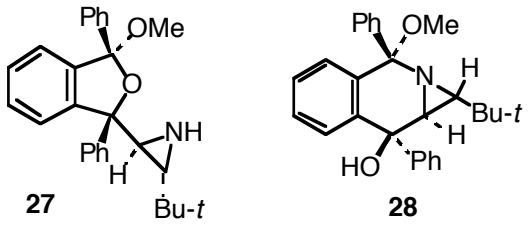


Figure 7. The correct structure for the methanolysis product of cycoadduct (**10**), structure (**27**) and the lit. proposed structure, compound (**28**).

The main difference between the two structures in the ^{1}H NMR spectrum would be the coupling between the NH and the adjacent CH in the aziridine moiety that is typical of the furanol compounds, and the coupling between 1-H and 3-H to the respective geminal OH, expected for the tetrahydroisoquinoline compounds. The methanol adduct of cycloadduct (**10**), compound (**27**) showed a broad doublet of doublets at δ_H 2.60 (J = 6.6 and 2.7 Hz), a doublet at δ_H 2.40 (J = 9.3 Hz) and a broad triplet at δ_H 1.56 (J = 7.8 Hz). The first two signals collapse into a sharp doublet at δ_H 2.60 (J = 2.7 Hz) and a broad singlet at δ_H 2.40 after D_2O treatment. The triplet disappears after D_2O treatment. The 2.7 Hz coupling constant is due to 3-H to 2-H *trans* coupling in the aziridine. The broad singlet observed after D_2O exchange in one of the aziridine C-H is shading the 2.7 Hz coupling constant with its trans vicinal H, that is visible in the other aziridine CH. The NH signal appeared as a broad triplet with a coupling constant of 7.8 Hz. This lies between the values of 9.3 and 6.6 Hz that are observed for the coupling constants of the two CH with its vicinal NH. That value as well as the broad triplet signal can be interpreted as a nonresolved doublet of doublets. The confirmation of the furanol structure and the stereochemistry was obtained by an X-Ray crystal structure determination (Figure 8).

The cycloadduct (**10**) was also treated with $LiAlH_4$ according to the literature procedure to see if in this case the six membered ring is preserved. ^1H NMR spectra either in $CDCl_3$ or C_6D_6 showed no NH-CH coupling in the aziridine moiety region which led us to conclude that the compound would be a tetrahydroisoquinoline. This product is reported as a solid, mp 66 °C, but we could not crystallize our sample despite several attempts. The IR band registered for the mobile proton is □ 3450 cm^{-1} (br), a value that is near the literature □ 3459 cm^{-1} (br). The comparison of the ^1H NMR spectra now obtained and that in the literature showed a significant difference in the peak corresponding to 3-H: a singlet at $\square_H = 4.37$ as the value reported, and a singlet at $\square_H = 5.33$ in our spectrum. All the others signals match quite well with the results published. So we conclude that in this case the tetrahydroquinoline structure (**29**) suggested by Hassner and Anderson is correct (Figure 9).

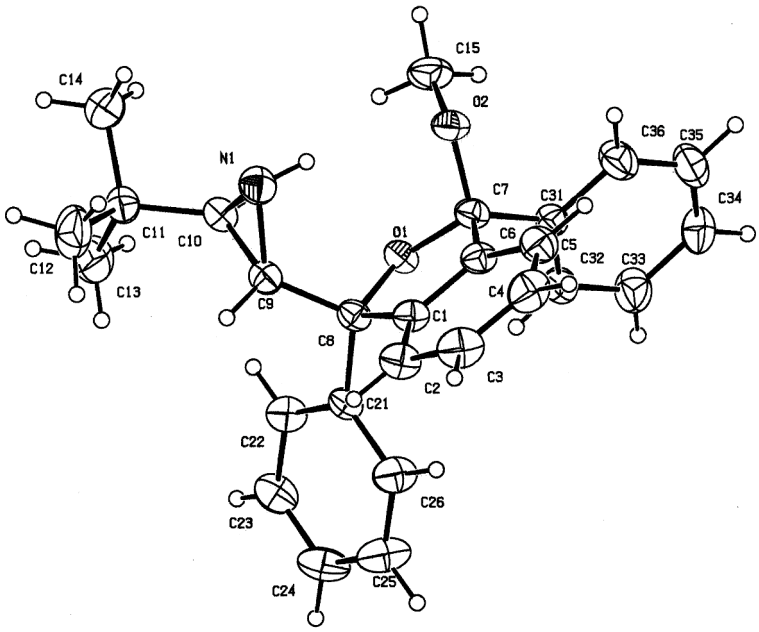
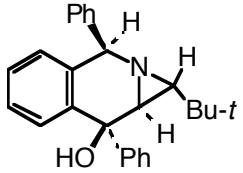


Figure 8. The molecular structure of compound (**27**)



29

Figure 9. Structure (**29**) obatined by reaction of the adduct (**10**) with $LiAlH_4$

In conclusion, tetrahyroquinolines were obtained with excellent yields either from the *endo* or the *exo* cycloadduct of the methyl 2-(2,6-dichlorophenyl)-2*H*-azirine-3-carboxylate with isobenzofuran as single isomers. Also benzofuranols were obtained in one case as a mixture of isomers. 1,3-Diphenylisobenzofuran adducts always gave benzofuranols as the hydrolysis or methanolysis products.

