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STUDY OF THE CATALYTIC PROPERTIES OF TRIS (3,6-DIOXAHEPTYL) AMINE (TDA-1) IN HETEROAROMATIC NUCLEOPHILIC SUBSTITUTION OF CHLOROPYRIDINES AND THEIR N-OXIDES

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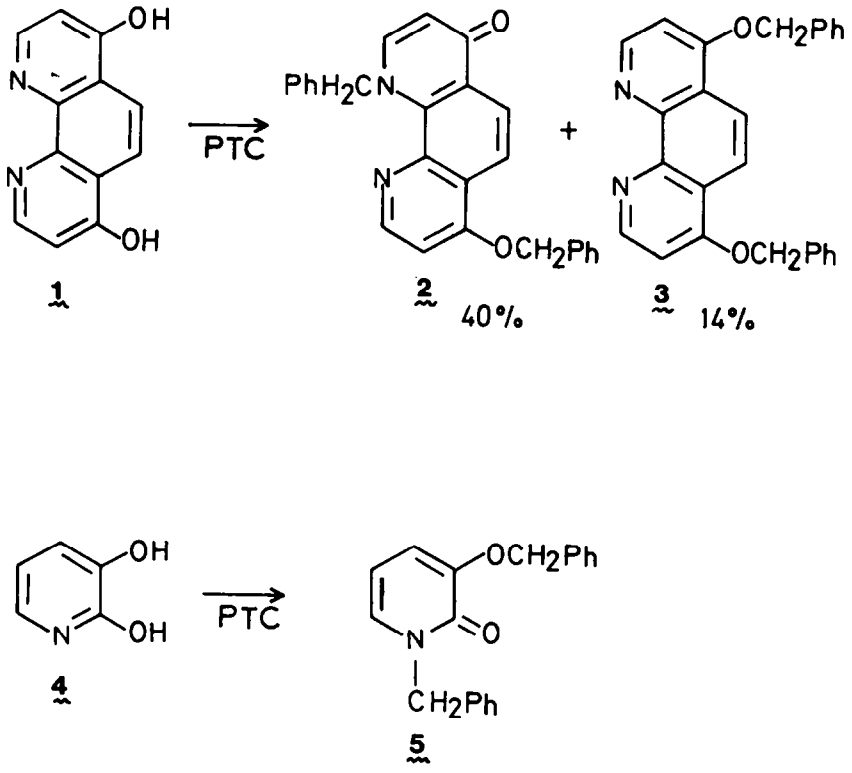
Abstract.-Catalytic properties of tris(3,6-dioxaheptyl)amine (TDA-1) have been analyzed in reactions of alkoxy-dehalogenation of 2- and 4-chloropyridine and their N-oxides under solid-liquid phase transfer catalysis conditions. Alkoxypyridines were obtained in excelent yields but with N-oxides a competitive alkaline cleavage of the performed ether was observed.

Direct oxidation procedures cannot be applied to 2- or 4-hydroxypyridines for the preparation of N-oxides, but they are easily achieved from alkoxy or chloropyridines. In order to get some hydroxypyridine N-oxides related to the recently synthesized toxine "orellanine" (3,3',4,4'-tetrahydroxybipyridine-N,N'-dioxide) (1,2), we tried to prepare some alkoxypyridines which could be transformed into their corresponding N-oxides.

It is known that direct alkylation of hydroxypyridines could yield either N-alkylpyridones or alkoxypyridines depending on the experimental conditions (3). Attempted O-alkylation of 4,7-dihydroxy-1,10-phenanthroline with benzyl chloride under phase transfer catalysis conditions (PTC) yielded the O,O'-dibenzyl-derivative 3 in very low yield, and the N,O-dibenzylderivative 2 as major compound. The 2,3-dihydroxypyridine gave only the pyridone 5 as reaction product (Scheme 1).

