One-pot synthesis of benzyltriphenylphosphonium acetates from the corresponding activated benzyl alcohols

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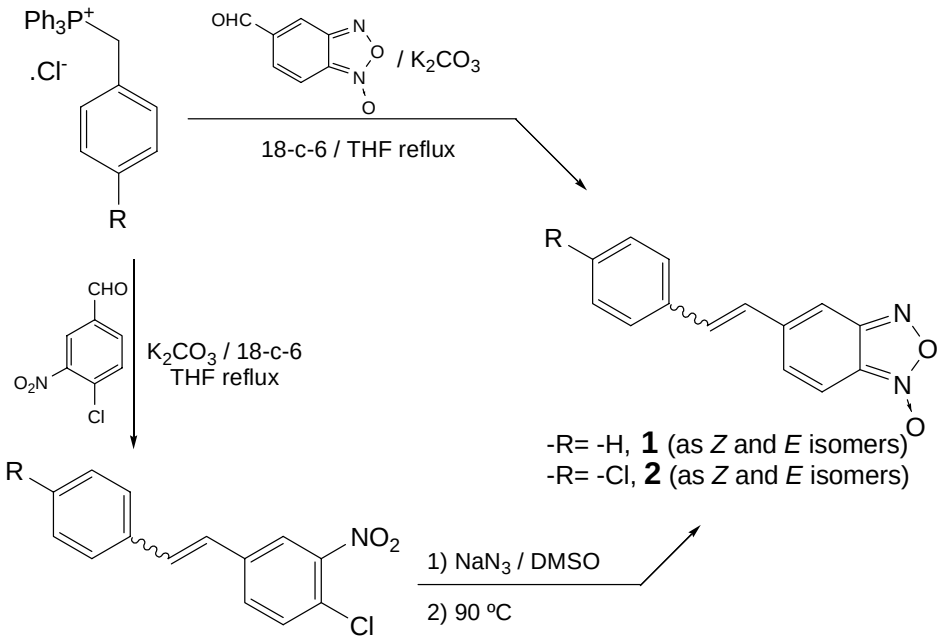
Abstract
A simple synthetic methodology for the preparation of benzyltriphenylphosphonium acetates is described. The reaction, using different benzyl alcohols substituted with an electron-donating group, involves the generation of a good leaving group and substitution with triphenylphosphine. In these cases the reactions take place with good yields. Furthermore, the obtained salts (**16** and **17**) have been used for the synthesis of 5-substituted benzofuroxan derivatives.