Reaction of a less electrophilic azirine, the ethyl 2*H*-azirine-2-carboxylate with 1,3-diphenylisobenzofuran was made possible at room temperature in the presence of $ZnCl_2$. The hydrolysis reaction that followed the cycloaddition in the acidic conditions used could be reversed to give back the original cycloadduct. Cycloadduct of the *tert*-butyl-2*H*-azirine to 1,3-isobenzofuran was reacted with methanol in the conditions reported in literature[2] and the structure of methanol adduct rectified. Reaction of the same cycloadduct with $LiAlH_4$ gave the tetrahydroquinoline reported earlier.[2]

EXPERIMENTAL

General

^{1}H NMR spectra were recorded on a Varian Unity Plus 300 (300 MHz) spectrometer. *J* values are in Hz. Infrared spectra were recorded on a Bomem MB 104 or on a Perkin-Elmer 1600 FT-IR spectrophotometer. Samples were run as nujol mulls. MS spectra were recorded on a VG Autospec M. machine as electron impact spectra (70 eV). Microanalyses were performed in a LECO-CHNS-932 machine. Melting points (mp) were determined on a Gallenkamp block and are uncorrected. Dry column flash chromatography was carried out using Kieselgel 60 and water pump vacumm. TLC was carried out on 0.25 mm silica gel layer 60DC-Ferigplatter Durasil-25 UV_{254}. THF was dried over sodium using benzophenone as indicator. Toluene was dried over sodium after fractional distillation. Dichloromethane (DCM) and methanol were either dried over CaH_2 or used as purchased. Dry flash chromatography was performed on silica gel 60 <0.063 mm for columm chromatography. Petroleum ether 40–60 ºC was distilled before use. The 2-*tert*-butyl-2*H*-azirine was obtained by pyrolysis of □-azidostyrene;[7] the methyl 2-(2,6-dichlorophenyl)-2*H*-azirine-3-carboxylate (**11**) was obtained by pyrolysis of the respective a-azido acrylate[8] and the azirine (**14**) by a Neber type reaction according to the Zwanenburg procedure.[3] Isobenzofuran was obtained according to Man *et al.*[9]

Methyl 1-(2,6-Dichlorophenyl)-1,3,8,8a-tetrahydro-3,8-epoxyazirino[1,2,*b*]isoquinoline-8a-carboxylate (12b and 13b)

Azirine (**11**) (1.90 g, 7.78 mmol) was added to a solution of isobenzofuran (1.06 g, 9.00 mmol) freshly prepared in toluene (60 mL). The solution was kept at rt for 16 h. The solvent was removed by evaporation to leave an oil, that proved, by ^{1}H NMR spectrum, to be a mixture of *endo* and *exo* adducts (1:1.3). Dry flash column chromatography [silica; pet. ether/ether; gradient polarity] gave three fractions: (*i*) *the exo isomer* (**13b**) (1.16 g, 41 %), mp 122.8–125.0 ºC (from ether/pet. ether). ^{1}H NMR (300 MHz, $CDCl_3$): □ = 7.45 (dd, *J* = 5.4, 4.8 Hz, 2 H), 7.29 (d, *J* = 7.8 Hz, 2 H), 7.22–7.19 (m, 2 H), 7.15 (t, *J* = 7.8

Hz, 1 H), 6.13 (s, 1 H), 5.78 (s, 1 H), 4.15 (s, 1 H), 3.39 (s, 3 H, OMe). ^{13}C NMR (75 MHz, $CDCl_3$): □ = 168.2 (CO), 143.6 (C), 143.1 (C), 135.7 (C), 131.0 (C), 128.9 (CH), 128.1 (CH), 127.6 (CH), 127.2 (CH), 121.7 (CH), 120.5 (CH), 93.3 (CH), 77.0 (CH), 54.0 (C), 52.1 (OMe), 48.4 (CH). IR (Nujol Mull): □ = 1721, 1582, 1558 cm^{-1}. Anal. Calcd for $C_{18}H_{13}NO_3Cl_2$: C 59.69, H 3.62, N 3.87; Found C 59.77, H 3.79, N 3.96.