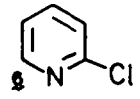
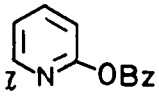
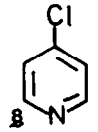
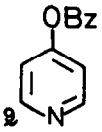
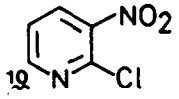
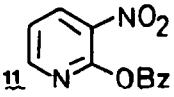
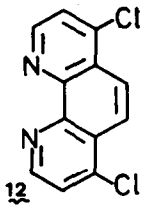
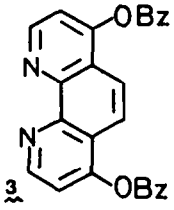
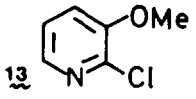
To overcome these problems the corresponding 2- and 4-chloropyridines were selected as starting materials for transformation into either the alkoxypyridines or the N-oxides. Oxidation of the alkoxypyridines or alkoxy dehalogenation of the chloropyridine N-oxides will yield the alkoxypyridine N-oxides (Scheme 2).



Scheme 1

Although some alkoxypyridines have been prepared previously from chloropyridines by different procedures (3), we used PTC reactions with tris(3,6-dioxaheptyl)amine (TDA-1) as catalyst. This compound has recently been described as a convenient catalyst for a wide variety of substrates (4). Reactions were carried out with benzyl alcohol under solid/liquid PTC conditions providing the benzyloxypyridines listed in table 1 in high yield.

Table 1. Reactions of chloropyridines with benzyl alcohol and TDA-1 under solid-liquid PTC

Pyridine	Reaction product	Temp./Time (°C) (hr)	m.p. (°C)	Yield (%)	Yield (%)
		120/4	Liquid	84	85[5]
		120/18	51-2 55-6	86	22[6]
		25/1	41-43	87	
		120-2	165-168	63	
	N.R.				

a: All products were isolated by column chromatography using silicagel and methylene chloride or methylene chloride/ethanol (9:1) as eluents.

Because the negative result in the case of 2-chloro-3-methoxypyridine 13, it was transformed into the N-oxide 14 by treatment with m-chloroperbenzoic acid (MCPBA) (7), and the alkoxy dechlorination was attempted. According to the results depicted in table 2, compound 14 could be converted into the corresponding 2-pyridone or 2-alkoxy derivative depending on the experimental conditions. Only 1-hydroxy-3-methoxy-2(H)-pyridone 15 was always obtained when compound 14 was treated with benzyl alcohol under PTC and TDA-1 in refluxing toluene, or with potassium hydroxide in refluxing methanol and TDA-1. Compound 15 was also isolated when the N-oxide 14 reacted with sodium methoxide in refluxing methanol.

Formation of compound 15 can better be explained as a consequence of the thermal alkaline breakdown of the initially formed 2,3-dialkoxypyridine N-oxide, instead of a nucleophilic dechlorination of compound 14 by OH^- ion attack. In fact, when the reaction was carried out with potassium hydroxide and potassium carbonate in refluxing toluene and TDA-1, only a trace of compound 15 was detected and the unaltered starting material was recovered.

Influence of TDA-1 in the cleavage of the dialkoxypyridine N-oxide was shown by the results from the reaction of 14 with benzyl alcohol under the same conditions mentioned above, but in absence of TDA-1. In this case compound 15 was isolated together with 1-benzyloxy-3-methoxy-2(H)pyridone 16 as a consequence of the thermal rearrangement of 2-benzyloxy-3-methoxypyridine N-oxide (9).