Keywords: Phosphonium acetates, benzyl alcohols, Wittig reaction

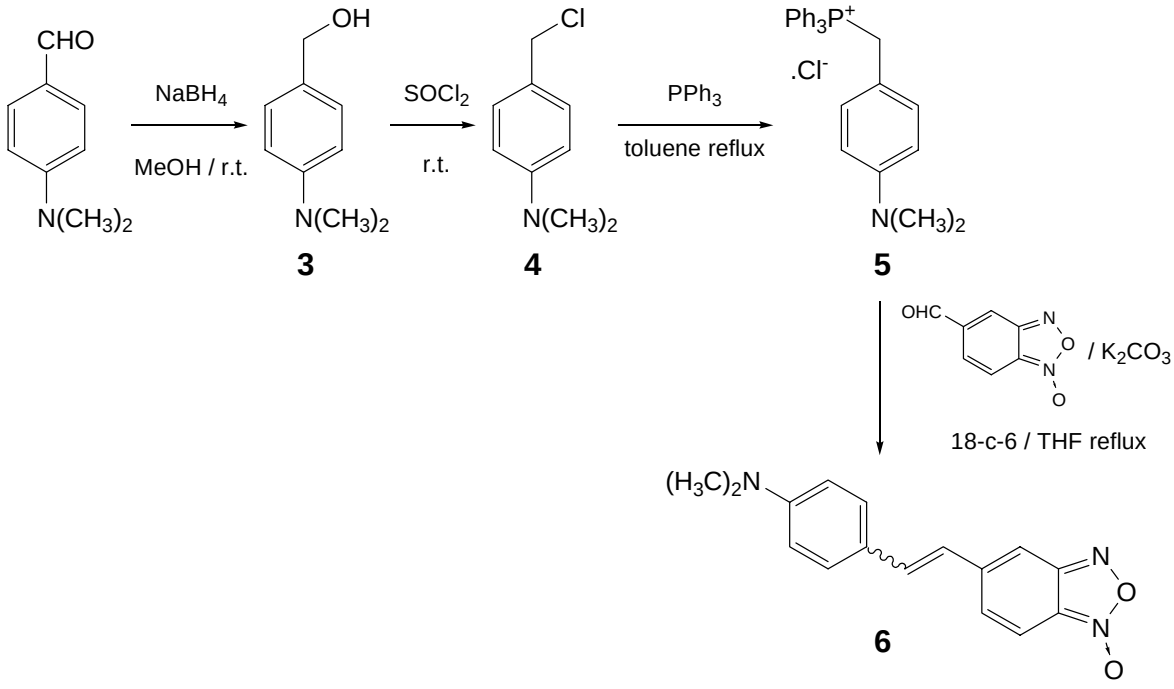
Introduction

Recently, therapeutically active benzofuroxans, such as **1** and **2** (Scheme 1), have emerged as an important class of anti-*T. cruzi* agents.[1] The relevance in the activity of the phenylethenyl substituent and the *N*-oxide group to this activity was identified through QSAR studies.[2] The synthetic routes that have been considered for the production of the phenylethenyl moiety are shown in Scheme 1. Among the various methods reported for the Wittig reaction we selected the mild conditions, promoted by crown ether catalysis, of the Bodens methodology.[3]

Continuing with this research we tried to prepare and evaluate as new anti-*T. cruzi* agents some analogs of **1** and **2**, with R an electron-donating substituent. Our first approach involved the preparation of compound **6** (Scheme 2). In order to synthesize this derivative we planned the synthetic methodology shown in Scheme 2 where we used the conventional synthesis of the phosphonium salt **5** that involves halide nucleophilic substitution with triphenylphosphine.



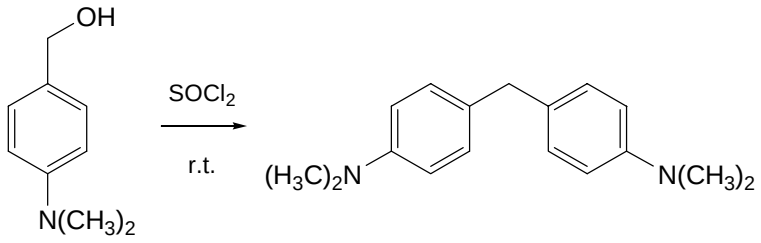
Scheme 1



Scheme 2

However, compound **4** was not generated under any of the conditions tried by us.[4] Alcohol **3** proved to be significantly reactive during its purification (silica gel chromatographic column, petroleum:ethyl acetate (9:1)), and while attempting to prepare the chloride ($SOCl_2$, room

temperature) it afforded an unexpected product, compound **7** (Scheme 3). Product **7** was characterized by NMR (^{1}H-, ^{13}C-, HMQC, and HMBC), IR and MS analysis.[5] Single crystals of **7** adequate for structural X-ray diffraction studies [6] were obtained by slow evaporation from a petroleum solution. Figure 1 shows the ORTEP diagram of derivative **7**.