(*ii*) The second fraction gave *the endo isomer* (**12b**) (0.53 g, 19 %), mp 126–127 ºC (from ether/pet. ether). ^{1}H NMR (300 MHz, $CDCl_3$): □ = 7.55–7.45 (m, 1H), 7.40–7.30 (m, 3 H), 7.19 (d, *J* = 7.2 Hz, 2 H), 7.08 (t, *J* = 7.2 Hz, 1 H), 6.39 (s, 1 H), 6.35 (s, 1 H), 3.63 (s, 3 H, OMe), 1.86 (s, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): □= 169.6 (CO), 139.1 (C), 138.4 (C), 134.7 (C), 131.0 (C), 128.8 (CH), 128.6 (CH), 128.5 (CH), 128.0 (CH), 120.6 (CH), 120.3 (CH), 94.8 (CH), 81.9 (CH), 59.0 (CH), 54.7 (C), 52.7 (OMe). IR (Nujol Mull): □ = 1747, 1582, 1559 cm^{-1}. Anal. Calcd for $C_{18}H_{13}NO_3Cl_2$: C 59.69, H 3.62, N 3.87; Found C 59.63, H 3.81, N 3.94.

(*iii*) The third fraction gave *the 3,8-dihydroxyazirino*[1,2-*b*]*isoquinoline* (**22**) (0.42 g, 14%), mp 153–155 ºC, identified by comparison of its ^{1}H NMR with the ^{1}H NMR spectrum an authentic sample (see its synthesis ahead).

Ethyl 3,8-Diphenyl-8a-methyl-1,3,8,8a-tetrahydro-3,8-epoxyazirin[1,2-*b*]isoquinoline-1-carboxylate (15) and ethyl 2-methyl-2-(3-hydroxy-1,3-diphenyl-1,3-dihydroisobenzofuran-1-yl)aziridine-3-carboxylate (25)

i) The azirine (**14**) (0.79 g, 6.21 mmol) was dissolved in dry toluene (50 mL) and 1,3-diphenylisobenzofuran (1.17 g, 4.35 mmol) was added. The mixture was refluxed for 22 h. The solvent was removed leaving a yellow oil that was subjected to dry flash chromatography [silica; pet. ether/ether; polarity gradient]. The first fraction was the starting 1,3-diphenylisobenzofuran (0.1 g, 8.5 %) and the second fraction gave the product (**15**) obtained as an oil (1.27 g, 73.5 %). Crystalization of the oil from pet. ether/ether gave a pale yellow solid, mp 139–141 ºC. ^{1}H NMR (300 MHz, $CDCl_3$): □ = 7.81–7.74 (m, 4 H), 7.60–7.45 (m, 6 H), 7.37 (br d, *J* = 6.9 Hz, 1H), 7.28 (dt, *J* = 7.5 Hz, 1.5 Hz, 1H), 7.22 (dt, *J* = 7.5 Hz, 1.5 Hz, 1 H), 7.11 (br d, *J* = 6.9 Hz, 1 H), 4.27 (dq, *J* = 7.2, 3.0 Hz, 2 H), 3.76 (s, 1 H), 1.31 (t, *J* = 7.2 Hz, 3 H), 1.29 (s, 3H). ^{1}H NMR (300 MHz, C_6D_6): □= 8.02 (dd, *J* = 8.1, 1.5 Hz, 2 H), 7.77 (dd, *J* = 8.1, 1.5 Hz, 2 H), 7.25–7.05 (m, 7 H), 7.05–6.84 (m, 3 H), 3.95 (s, 1 H), 3.90 (dq, *J* = 7.2, 3.3 Hz, 2 H), 1.40 (s, 3 H), 0.83 (t, *J* = 7.2 Hz, 3 H). ^{13}C NMR (75.5 MHz, $CDCl_3$): □ = 168.5 (CO), 148.0 (C), 145.2 (C), 133.4 (C), 132.4 (C), 129.4 (CH), 129.1 (CH), 128.9 (CH), 128.6 (CH), 128.3 (CH), 127.5 (CH), 127.1 (CH), 127.0 (CH), 121.5 (CH), 120.7 (CH), 101.5 (C), 90.6 (C), 61.2 (CH_2), 52.6 (C), 45.6 (CH), 14.3

(Me), 11.6 (Me). IR (Nujol Mull): □ = 1746 cm^{-1}. Anal. Calcd for $C_{26}H_{23}NO_3$: C 78.57, H 5.83, N 3.52; Found: C 78.40, H 5.92, N 3.56.

ii) Compound (**25**) (0.51 g, 1.23 mmol) was dissolved in dry toluene (50 mL) and 4Å molecular sieves (2.0 g) were added to the solution. The solution was refluxed for 16 h. The molecular sieves were filtered off and the solvent was removed under reduce pressure to give an oil, that proved to be mainly the desired product. Crystallization from ether/pet. ether gave a pale yellow solid, compound (**15**) (0.28 g, 55%).

