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Aromatisation of 2-phenyl-1-pyrroline to 2-phenylpyrrole using activated carbon

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2-phenyl-1-pyrroline was selectively dehydrogenated to 2-phenylpyrrole using activated carbon. Aromatisation reactions were performed using toluene at reflux. Only 30 min were sufficient for the dehydrogenation to occur. Maximum conversion values were obtained at ca. 98%, corresponding to maximum yields of 2-phenylpyrrole of ca. 45%. The final product showed high purity.

KEY WORDS: activated carbon; aromatisation; dehydrogenation; 2-phenylpyrrole; 2-phenyl-1-pyrroline.

1. Introduction

Pyrrole and its derivatives are among the most prominent heterocyclic organic compounds. They are commonly found as structural motifs in bio-active molecules, such as porphyrins, alkaloids and co-enzymes. They play important roles in the natural products, synthetic pharmaceuticals, electrically conducting materials (such as polypyrroles), non-linear optics, and supramolecular chemistry [1,2,3]. Therefore, there is a significant interest in developing versatile new synthetic routes for this type of compounds, namely for substituted pyrrole derivatives.

In particular, 2-phenylpyrrole has been synthesised by several authors using different synthetic routes. Guillard *et al.* [4], using a four step sequence starting from the reaction of phenylacrolein and methylazidoacetate, followed by cyclisation, synthesised 2-phenylpyrrole in 35% overall yield. This compound was synthesised in 50% yield by Moreau *et al.* [5] by reacting benzoyl chloride with the product of the dilithiation of (trimethylsilyl)(allyl)amine, in diethyl ether, for 24 h, at room temperature. Standen *et al.* [6] reacted the oxime derived from 4-chlorobutyrophenone with KO^{t}Bu in ^{t}BuOH, at 20 °C, giving 3-phenyl-5,6-dihydro-(4*H*)-1,2-oxazine, which was treated with KOH/DMSO, for 1 h, at 100 °C, and obtained 2-phenylpyrrole in 44% yield. Quast *et al.* [7] treated benzaldehyde with *trans*-cyclopropanediammonium dibromide and sodium acetate, in methanol, and a 64% yield was obtained, after 16 h. Taylor *et al.* [3] used a one-pot synthesis of 2-phenylpyrrole (70% yield) from 3,5-dihydro-1,2-dioxines, which in turn are prepared from the photo-oxidation of 1-phenyl-1,3-pentadiene. This method deals with an initial Kornblum-de la Mare rearrangement of the corresponding 3,5-dihydro-1,2-dioxine to its isomeric 1,4-diketone and subsequent *in situ* condensation of this species with NH_4CO_3, in refluxing DMF.

Syntheses of 2-phenylpyrrole involving more readily accessible starting materials have also been published in the literature. For example, Zappia *et al.* [8] converted acetophenone, via its *O*-(2-hydroxyethyl)-oxime into 2-phenylpyrrole, for 5 h, in 59% overall yield, by reacting the oxime with KO^{t}Bu in refluxing ^{t}BuOH. The Pd-catalysed coupling of pyrrole with phenyl halides leads to a straightforward synthesis of 2-phenylpyrrole. For instance, coupling of bromobenzene and pyrrol-1-yl-zinc halides prepared *in situ*, in the presence of the catalytic system $[PdCl_2(PPh_3)_2]/PPh_3$, for 2 h, at 140 °C, obtaining 40–75% yield [9]. More recently Sames *et al.* [10] developed a method where the coupling of pyrrole and iodobenzene is carried out using a $Pd(OAc)_2/PPh_3$/MgO catalytic system, in dioxane (86% yield). These Pd-based coupling methods are indeed the most effective of all reported in the literature but have the disadvantage of becoming too expensive when production of significant amounts of 2-phenylpyrrole is required.