Scheme 3

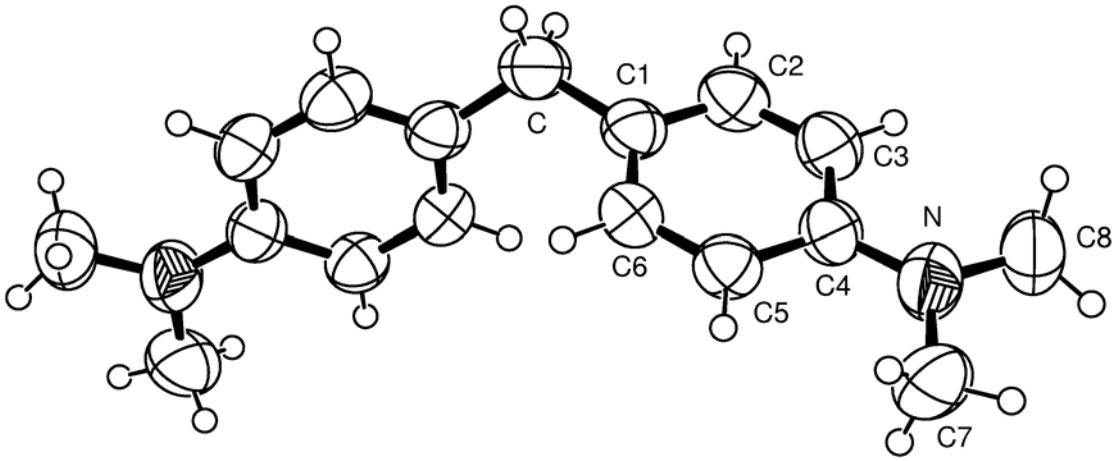
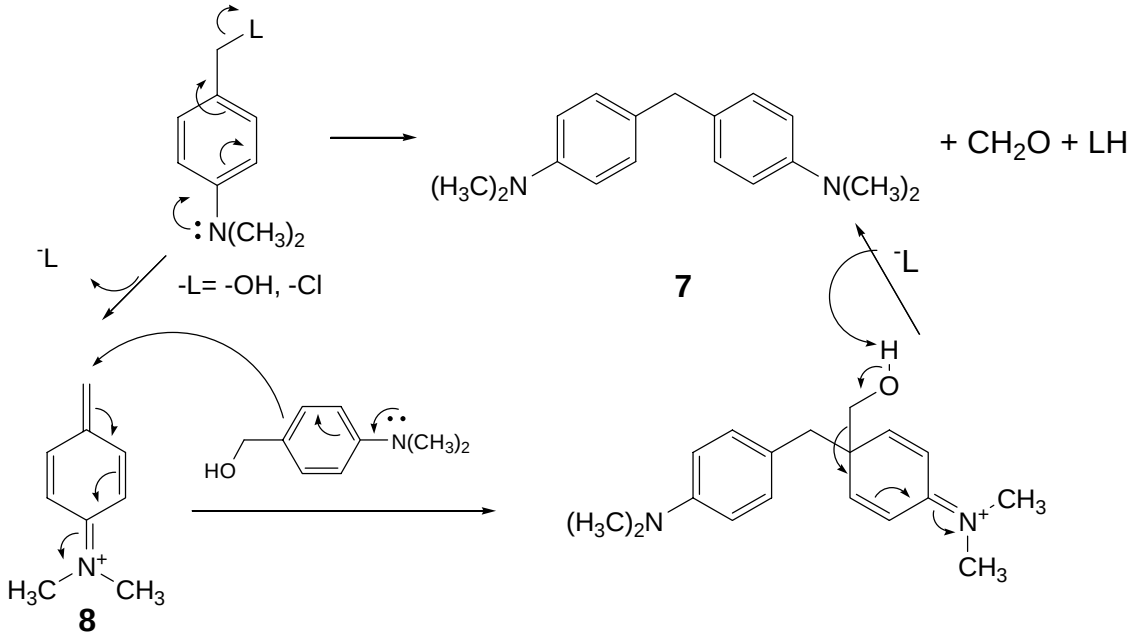


Figure 1. Molecular plot of **7** showing the labeling of the non-H atoms and their displacement ellipsoids at the 50% probability level. The hydrogen atoms were positioned stereochemically and refined with the riding model. The methyl H-atom positions were optimized by treating them as rigid groups allowed to rotate around the corresponding C-N bond during the refinement. The two molecular halves are related to each other by a crystallographic two-fold axis along the vertical.[7]