Methyl 3-(2,6-Dichlorophenyl)-2-(1,3-diphenyl-3-hydroxy-1,3-dihydroisobenzofuran-1-yl)aziridine-2-carboxylate (17)

Silica gel (particle size <0.063 mm) (1.0 g) was added to a solution of compound (**12a**) (0.36 g, 0.70 mmol) in DCM (25 mL) at rt. After 36 h the silica was filtered off and washed with ether. The solvent and washings were evaporated to leave a pure solid (0.35 g, 94 %), mp 165–169 ºC. ^{1}H NMR (300 MHz, $CDCl_3$): □= 7.86 (br s, 2 H), 7.45–7.20 (m, 14 H), 7.10 (br m, 1 H), 5.64 (br s, 1 H, OH), 3.64 (br s, 1 H, CH aziridine), 3.24 (s, 3 H), 3.05 (br s, 1 H, NH). ^{13}C NMR (75 MHz, $CDCl_3$): □= 169.7 (CO), 142.7 (C), 141.7 (C), 136.2 (C), 129.7 (CH), 129.3 (CH), 129.1 (CH), 128.8 (CH), 128.5 (CH), 127.7 (CH), 126.7 (CH), 123.8 (CH), 108.6 (C), 90.5 (C), 52.5 (OMe), 50.9 (CH), 43.0 (C). IR (Nujol Mull): □ = 3406, 1740, 1727, 1561 cm^{-1}. HREIMS: *m/z* calcd for $C_{30}H_{23}NO_4\ Cl_2 - H_2O$ 513.0884; found 513.0898.

Methyl 3-(2,6-Dichlorophenyl)-2-(1,3-diphenyl-3-methoxy-1,3-dihydroisobenzofuran-1-yl)aziridine-2-carboxylate (18 and 19)

A suspension of the compound (**12a**) (0.54 g, 1.05 mmol) in methanol (20 mL) was left for 24 h and then evaporated to leave a solid (0.48 g) that was a clean mixture of compounds (**18**) and (**19**) (1:1 ratio) by ^{1}H NMR spectrum. Dry flash column chromatography [silica; pet. ether/ether, gradient polarity] gave the same mixture of the two compounds (0.40 g, 70 %). ^{1}H NMR (300 MHz, $CDCl_3$): □= 8.40 (d, *J* = 7.2 Hz, 1 H), 8.05 (d, *J* = 7.5 Hz, 1 H), 7.89 (d, *J* = 6.9 Hz, 2 H), 7.77 (d, *J* = 7.2 Hz, 2 H), 7.03–7.63 (m, 28 H), 3.44 (d, *J* = 10.5 Hz, 1 H, NH), 3.33 (d, *J* = 9.9 Hz, 1 H), 3.25 (s, 3 H, OCH_3), 3.11 (s, 3 H, OCH_3), 3.06 (d, *J* = 9.9 Hz, 1 H, NH), 2.93 (d, *J* = 10.5 Hz, 1 H), 2.80 (s, 3 H, OCH_3), 2.67 (s, 3 H, OCH_3). ^{13}C NMR (75 MHz, $CDCl_3$): □= 169.8 (CO), 169.5 (CO), 142.3 (C), 142.1 (C), 141.7 (C), 141.0 (C), 140.8 (C), 140.5 (C), 139.8 (C), 139.5 (C), 135.9 (C), 135.5 (C), 132.0 (C), 131.4 (C), 129.0 (CH), 128.81 (CH), 128.75 (CH), 128.6 (CH), 128.5 (CH), 128.4 (CH), 128.2 (CH), 128.1 (CH), 127.9 (CH), 127.6 (CH), 127.3 (CH), 127.0 (CH), 126.9 (CH), 126.1 (CH), 125.1 (CH), 123.7 (CH), 122.8 (CH), 111.4 (C), 110.2 (C), 89.2(C), 89.0 (C), 52.5 (OMe), 52.1(OMe), 51.7 (OMe), 51.1(OMe), 41.7 (C), 39.2 (CH). Anal. Calcd for $C_{31}H_{25}NO_4\ Cl_2$: C 68.14, H 4.61, N 2.56; Found C 68.11, H 4.66, N 2.63.