The synthesis of 2-phenylpyrrole can also be achieved by catalytic dehydrogenation of 2-phenylpyrrolidine and 2-cyclohexylpyrrolidine using a nickel-on-nickel chromite (Ni·NiCrO) heterogeneous catalyst, at 300 °C, leading to yields of 46% and 16%, respectively [11]. Alternatively, the dehydrogenation of pyrrolidine with sulphur gives 2-phenylpyrrole (22% yield) and 2-phenyl-1-pyrroline (43% yield) [12]. On the other hand, the latter compound can be further dehydrogenated by sulphur to 2-phenylpyrrole in 39% yield.

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Other dehydrogenation agents such as selenium [13], quinones (2,3,5,6-tetrachloro-1,4-benzoquinone (chloranil) [14,15] or 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) [14,16]) or Pd supported on activated carbon catalysts [17,18], have been used for the conversion of other substituted 1-pyrrolines to the corresponding pyrrole derivatives.

In fact, the dehydrogenation of 2-phenyl-1-pyrroline (figure 1, reaction b) could be envisaged as a cheaper route to 2-phenylpyrrole, since this compound is easily accessible from the cyclisation reaction between the Grignard reagent PhMgBr and 4-chlorobutyronitrile (figure 1, reaction a) [19], both available commercially.

In the light of the results obtained by Schuikin and Naryschkina with five- and six-membered cycloalkanes, at ca. 600 °C [20], we report in this work the aromatisation of 2-phenyl-1-pyrroline to 2-phenylpyrrole using a commercial activated carbon as dehydrogenation agent under mild reaction conditions. We have tried to find a previous report of this specific reaction, but to the best of our knowledge, the aromatisation of pyrrolines with activated carbon is unprecedented. This method provides a cheap alternative synthetic route to that based on Pd catalysts.

2. Experimental

2.1. General

Diethyl ether, toluene and bromobenzene were predried over activated 4 Å molecular sieves and then distilled under an atmosphere of dinitrogen from sodium and stored under dinitrogen; *p*-xylene (Acrös) was used as received. Deuterated chloroform (Aldrich) was the solvent employed for the characterisation of the organic compounds by Nuclear Magnetic Resonance (NMR) spectroscopy, and was used as received. The ^{1}H NMR spectra were recorded on a Varian Unity 300 spectrometer (300 MHz) and referenced internally using tetramethylsilane ($\delta = 0$). All chemical shifts are quoted in δ (ppm) and coupling constants are given in Hz. Multiplicities are abbreviated as follows: singlet (s), doublet (d), triplet (t), multiplet (m), broad (br). Elemental analyses were performed on a Fisons Instrument Mod EA-1108 analyser by the Laboratório de Análises in this Institute.

2.2. Synthesis of 2-phenyl-1-pyrroline

This procedure was adapted from the method described by Craig *et al.* [19] (figure 1, reaction a). Magnesium turnings (9.24 g, 0.380 mol) were slightly ground in a mortar and transferred to a two-necked round-bottom flask equipped with an addition funnel and a reflux condenser. All the system was flushed with nitrogen and a few iodine crystals and 250 cm^3 of diethyl ether were added. The synthesis of PhMgBr was initiated by the addition of ca. 40 drops (of a total of 39.5 cm^3, 0.375 mol) of bromobenzene without stirring. Stirring was turned on after cloudiness was observed (ca. 10 min.), and the remaining bromobenzene was added dropwise, producing a slight reflux of the solvent. The mixture was further allowed to stir for 2 h, after which a solution of 4-chlorobutyronitrile (23.2 mL, 0.375 mol) in 250 cm^3 of diethyl ether was added dropwise. Precipitation of a beige gel-like solid was observed and the mixture was refluxed for 90 min. A Dean-Stark trap was set up in between the flask and the reflux condenser. The diethyl ether was then distilled off and replaced by *p*-xylene, keeping the total volume approximately constant. The resulting mixture containing a beige precipitate was treated with a saturated NH_4Cl aqueous solution and the organic layer was separated in a separatory funnel. The aqueous layer was further extracted with dried diethyl ether and the organic phase added to the *p*-xylene extract. The resulting organic fraction was extracted twice with a 10% aqueous HCl solution, and the yellow aqueous phase was separated and neutralised, in an ice bath, with a concentrated NaOH solution. Dried diethyl ether was added and, after extraction, the organic layer was collected and washed with distilled water. After separation, the organic phase dried with $MgSO_4$, filtered and evaporated to dryness in a rotatory evaporator. The 2-phenyl-1-pyrroline was purified by a trap-to-trap distillation (ca. 90 °C, at 10^{-1} mbar). Yield, 30.64 g (56.3%).