The generation of compound **7** could be the result of the presence, in **3** and possibly in **4**, of a good leaving group and a nucleophilic moiety in the same structure. This combination promotes the formation of intermediate **8** that could react as indicated in Scheme 4. Assuming these processes, an acidic medium that reduces the nucleophilicity of the amine could avoid the formation of secondary product **7**. This option, the use of an acidic medium, provides the possibility of carrying out the preparation of the phosphonium salt in a one-pot process from the

corresponding alcohol and avoids isolation of the halide intermediate. An alternative methodology directly from the alcohol by using the $Ph_3P{\cdot}HBr$ salt has been reported, but this procedure requires high thermal activation and a costly reagent.[8-10]



Scheme 4

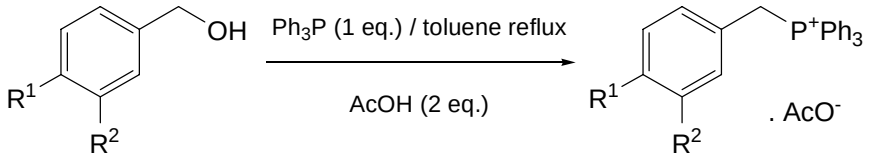
Herein, we report our research on the development of a new efficient synthetic methodology to prepare phosphonium salts from the corresponding benzyl alcohols substituted with an electron-donating group. This procedure was inspired by some previous reports with disadvantages such as prolonged reaction times,[11] lack of generality,[12] or use of deprotecting-groups as reagents.[13] In our case, neither the aliphatic alcohols studied nor benzyl alcohols substituted with mesomeric electron-withdrawing groups gave the expected salts.

Results and Discussion

In our research, the preparation of phosphonium salts from benzyl alcohols substituted with an electron-donating group was explored as shown in Table 1. For instance, a mixture of the appropriate alcohol (1 equivalent), triphenylphosphine (1 equivalent) and dry toluene as solvent was heated at reflux, under an inert atmosphere, and then glacial acetic acid (2 equivalents) was added dropwise over 30 minutes. Then, the mixture was heated at reflux until the benzyl alcohol could no longer be detected (Table 1). The corresponding acetates (**16-21**), as oils, were treated successively with hexane in order to eliminate excess triphenylphosphine. Products **16-21** were characterized by NMR (^{1}H-, ^{13}C-, HMQC, and HMBC) and IR spectroscopy.

The anhydrous conditions of the reactions were ensured using adequate solvent quality and a nitrogen atmosphere to minimize the formation of triphenylphosphine oxide, the main product of reaction when undried toluene was employed.

Table 1. Conditions and results in the preparation of the phosphonium acetates **16-21**



Entry	Substrate	Product	Time (h)	Yield (%) [a]	δ_{CH2} [b,c]	J_{H-P} [b,d]
a	-R^1= -$N(CH_3)_2$, -R^2= -H, **3**	-R^1= -$N(CH_3)_2$, -R^2= -H, **16**	4	40 [e]	4.99 [f]	13.8
b	-R^1= -OH, -R^2= -H, **9**	-R^1= -OH, -R^2= -H, **17**	4.5	55	4.97	14.6
c	-R^1= -OAc, -R^2= -H, **10**	-R^1= -OH, -R^2= -H, **17**	1.5	97		
d	-R^1,-R^2= -OCH_2O-, **11**	-R^1,-R^2= -OCH_2O-, **18**	73	16	5.04	15.1
e	-R^1= -OCH_3, -R^2= -H, **12**	-R^1= -OCH_3, -R^2= -H, **19**	48	25	5.06	15.1
f	-R^1= -H, -R^2= -H, **13**	-R^1= -H, -R^2= -H, **20**	48	10	5.17	15.6
g	-R^1= -Cl, -R^2= -H, **14**	-R^1= -Cl, -R^2= -H, **21**	67	5	5.17	14.9
h	-R^1= -NO_2, -R^2= -H, **15**	- [g]	48	-	-	-