Methyl 3-(2,6-Dichlorophenyl)-2-(1,3-diphenyl-3-methoxy-1,3-dihydroisobenzofuran-1-yl)aziridine-2-carboxylate (20)

A suspension of the adduct (**13a**) (0.50 g, 0.97 mmol) in 20 mL of methanol was left in reflux for 48 h. The solvent was then removed to leave an oil (0.54 g) that was a 1:1 mixture of the initial adduct and the product. Further heating, for 24 h, of a new suspension of this material in fresh methanol did not force the reaction to go further. The product was obtained in a pure form by performing a dry flash chromatography (pet. ether/ether; polarity gradient), 0.16 g (31%) of a solid, mp 152–153 ºC (DCM/pet. ether). ^{1}H NMR (300 MHz, $CDCl_3$): = 7.80–7.90 (m, 3 H), 7.45–7.30 (m, 6 H), 7.30–7.03 (m, 8 H), 4.28 (d, *J* = 10.5 Hz, 1 H),[a] 3.47 (s, 3 H, OMe), 3.37 (s, 3 H, OMe), 3.31 (d, *J* = 10.5 Hz, 1H, NH).[b] ^{13}C NMR (75 MHz, $CDCl_3$): = 169.9 (CO), 146.2 (C), 140.6 (C), 139.1 (C), 138.1 (C), 136.4 (C), 133.3 (C), 129.4 (CH), 128.5 (CH), 128.4 (CH), 128.2 (CH), 127.8 (CH), 126.4 (CH), 126.1 (CH), 125.8 (CH), 123.5 (CH), 111.6 (C), 91.9 (C), 51.8 (OMe), 50.7 (C), 41.7 (CH). IR (Nujol Mull): = 3261, 1731, 1582, 1560 cm^{-1}. Anal. Calcd for $C_{31}H_{25}NO_4Cl_2$: C 68.14, H 4.61, N 2.56; Found C 68.12, H 4.73, N 2.63.

[a] collapses to a singlet after D_2O exchange

[b] disappears after D_2O exchange

Methyl 1-(2,6-Dichlorophenyl)-3-methoxy-8-hydroxy-1,3,8,8a-tetrahydroazirino[1,2-*b*]isoquinoline-8a-carboxylate (21)

The adduct (**13b**) (1.0 g, 2.76 mmol) was dissolved in methanol (50 mL) and the solution was heated to reflux for 1 day. The solvent was removed to leave a pure solid (1.0 g, 2.54 mmol, 92%), mp 148.0–149.0 ºC (from ether/pet.ether). ^{1}H NMR (300 MHz, $CDCl_3$): = 7.77 (d, *J* = 7.5 Hz, 1 H), 7.55 (d, *J* = 7.5 Hz, 1 H), 7.44 (m, 2 H), 7.24 (d, *J* = 7.8 Hz, 2 H), 7.09 (t, *J* = 7.8 Hz, 1 H), 5.51 (d, *J* = 4.5 Hz, 1 H),[a] 5.30 (s, 1 H), 4.05 (d, *J* = 4.5 Hz, 1 H, OH),[b] 3.87 (s, 3 H), 3.51 (s, 3 H), 3.26 (s, 1 H). ^{13}C NMR (75.5 MHz, $CDCl_3$): = 172.3 (CO), 135.6 (C), 133.6 (C), 131.3 (C), 130.3 (C), 128.8 (CH), 128.4 (CH), 128.2 (CH), 128.1 (CH), 125.0 (CH), 124.9 (CH), 89.0 (CH), 65.1 (CH), 57.9 (OMe), 52.5 (OMe), 48.2 (C), 40.1(CH). IR (Nujol Mull): = 3507, 1715, 1561 cm^{-1}. Anal. Calcd for $C_{19}H_{17}NO_4Cl_2$: C 57.88, H 4.35, N 3.55; Found C 57.86, H 4.47, N 3.68.

[a] collapses to a singlet after D_2O exchange

[b] disappears after D_2O exchange

Methyl 1-(2,6-Dichlorophenyl)-3,8-hydroxy-1,3,8,8a-tetrahydroazirino[1,2-*b*]isoquinoline-8a-carboxylate (22)