Anal. found (calc. for $C_{10}H_{11}N$): C 82.35 (82.72); H 8.44 (7.64); N 9.54 (9.65).

^{1}H NMR ($CDCl_3$): δ 7.81 (m, 2H, *o*-Ph), 7.36 (m, 3H, *m*- and *p*-Ph), 4.02 (m, 2H, pyrroline 5-H), 2.88 (m, 2H, pyrroline 3-H), 1.95 (m, 2H, pyrroline 4-H).

2.3. Pre-treatments and characterisation of activated carbon

Commercial activated carbon Charcoal Activated GR Merck (powder, with a particle size of 30 μm, 1% ashes and 10% humidity) was washed abundantly with distilled water and dried in the oven at 120 °C, for 24 h (C-24H), 1 week (C-1W), 1 month (C-1M), 2 months (C-2M) and 6 months (C-6M). An alternative pre-treatment consisted in heating unwashed carbon sample to 300 °C, in vacuum (ca. 10^{-1} mbar), for 2 h (sample C-MV).

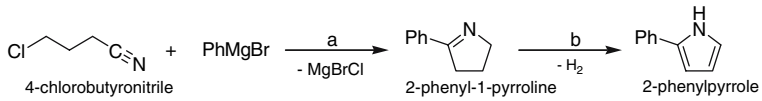

Figure 1. Reaction sequence for the synthesis of 2-phenylpyrrole.

The characterisation of these samples (e.g. specific surface area, total pore volume, micropore volume) was carried out in an ASAP 2010 apparatus, from Micromeritics Instrument Corp., by adsorption of N_2, at 77 K.

2.4. Aromatisation of 2-phenylpyrrole

Procedure A – In a typical experiment, the 2-phenyl-1-pyrroline (1 g, 6.887 mmol) was dissolved in toluene and the desired amount of activated carbon (sample C-2M) was added. The amount of toluene used was ca. five times the amount of carbon added (w/v). The mixture was refluxed for 30 min (reaction temperature: 120–130 °C), and then filtered while hot (close to the boiling point) through a sintered glass frit containing a Celite bed. The solvent was evaporated under vacuum to dryness. The resulting oily material was redissolved in boiling ethanol, and stored at −20 °C, giving rise to orange crystals of 2-phenylpyrrole, which were filtered, dried under vacuum and weighed.

Procedure B – This is identical to procedure A, except that additional washings/extractions of the carbon were carried out with fresh amounts of toluene, in order to recover the potentially adsorbed products. Accordingly, after the filtration mentioned in procedure A, the mixture was further refluxed for an additional period of 60 min, and filtered in the same conditions as described before. This operation was repeated two more times, making a total of three extractions. All the filtered toluene fractions were gathered and evaporated to dryness. Recrystallisation of 2-phenylpyrrole was carried out as described in procedure A.

Anal. found (calc. for $C_{10}H_9N$): C 83.98 (83.88); H 6.72 (6.34); N 9.46 (9.78).

^{1}H NMR ($CDCl_3$): 8.44 (br s, 1H, N*H*), 7.45 (d, $^3J_{HH}$ = 7.5, 2H, *o*-Ph), 7.35 (t, $^3J_{HH}$ = 7.5, 2H, *m*-Ph), 7.19 (t, $^3J_{HH}$ = 7.5, 1H, *p*-Ph), 6.86 (m, 1H, pyrrole 5-H), 6.51 (m, 1H, pyrrole 3-H), 6.29 (m, 1H, pyrrole 4-H).