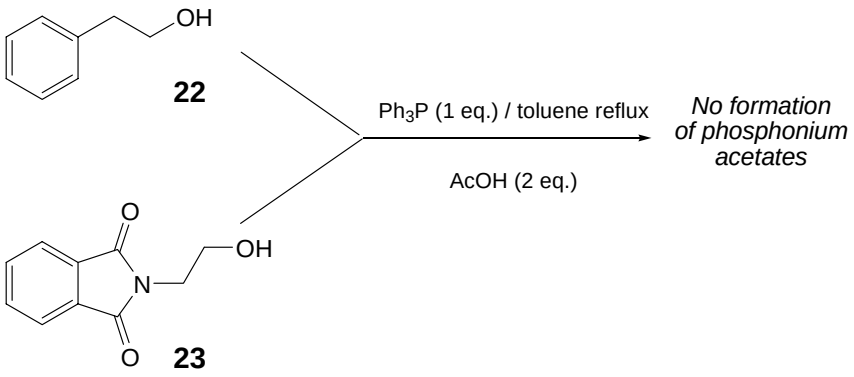
[a] Isolated yields are unoptimised. [b] ^{1}H-NMR signal of methylene group bonded to phosphorus. Solvent: DMSO-d_6. [c] In ppm. [d] In Hertz. [e] The formation of **7** was observed chromatographically. [f] Solvent: acetone-d_6. [g] No presence of phosphonium salt and no disappearance of the corresponding alcohol were observed after 48 h of reaction.

In the cases of alcohols **10** and **11**, entries **c** and **d** (Table 1), respectively, the acidic conditions produced side reactions. On one hand, the integrity of the methylenedioxy moiety in product **18** was low, giving the desired phosphonium salt in low yield (entry **d**). On the other hand, the acetyl group (entry **c**) was lost, maybe as was previously reported,[13] by reaction of the benzyl alcohol with the ester in acid medium, producing product **17** from the alcohol **10**.

It was clear that the substituent electron-donor capabilities in the different benzyl alcohols affected the yield and the time of the reactions. The best results were obtained with the activated alcohols **3**, **9**, **10** and **12**, while an inductive electron-withdrawing substituent, in alcohol **14**, gave

the worst result. On the other hand, in contrast with an earlier report[13a] phosphonium salt **20** was obtained after 48 h of reflux. No formation of the desired salt was observed after prolonged reaction time of alcohol **15**, the benzyl alcohol with a strong electron-withdrawing substituent.

In order to extend this methodology to other alcohols we tried this procedure with the aliphatic alcohols **22** and **23** (Scheme 5). However, after prolonged reaction times neither of the desired products was generated. Other conditions were examined in order to obtain the phosphonium salts, i.e. microwave irradiation in the case of alcohol **23**,[14] but without success. Moreover, the acetate counteranion did not show any deleterious effect in the following Wittig reaction. The phosphonium acetates **16** and **17** were submitted successfully to the Bodens modification with 5-formylbenzofuroxan and 4-chloro-3-nitrobenzaldehyde, respectively.



Scheme 5

Conclusions

In summary, the present methodology describes a simple, convenient and efficient procedure for the preparation of phosphonium salts in one-pot procedure from the corresponding benzyl alcohol. The procedure is adequate for benzyl alcohols substituted with an electron-donating group that favors formation of the electrophilic benzyl carbocation for attack by triphenylphosphine. The experimental procedure is simple, convenient and does not require any special precautions for the isolation of salts.

Experimental Section

General Procedures. The alcohols **13** and **22** are commercially available. The alcohols **3**,[15] **9-12**, **14** and **15** were prepared by reduction with $NaBH_4$ from the corresponding aldehyde[16] and **23** as previously reported.[17] Elemental analyses were obtained from vacuum-dried samples (over phosphorous pentoxide at 3-4 mm Hg, 24 h at room temperature) and performed on a Fisons EA

1108 CHNS-O analyzer. NMR spectra were acquired with a Bruker DPX-400 instrument at 303 K, in approximately 10 % w/v solution, using the standard sequences for the HMQC and HMBC experiments and samples were dissolved in the indicated deuterated solvents. TMS (tetramethylsilane) was used as internal reference. FTIR spectra were recorded with a resolution of 4 cm^{-1}, on a Perkin-Elmer 1310 spectrometer, using KBr wafers containing 1% of the sample. Electron impact (EI) mass spectra were obtained at 70 eV on a Shimadzu GC-MS QP 1100 EX instrument.