The adduct (**12b**) (0.15 g, 0.41 mmol) was dissolved in dichloromethane (15 mL) and silica gel (particle size <0.063 mm) (*ca*. 3.0 g) was added. The suspension was left under magnetic stirring at rt for 1 day. The silica was removed by filtration and washed with portions of dichloromethane (2 x 15 mL) and ether (2 x 15 mL). The solutions were combined and evaporated to give a pure white solid (0.46 g, 0.38 mmL, 93%), mp 153–155 ºC (from ether/pet. ether). ^{1}H NMR (300 MHz, $CDCl_3$): □ = 7.48 (m, 3 H), 7.38 (m, 1 H), 7.25 (d, *J* = 8.4 Hz, 2 H), 7.12 (t, *J* = 8.4 Hz, 1 H), 6.07 (d, *J* = 7.6 Hz, 1 H),[a] 5.77 (d, *J* = 6.6 Hz, 1 H)[a], 4.27 (d, *J* = 7.6 Hz, 1 H, OH)[b], 3.93 (d, *J* = 6.6 Hz, 1 H, OH),[b] 3.58 (s, 3 H, OMe), 2.54 (s, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): □= 169.9 (CO), 135.4 (C), 132.9 (C), 131.2 (C), 130.5 (C), 130.1 (C), 130.0 (C), 129.04 (CH), 129.0 (CH), 129.01 (CH), 128.6 (CH), 128.2 (CH), 83.6 (CH), 66.9 (CH), 52.6 (OMe), 50.5 (C), 46.4 (CH). IR (Nujol Mull): □ = 3410, 3130, 3072, 1746, 1580, 1559 cm^{-1}. HRFABMS: *m/z* calcd. for $C_{18}H_{15}NO_4Cl_2$ 380.0456; found 380.0444.

[a] collapses to a singlet after D_2O exchange

[b] disappears after D_2O exchange

Methyl 3-(2,6-Dichlorophenyl)-2-(3-methoxy-1,3-dihydroisobenzofuran-1-yl)aziridine-2-carboxylate (23 and 24)

The adduct (**12b**) (0.63 g, 1.74 mmol) was dissolved in 40 mL of methanol and allowed to stay, under magnetic stirring, for 24 h. The solvent was removed in the rotary evaporator to leave an oil (0.50 g) that proved to be a 1:1 mixture of two compounds. Two fractions were obtained by flash chromatography [silica; pet. ether/ether, gradient polarity]. The first fraction gave the isomer (**23**) (0.20 g, 29%), mp 127.5–129.0 ºC (from DCM/pet. ether). ^{1}H NMR (300 MHz, $CDCl_3$): □= 7.40 (br s, 4 H), 7.32–7.25 (m, 2 H), 7.25–7.15 (m, 1 H), 6.46 (br. s, 1 H),[a] 6.17 (br. s, 1 H),[a] 3.57 (s, 3 H, OMe), 3.41 (s, 3 H, OMe), 3.33 (br d, *J* = 9.1 Hz, 1 H, CH),[b] 2.72 (d, *J* = 9.1 Hz, 1 H, NH).[c].^{13}C NMR (75 MHz, $CDCl_3$): □= 170.5 (CO, br), 139.0 (br), 138.2 (br), 135.5 (br), 131.0 (br), 129.2 (br), 129.0 (CH), 128.7 (CH), 128.3 (br), 123.2 (br), 122.3 (br), 107.4 (CH), 82.7 (CH), 53.8 (CH or OMe), 52.8 (br), 48.3 (br), 44.1 (br). IR (Nujol Mull): □ = 3295, 1709, 1579, 1559 cm^{-1}. Anal. Calcd for $C_{19}H_{17}NO_4Cl_2$: C 57.88, H 4.35, N 3.55; Found C 57.60, H 4.55, N 3.64.

[a] collapses to a sharp doublet (*J*= 1.2 Hz) after D_2O exchange

[b] collapses to a singlet after D_2O exchange

[c] disappears after D_2O exchange

The second fraction gave the isomer (**24**) (0.26 g, 38%), mp 133.0–134.0 ºC (from DCM/pet. ether). ^{1}H NMR (300 MHz, $CDCl_3$): □= 7.15–7.25 (m, 4 H), 7.23 (d, *J* = 7.2 Hz, 2 H), 7.10 (t, *J* = 7.2 Hz, 1 H), 6.25 (s, 1 H), 6.04 (s, 1 H), 3.61 (s, 3 H, OMe), 3.57 (s, 3 H, OMe), 3.35 (br s, 1 H),[a] 2.65 (br s, 1H, NH).[b] ^{13}C

NMR (75 MHz, $CDCl_3$): δ = 171.1 (CO), 138.4 (C), 137.9 (C), 135.8 (C), 132.0 (C), 129.0 (CH), 128.8 (CH), 128.7 (CH), 128.0 (CH), 123.9 (CH), 123.0 (CH), 106.9 (CH), 80.8 (CH), 56.1(OMe), 52.5 (OMe), 47.5 (CH or C), 41.1 (CH or C). IR (Nujol Mull): ν = 3297, 1746, 1583, 1557 cm^{-1}. Anal. Calcd for $C_{19}H_{17}NO_4Cl_2$: C 57.88, H 4.35, N, 3.55; Found C 57.60, H 4.55, N 3.64.