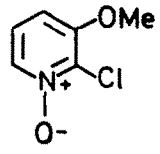
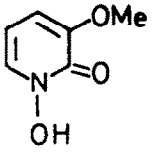
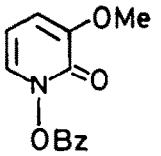
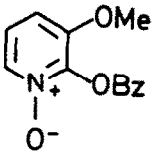
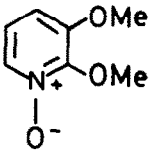
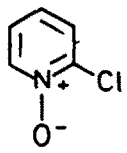
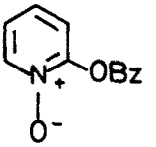
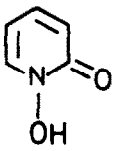
This alkaline cleavage can be related to the one observed in the reaction of 3-chloro and 3-bromopyridines and sodium methoxide, in which 3-pyridinol was isolated as a side reaction product (10). The methoxy dehalogenation is a very slow reaction and the alkaline cleavage of the ether ocurs simultaneously. In contrast, 2- and 4-chloropyridines undergo methoxy dehalogenation rapidly enough to prevent the cleavage. This feature has also been found by us in the reaction of 2-chloropyridine N-oxide 17 with benzyl alcohol under PTC, isolating only a trace of the corresponding 1-hydroxy-2(H)pyridone 19 when the reaction takes place in presence of TDA-1 and none of it in absence of TDA-1.

In order to avoid this breakdown, compound 14 was treated with sodium methoxide in methanol and dimethylformamide (DMF) at room temperature (11) and 42% yield of 2,3-dimethoxypyridine N-oxide 20 was obtained, recovering the rest of unchanged starting material. This yield of compound 20 is better than that obtained from direct oxidation of 2,3-dimethoxypyridine with MCPBA (13%).

Reaction of 14 with benzyl alcohol and TDA-1 at room temperature in benzene yielded the 2-benzyloxy-3-methoxypyridine N-oxide 21 which rapidly rearranged, on standing, to compound 16.

Finally, it can be concluded that TDA-1 is a suitable catalyst for the alkoxy dechlorination of 2- and 4-chloropyridines with or without electron-withdrawing groups under PTC conditions giving alkoxypyridines in high yield, but is ineffective in the case 2-chloro-3-methoxypyridine. When chloropyridine N-oxides were used, a competitive alkaline cleavage was observed especially in 2-chloro-3-methoxypyridine N-oxide where the nucleophilic displacement of chlorine ocurs very slowly due to the presence of an electron-donor group in 3-position.

Table 2. Alkoxy dehalogenation reactions of Pyridine N-oxides

Pyridine N-oxide	Conditions	Reaction Products (%)[a]
 14	BzOH, KOH, K_2CO_3 Toluene/120°/TDA-1 2 hr.	 15 (69)
	MeOH, KOH, K_2CO_3 60°/TDA-1/17 hr.	15 (62)
	KOH, K_2CO_3 Toluene/120°/TDA-1 3 hr.	15 (10)
	BzOH, KOH, K_2CO_3 Toluene/120°/4 hr.	15 (36)  16 (39)
	BzOH, KOH, K_2CO_3 Benzene/25°/TDA-1 22 hr.	 21 (56)[b]
	MeONa/MeOH 60°/1.5 hr.	15 (80)
	MeONa/MeOH/DMF 25°/17 hr.	 20 (42)
 17	BzOH, KOH, K_2CO_3 Toluene/120°/TDA-1 0.5 hr.	 18 (47)[c]  19 (traces)
	BzOH, KOH, K_2CO_3 Toluene/120°/1 hr.	18 (70)

a: Yield given in isolated product, b: It rapidly rearranges to compound 16, c: Difficult to separate from TDA-1, the actual yield being higher (80% by ^1H NMR).

Table 3. ^{1}H Chemical shifts (δ) and coupling constants (Hz) by alkoxypyridines and N-oxides at 90 MHz