General experimental procedure. To a solution of the appropriate benzyl alcohol (3.3 mmol) and Ph_3P (870 mg, 3.3 mmol) in dry toluene (5.0 mL) heated at reflux were added, dropwise, HOAc (0.38 mL, 6.6 mmol) in dry toluene (3.0 mL) as solvent. The mixture was heated at reflux for 4–73 h (see Table 1). The solvent was evaporated *in vacuo* and the residue was treated with petroleum (10.0 mL) and after heating at reflux for 1 h, the solvent was discarded. This procedure was repeated until absence of Ph_3P in the organic solvent (checked by TLC). The resulting syrup is the product.

Selected spectroscopic data for synthesized compounds

(4-Dimethylaminobenzyl)triphenylphosphonium acetate (16). Brown-orange oil; ^{1}H NMR (acetone-d_6), δ (ppm): 1.96 (s, 3H), 2.91 (s, 6H), 4.99 (d, 2H, *J* = 13.8 Hz), 6.56 (d, 2H, *J* = 8.6 Hz), 6.69 (dd, 2H, *J* = 2.3 Hz, *J* = 8.6 Hz), 7.72-7.80 (m, 12H), 7.88-8.00 (m, 3H); ^{13}C NMR (acetone-d_6), δ (ppm): 29.0 (d), 39.0, 39.7, 112.6, 128.9, 130.5, 132.2, 133.4, 134.4, 134.7, 135.5, 164.5; $C_{29}H_{30}NO_2P$: found, C 76.5, H 6.3, N 2.7; require, C 76.5, H 6.6, N, 3.1.

(4-Hydroxybenzyl)triphenylphosphonium acetate (17). Colorless oil; ^{1}H NMR (DMSO-d_6), δ (ppm): 1.74 (s, 3H), 4.97 (d, 2H, *J* = 14.6 Hz), 6.61 (d, 2H, *J* = 8.4 Hz), 6.72 (dd, 2H, *J* = 2.1 Hz, *J* = 8.4 Hz), 7.60-7.78 (m, 12H), 7.85-7.98 (m, 3H); ^{13}C NMR (DMSO-d_6), δ (ppm): 28.6 (d), 39.0, 115.9, 116.6, 118.5, 119.3, 131.0, 134.8, 135.9, 158.9, 174.0; $C_{27}H_{25}O_3P$: found, C 75.3, H 6.1; require, C 75.7, H 5.9.

(3,4-Methylendioxybenzyl)triphenylphosphonium acetate (18). Brown-yellow oil; ^{1}H NMR (DMSO-d_6), δ (ppm): 1.24 (s, 3H), 5.04 (d, 2H, *J* = 15.1 Hz), 5.98 (s, 2H), 6.42-6.48 (m, 2H), 6.79 (d, 1H, *J* = 7.9 Hz), 7.60-7.80 (m, 12H), 7.86-7.95 (m, 3H); ^{13}C NMR (DMSO-d_6), δ (ppm): 25.5 (d), 30.0, 102.2, 109.5, 111.5, 118.2, 119.1, 129.6, 131.0, 132.3, 134.8, 136.0, 148.2, 162.0; $C_{28}H_{25}O_4P$: found, C 73.5, H 5.7; require, C 73.7, H 5.5.

(4-Methoxybenzyl)triphenylphosphonium acetate (19). Brown oil; ^{1}H NMR (DMSO-d_6), δ (ppm): 1.89 (s, 3H), 3.70 (s, 3H), 5.06 (d, 2H, *J* = 15.1 Hz), 6.80 (d, 2H, *J* = 8.6 Hz), 6.86-6.90 (m, 2H), 7.70-7.80 (m, 12H), 7.88-7.94 (m, 3H); $C_{28}H_{27}O_3P$: found, C 75.7, H 6.4; require, C 76.0, H 6.1.