[a] collapses to a sharp singlet after D_2O exchange

[b] disappears after D_2O exchange

Ethyl 2-Methyl-2-(3-hydroxy-1,3-diphenyl-1,3-dihydroisobenzofuran-1-yl)aziridine-3-carboxylate (25)

To a solution of the azirine (**14**) (0.5 g, 3.9 mmol) in dry toluene (50 mL) were added 1,3-diphenylisobenzofuran (0.95 g, 3.5 mmol.) and zinc chloride (10 mg). The solution was allowed to stay at rt, under magnetic stirring, for 1.5 days. The solvent was evaporated to leave an oil, that was purified by dry flash column chromatography [silica; pet. ether/ether, polarity gradient]. After purification a solid was obtained (0.96 g, 67%), mp 126–128 ºC (from ether/light petroleum). ^{1}H NMR (300 MHz, $CDCl_3$): δ= 7.69 (s, 1 H), 7.60–7.50 (m, 2 H), 7.50–7.30 (m, 8 H), 7.30–7.20 (m, 3 H), 4.36 (q, *J* = 7.2 Hz, 2 H), 3.78 (d, *J* = 7.5 Hz, 1 H),[a] 1.42 (s, 3 H), 1.38 (t, *J* = 7.2 Hz, 3 H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ= 170.2 (CO), 146.4 (C), 142.1 (C), 139.5 (C), 139.0 (C), 129.1 (CH), 128.7 (CH), 128.5 (CH), 127.9 (CH), 127.86 (CH), 127.8 (CH), 126.3 (CH), 124.0 (CH), 123.6 (CH), 107.0 (C), 91.1 (C), 61.9 (CH_2), 45.2 (C), 40.1 (CH), 14.4 (Me), 14.3 (Me). IR (Nujol Mull): ν = 3282, 3212, 3059, 1721 cm^{-1}. Anal. Calcd for $C_{26}H_{25}NO_4$: C 75.16, H 6.06, N 3.37; Found C 75.07, H 6.13, N 3.59.

^{1}H NMR (300 MHz, C_6D_6): δ= 7.95–7.85 (m, 2 H), 7.74 (s, 1 H), 7.70–7.60 (m, 2 H), 7.35–7.25 (m, 1 H), 7.20–7.00 (m, 8 H), 3.82 (dq, *J* = 7.2, 1.8 Hz, 2 H), 3.77 (d, *J* = 7.8 Hz, 1 H),[a] 1.15 (s, 3 H), 0.90 (d, *J* = 7.8 Hz, 1 H, NH),[b] 0.84 (t, *J* = 7.2 Hz, 3 H).

[a] collapses to a singlet after D_2O exchange

[b] disappears after D_2O exchange

3-*tert*-Butyl-2-(1,3-diphenyl-3-methoxy-1,3-dihydroisobenzofuran-1-yl)aziridine (27)

The reaction was run under the conditions stated by Hassner and Anderson. The adduct (**10**) was refluxed in methanol for 24 h. Evaporation of the solvent gave a solid that was crystalized giving colorless crystals, yield 30%,[2] mp 121–122 ºC[a] (pet. ether). ^{1}H NMR (300 MHz, C_6D_6): δ= 7.67 (d, *J* = 7.2 Hz, 2 H), 7.52 (d, *J* = 7.2 Hz, 6 H), 7.26–7.32 (m, 1 H), 6.90–7.10 (m, 9 H), 3.17 (s, 3 H), 2.60 (dd, *J* = 6.6, 2.7 Hz, 1 H),[b] 2.48 (d, *J* = 9.3 Hz, 1 H),[c] 1.56 (t, *J* = 7.5 Hz, 1 H, NH),[d] 1.07 (s, 9 H). ^{1}H NMR (300 MHz, CD_3Cl): δ= 7.80–7.20 (m, 14 H), 3.34 (s, 3 H, OMe), 2.52 (br d, *J* = 3 Hz, 1 H), 2.32 (br s, 1 H), 0.98 (s,

9 H). ^{13}C NMR (75.5 MHz, $CDCl_3$): □= 142.4 (C), 141.9 (C), 140.0 (C), 129.9 (C), 129.0 (CH), 128.8 (CH), 128.7 (CH), 128.63 (CH), 128.58 (CH), 127.6 (CH), 127.1 (CH), 123.7 (CH), 111.7 (C), 90.9 (C), 51.6 (OMe), 44.7 (CH), 42.2 (CH), 31.0 (C), 11.6 (27.5). IR (Nujol Mull): □ = 3281 cm^{-1}.[e)]

[a)] reported mp 118 ºC.

[b)] collapses to a sharp doublet (J = 2.7 Hz) after D_2O exchange.

[c)] collapses to a broad singlet after D_2O exchange.