Compound	H_2	H_3	H_4	H_5	H_6	H_7	H_8	H_9	Others
2 *a	6.54(d) J=7.8	7.68(d) J=7.8		8.53(d) J=9.0	8.16(d) J=9.0		6.90(d) J=5.2	8.62(d) J=5.2	N-CH_2: 6.59(s) O-CH_2: 5.29(s) C_6H_5: 7.10-7.26(m) 7.38-7.50(m)
3 a	8.95(d) J=5.4	7.05(d) J=5.4		8.20(s)	8.20(s)		7.05(d) J=5.4	8.95(d) J=5.4	O-CH_2: 5.28(s) C_6H_5: 7.30-7.55(m)
5 a			6.65(dd) J=7.2 J=1.8	6.00(t)	6.92(dd) J=6.9 J=1.8				O-CH_2: 5.17(s) N-CH_2: 5.10(s) C_6H_5: 7.25-7.47(m)
7 b		6.80-7.05(m)	7.70(ddd) J=8.4 J=7.2 J=1.8	6.80-7.05(m)	8.20(ddd) J=5.1 J=1.8 J=0.6				
9 b	8.40(dd) J=4.7 J=1.2	6.85(dd) J=4.7 J=1.2		6.85(dd) J=4.7 J=1.2	8.40(dd) J=4.7 J=1.2				O-CH_2: 5.08(s) C_6H_5: 7.40(s)
11 b			8.25(dd) J=7.8 J=1.8	6.97(dd) J=7.8 J=4.8	8.32(dd) J=4.8 J=1.8				O-CH_2: 5.58(s) C_6H_5: 7.37-7.52(m)
15 b			6.80(dd) J=7.2 J=1.8	6.12(t)	7.42(dd) J=7.2 J=1.8				O-CH_3: 3.68(s)
16 b			6.53(dd) J=7.0 J=1.8	5.85(t)	6.80(dd) J=7.0 J=1.8				O-CH_3: 3.82(s) O-CH_2: 5.28(s) C_6H_5: 7.35(s)
18 b		c	c	7.03(m)	8.25(d) J=6.0				O-CH_2: 5.30(s) C_6H_5: 7.30-7.50(m)
19 b		6.55(dd) J=8.0 J=2.0	7.40(ddd) J=8.0 J=7.0 J=2.0	6.20(dt) J=7.0 J=2.0	7.92(dd) J=7.0 J=2.0				
20 b			7.12(d) J=4.2	7.87(t) J=4.2	7.12(d) J=4.2				O-CH_3: 3.90(s) O-CH_3: 3.85(s)
21 a			c	c	7.80(dd) J=4.5 J=1.5				O-CH_2: 5.40(s) O-CH_3: 3.75(s) C_6H_5: 7.25-7.35(m)

* Recorded at 300 MHz; a: In $CDCl_3$ solution; b: In DMSO-d_6 solution; c: Overlapped by phenyl proton signals.

Table 4. Melting points, IR, MS, and elemental analyses of new compounds

Compound	M.P. °C	IR: ν cm^{-1}	M$^+$: m/z		C	H	N
2	159-160	(KBr) 1630 1695	392	Calc.: Found:	79.57 79.26	5.14 5.34	7.14 6.86
3	165-168	(KBr) 1575 1500	392	Calc.: Found:	79.57 78.94	5.14 5.47	7.14 7.17
11	41-43	(KBr) 1595 1560 1510	230	Calc.: Found:	62.61 62.79	4.38 4.34	12.17 12.30
15	159-160	(KBr) 3080-2600 1625 1570 1540	141	Calc.: Found:	51.06 50.70	4.99 4.97	9.93 9.68
16	oil	($CHCl_3$) 1660 1600	231				
20	36-38	(KBr) 1495 1449	155	Calc.: Found:	54.18 53.95	5.85 6.01	9.03 8.83

EXPERIMENTAL

Melting points are uncorrected. The IR spectra were recorded on a Perkin-Elmer model 257 spectrometer. The H NMR were performed on a Varian EM 390 (90 MHz) and a Varian XL 300 (300 MHz) using TMS as internal reference. Mass spectra were determined with a VG-12-250 spectrometer at 70 eV. IR and analyses of new compounds are reported in Table 4.

Toluene was dried over sodium metal. Methanol was dried with sodium metal and subsequent distillation. Dimethylformamide was stored over molecular sieves 4 A. Commercial products were used without further purification and the following compounds were obtained according to literature procedures: 4,7-dichloro-1,10-phenanthroline (12); 3-methoxy-2-chloropyridine was obtained by O-alkylation with dimethylsulfate under PTC conditions m.p. 46-47°(Lit. : 48-49°) (7); 2,3-dimethoxypyridine (11).