Benzyltriphenylphosphonium acetate (20). Colorless oil; ^{1}H NMR (DMSO-d_6), δ (ppm): 1.92 (s, 3H), 5.17 (d, 2H, *J* = 15.6 Hz), 6.98 (m, 2H), 7.23 (bt, 2H, *J* = 8.2 Hz), 7.31 (t, 1H, *J* = 8.2 Hz), 7.70-7.85 (m, 12H), 7.85-7.95 (m, 3H); $C_{27}H_{25}O_2P$: found, C 78.4, H 6.0; require, C 78.6, H 6.1.

(4-Chlorobenzyl)triphenylphosphonium acetate (21). Brown oil; I.R. (neat): ν 2960, 2920, 1717, 1647, 1541, 1437, 1010, 725, 695, 617 cm^{-1}; ^{1}H NMR (DMSO-d_6), δ (ppm): 2.09 (s, 3H),

5.17 (d, 2H, *J* = 14.9 Hz), 6.98 (d, 2H, *J* = 8.5 Hz), 7.18-7.25 (m, 2H), 7.54-7.78 (m, 12H), 7.85-7.95 (m, 3H); ^{13}C NMR (DMSO-d_6), δ (ppm): 29.0 (d), 39.0, 125.0, 128.8, 129.6, 131.0, 132.3, 134.0, 134.9, 136.1, 163.5; $C_{27}H_{24}ClO_2P$: found, C 72.3, H 5.1; require, C 72.6, H 5.4.

Acknowledgements

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References and Footnotes

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4. Assayed conditions. A mixture of alcohol **3** (1.00 g, 6.7 mmol) and thionyl chloride (0.79 g, 6.7 mmol) was stirred at different temperatures (room temperature to 0 ºC) for different times (24 h to 15 min). The reaction mixture was treated with ice, $NaHCO_3$ -saturated solution (until basic pH), and extracted three times with EtOAc (20 mL). Then, the organic layer was washed with brine, dried with sodium sulfate and evaporated in vacuo. The residue was purified by chromatography (SiO_2, petroleum:EtOAc (0 to 10 %)).
5. I.R. (KBr): ν 2805, 1615, 1522, 1342, 1013, 795 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ: 2.89 (s, 12H), 3.78 (s, 2H), 6.67 (d, 4H, *J*=8.6 Hz), 7.04 (d, 4H, *J*=8.6 Hz); ^{13}C-NMR ($CDCl_3$) δ: 40.5, 41.5, 113.0, 130.0, 149.0, 153.5; MS (EI, 70 eV) *m/z* (%): 254 (M^+, 100), 210 (M^+-44, 38), 167 (M^+-88, 2), 134 (M^+-120, 36).
6. The molecular structure of compound **7**, $C_{17}H_{22}N_2$, was determined by X-ray diffraction. The substance crystallizes in the tetragonal $P4_12_12$ space group with a=b=6.346(1), c=36.640(4) Å, and Z=4. The structure was solved from 1169 reflections with I>2σ(I) and refined to an agreement R1-factor of 0.0422. The molecule is located on a crystallographic

two-fold axis that symmetry relates the two molecular halves hence resembling a two-bladed propeller. As expected, each half is planar [rms deviation of atoms from the least-squares plane of 0.042 Å]. Because of the small anomalous atomic dispersion, the correct molecular stereoisomer in the lattice could not be determined. Crystal data, data collection procedure, structure determination method and refinement results for the compound are summarized in Table S1 (Supplementary material). Atomic fractional coordinates and equivalent isotropic displacement parameters are given in Table S2. Interatomic bond distances and angles are in Table S3. Listings of atomic anisotropic displacement parameters (Table S4), hydrogen atoms positions and isotropic displacement parameters (Table S5), and calculated and observed structure factor amplitudes (Table S6) are also given.[7] Crystallographic data (excluding structure factors) for the structure in this paper have been deposited at the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 601663. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: 144-(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].

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