During the course of reaction aliquots of the reaction supernatant solution were taken close to boiling point, which were filtered through cotton wool placed in a Pasteur pipette, and then evaporated to dryness. The resulting solid was redissolved in $CDCl_3$ and analysed by ^{1}H NMR. The molar fraction of 2-phenylpyrrole ($x_{pyrrole}$) and 2-phenyl-1-pyrroline in the supernatant solution was determined by the relative intensity of the normalised peak integrals in the ^{1}H NMR spectrum.

3. Results and discussion

The synthesis of 2-phenyl-1-pyrroline used in this work (figure 1, reaction a) followed a procedure similar to that described by Craig *et al.* [19]. These authors claimed that the product obtained was 2-phenyl-2-pyrroline. However, in the present work, NMR spectroscopy shows undoubtedly that its cyclic imine isomer, 2-phenyl-1-pyrroline, is formed instead, since three CH_2 resonances integrating 1:1:1 are observed in the ^{1}H NMR spectrum.

Some preliminary attempts of aromatisation of 2-phenyl-1-pyrroline in the presence of activated carbon were made in refluxing hexane or toluene. We have found that better results were obtained in toluene. After 30 min of reaction, the molar fraction of 2-phenylpyrrole in the supernatant solution, $x_{pyrrole}$ (determined by ^{1}H NMR – see Experimental), was found to be constant up to 48 h of reaction, the maximum reaction time used in this study. Tests performed in both inert and oxygen atmosphere revealed no significant differences. Therefore experiments were carried out in air.

Several pre-treatments of the activated carbon were tested. The majority consisted in washing the commercial material with distilled water, using different drying times in the oven, at 120 °C: 24 h (sample C-24H), 1 week (sample C-1W), 1 month (sample C-1M) 2 months (sample C-2M) or 6 months (sample C-6M), as shown in table 1. The activated carbon was also tested without any pre-treatment (sample C-NT), and after heating to 300 °C in vacuum, at ca. 10^{-1} mbar, for 2 h (sample C-MV).

Table 1 shows small differences in the characterisation of the carbon samples. However, a slight improvement of the conversion of 2-phenyl-1-pyrroline (which is proportional to the molar fraction of 2-phenylpyrrole, $x_{pyrrole}$) is observed as the drying time increases. This small increase parallels the also very slight improvement of the carbon textural properties, such as the specific surface area (S_{BET}) and total pore volume (V_{tot}). However, the micropore volume (V_{mic}) remains practically unchanged.

According to these results, we have chosen the C-2M carbon sample pre-treatment drying time, and all the subsequent studies of this report were carried with carbon samples prepared under these conditions.

Table 1
Molar fractions of 2-phenylpyrrole ($x_{pyrrole}$) obtained in the dehydrogenation of 2-phenyl-1-pyrroline promoted by activated carbon samples with different pretreatments and their corresponding characterisation by adsorption of N_2, at 77 K

Sample	$x_{pyrrole}$[a]	S_{BET} (m^2/g)	V_{tot} (cm^3/g)	V_{mic} (cm^3/g)
C-24H	0.40	856	0.60	0.26
C-1W	0.41	862	0.61	0.26
C-1M	0.45	889	0.62	0.26
C-2M	0.48	948	0.70	0.28
C-6M	0.48	951	0.70	0.28
C-MV	0.31	890	0.62	0.26
C-NT	0.19	889	0.62	0.27

[a]Obtained by ^{1}H NMR, for the dehydrogenation of 1 g of 2-phenyl-1-pyrroline, using 5 g of activated carbon, for 30 min.