[d)] disappears after D_2O exchange.

[e)] reported value 3285 cm^{-1}.

1-*tert*-Butyl-3,8-diphenyl-1,3,8,8a-tetrahydroazirino[1,2-*b*]isoquinoline (29)

The adduct (**10**) (0.20 g, 0.54 mmol) was refluxed in THF (15 mL) in the presence of $LiAlH_4$ (1M solution in ether, 1.08 mL, 41 mg, 1.08 mmol) for 24 h, according to the procedure described by Hassner and Anderson. A foam was formed but no crystals were obtained after extensive trituration with different solvents. Yield 91 %.[10] ^{1}H NMR (300 MHz, $CDCl_3$): □ = 7.85 (dd, J = 7.8, 1.8 Hz, 1 H), 7.40 (dt, J = 7.5, 1.5 Hz, 1 H), 7.34 (dt, J = 7.5, 1.5 Hz, 1 H), 7.20–6.95 (m, 11 H), 5.33 (s, 1 H), 2.86 (d, J = 3 Hz, 1 H), 1.62 (d, J = 3 Hz, 1 H), 1.01 (s, 9 H).[a)] ^{13}C NMR (75.5 MHz, $CDCl_3$): □= 146.0 (C), 143.6 (C), 138.7 (C), 133.2 (C), 129.4 (CH), 128.5 (CH), 128.04 (CH), 128.01 (CH), 127.98 (CH), 127.4 (CH), 127.0 (CH), 126.9 (CH), 126.8 (CH), 72.8 (C), 64.3 (CH), 46.4 (CH), 45.8 (CH), 31.0 (C), 27.4 (Me). IR (Nujol Mull): □ = 3459 cm^{-1}.[b)]

[a)] described ^{1}H NMR spectrum for this compound □= 8.05–7.80 (m, 1 H), 7.65–7.0 (m, 13 H), 4.37 (s, 1 H), 2.86 (d, J = 3 Hz, 1 H), 1.61 (d, J = 3 Hz, 1 H), 1.00 (s, 9 H).

[b)] described IR spectrum for this compound □ = 3459 cm^{-1}.

Crystal structure determination of compound (21)

Crystal data: $C_{19}H_{17}NO_4Cl_2$, M = 394.24, monoclinic, a = 10.9897(9) Å, b = 10.2685(8) Å, c = 16.2557(13) Å, □ = 90º, □ = 95.0230(10)º, □= 90º, U = 1827.4(3) $Å^3$, □calcd = 1.433 g/cm^3, T = 293(2)K, space group $P2(1)/n$, Z = 4, □(Mo-K□) = 0.380 mm^{-1}, 10493 reflections collected, 4156 [$R(int)$ = 0.0382)], $R(F^2)$ = 0.906, $R(F)[I>2□(I)]$ = 0.0469.

Crystal structure determination of compound (25)

Crystal data: $C_{26}H_{25}NO_4$, M = 415.47, monoclinic, a = 11.1038(15) Å, b = 10.7831(14) Å, c = 18.409(3) Å, □ = 90º, □ = 96.114(3)º, □= 90º, U = 2191.7(5) $Å^3$, □calcd = 1.259 g/cm^3, T = 293(2)K, space group

*P*2(1)/n, *Z* = 4, □(Mo-K□) = 0.085 mm^{-1}, 11888 reflections collected, 4848 [*R*(*int*) = 0.0420)], $R(F^2)$ = 0.822, *R*(*F*)[*I*>2□(*I*)] = 0.0404.

Crystal structure determination of compound (27)

Crystal data: $C_{27}H_{29}NO_2$, M = 399.51, monoclinic, *a* = 11.7266(10) Å, *b* = 9.7610(8) Å, *c* = 19.9243(17) Å, □ = 90º, □ = 98.321(2)º, □= 90º, *U* = 2256.6(3) $Å^3$, □calcd = 1.176 g/cm^3, *T* = 293(2)K, space group *P*2(1)/n, *Z* = 4, □(Mo-K□) = 0.073 mm^{-1}, 11834 reflections collected, 4978 [*R*(*int*) = 0.0533)], $R(F^2)$ = 0.748, *R*(*F*)[*I*>2□(*I*)] = 0.0436.

Crystallography

Data were collected with Bruker Smart-CCD 1000 difractometer (three-circle goniometer with CCD detector, FN-Mo-2K-90 radiation). Details are listed in the experimental section. CCDC-257834 (**21**), 257833 (**25**), 257832 (**27**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/retrieving.html [or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; Fax: (internat.) + 44-1223-336-033; E-mail:deposit@ccdc.cam.ac.uk].

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10. Reported yield 78% (see reference 2).