Table 2
Conversions and yields of the dehydrogenation reaction of 2-phenyl-1-pyrroline to 2-phenylpyrrole in the presence of activated carbon, using workup procedures A and B (see Experimental)

Activ. Carbon (g)	Pyrroline (initial) (g)	Pyrroline (final) [a] (g)	Pyrroline conversion (%)	Pyrrole (A) (g)	Pyrrole Yield (A) (%)	Pyrrole (B) (g)	Pyrrole Yield (B) (%)
1	1	0.378	62.2	0.093	9.4	0.145	14.7
5	1	0.270	73.0	0.147	14.9	0.240	24.3
10	1	0.202	79.8	0.175	17.7	0.310	31.4
20	1	0.114	88.6	0.189	19.2	0.365	37.0
30	1	0.074	92.6	0.188	19.1	0.415	42.1
40	1	0.039	96.1	0.165	16.7	0.439	44.5
50	1	0.014	98.6	0.145	14.7	0.440	44.6

[a]Obtained by ^{1}H NMR.

In all the reactions studied in this work, the ^{1}H NMR spectra of the supernatant reaction solution showed exclusively the presence of the desired product 2-phenylpyrrole, along with some unreacted reagent. This demonstrates that this dehydrogenation reaction is highly selective. In fact, after isolation from recrystallisation in ethanol, the target compound showed high purity, as determined by ^{1}H NMR analysis, and its spectrum conforms to those reported in the literature [4,10,21].

As shown in table 2 and figure 2, good conversion values were obtained (up to 98%), depending upon the amount of carbon used. However, the yield in 2-phenylpyrrole remains low if no further extractions of the carbon are made with fresh amounts of toluene (see procedure A in Experimental). When the workup of procedure B is followed, the yield in 2-phenylpyrrole increases significantly, since a good part of the product, which may be adsorbed on the carbon surface, is then recovered. Nevertheless, the maximum yield does not go over 45%, remaining far from the conversion values of the starting reagent.

The fate and nature of the remaining material is unknown. It can be either unreacted 2-phenyl-1-pyrroline, 2-phenylpyrrole formed or other products resulting from their decomposition and/or adsorption, any of them possibly adsorbed physically or chemically to the activated carbon surface. In fact, specific surface area and pore size values of an activated carbon sample collected after dehydrogenation reaction (following procedure B), showed a decrease of ca. 14% in relation to parent activated carbon sample.

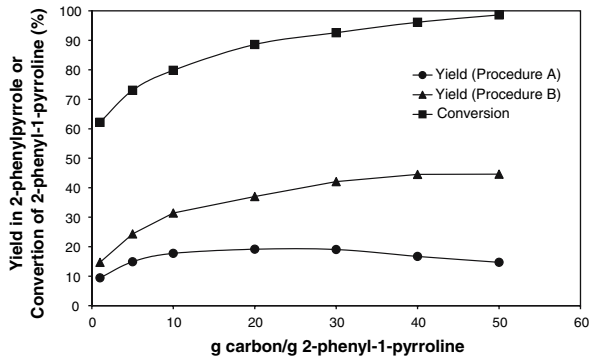

Figure 2. Conversion of 2-phenyl-1-pyrroline and yield in 2-phenylpyrrole using activated carbon as dehydrogenation agent (Procedures A and B – see Experimental).

The yields obtained in this work are somewhat higher than the other related dehydrogenation processes reported in the literature [12]. In comparison, our method has the advantage of requiring only 30 min to reach maximum conversion.

4. Conclusions

2-Phenyl-1-pyrroline was synthesised by a literature method and, in an unprecedented reaction, further dehydrogenated to 2-phenylpyrrole, using commercial activated carbon, in refluxing toluene. These studies showed that only 30 min were sufficient for the dehydrogenation to occur. Maximum conversion values of 2-phenyl-1-pyrroline were obtained at ca. 98%, corresponding to maximum yields of 2-phenylpyrrole of ca. 45%. The final product, after recrystallisation from ethanol, showed high purity.

Acknowledgments

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