Alkylation of 4,7-dihydroxy-1,10-phenanthroline with benzyl chloride.-A mixture of 4,7-dihydroxy-1,10-phenanthroline 1 (0.5 g, 2.4 mmol), 50% aqueous sodium hydroxyde (1 ml), benzyl chloride (0.6 ml, 5.0 mmol), tetrabutylammonium bromide (32 mg, 0.1 mmol) and benzene (2 ml) was refluxed with stirring for 3.5 hr. After cooling, methylene chloride (20 ml) was added, and the organic layer separated and dried over anhydrous sodium sulfate. The solvent was removed in vacuo and the residue (1 g) purified through a silica gel column, using methylene chloride to isolate compound 2 (380 mg, 40%). Elution with a mixture of methylene chloride/ ethanol 9:1 yielded compound 3 (130 mg, 14%). The spectroscopical and physical characteristics were in accordance with the compound obtained by nucleophilic displacement of 4,7-dichloro-1,10-phenanthroline with benzyl alcohol under PTC.

1-Benzyl-3-benzyloxy-2-(1H)pyridone (5) 2,3-Dihydroxy-pyridine 4 (0.5 g, 4.5 mmol) was treated with benzyl chloride (1.2 ml, 10 mmol) under the same conditions used for compound 1, obtanining, after chromatographic purification using silica gel and methylene chloride as eluent, compound 5 (260 mg, 20%), m.p. 105-107°. Lit. (13) 115-116°.

Reactions of chloropyridines with benzyl alcohol under PTC and TDA-1 Chloropyridines 6, 8, 10, 12 and 13 (5 mmol) were added to a suspension of powdered potassium hydroxide (20 mmol) and potassium carbonate (5 mmol) in dry toluene (50 ml), and benzyl alcohol (7.5 mmol). After adding TDA-1 (0.5 mmol) the reaction was stirred at the temperature and for the time shown in table 1.

1-Hydroxy-3-methoxy-2-(1H)pyridone (15) a) By solid-liquid PTC using benzyl alcohol and TDA-1: Compound 14 was treated under the same conditions used for chloropyridines. After the time shown in table 2, toluene was decanted, water added and acidified to pH 6. After concentration compound 15 was isolated by extraction of the residue with absolute ethanol, and recrystallized from benzene/ethanol. b) By PTC using methanol and TDA-1: Compound 14 was dissolved in

a mixture of powdered potassium hydroxide and potassium carbonate in dry absolute methanol. After refluxing for the time shown in table 2, methanol was evaporated in vacuo, the residue dissolved in water, and acidified to pH 6. Compound 15 was isolated as in a). c) By treatment with sodium methoxide in methanol: To a solution of sodium methoxide (9 mmol) in dry methanol (5 ml) was added compound 14 (3.1 mmol) and refluxed for 1.5 hr. The solution was filtered and methanol evaporated in vacuo. The residue was treated as in a) to isolate compound 15.

1-Benzyloxy-3-methoxy-2(1H)pyridone (16) To a mixture of powdered potassium hydroxide (12.4 mmol), potassium carbonate (3.1 mmol) and benzyl alcohol (3.7 mmol) in dry toluene (15 ml) was added compound 14 (3.1 mmol). Reaction mixture was refluxed with stirring for 4 hr, filtered, concentrated and the residue purified by column chromatography using methylene chloride as eluent, isolating compound 16 (280 mg, 39%). Alkaline residue was dissolved in water and worked up as in compound 14 a) to isolate compound 15 (200 mg, 47%).

2-Benzyloxypyridine N-oxide (18) a) By PTC and TDA-1: 2-Chloropyridine N-oxide 17 (1 g, 7.8 mmol) was treated with benzyl alcohol (0.92 g, 8.6 mmol) under the same conditions used for compound 14 a). After chromatographic purification through a silica gel column, using methylene chloride/ethanol 9:1 as solvent, compound 19 (700 mg, 47%) was obtained, m.p. 101-102°Lit (6) 103-106°. Alkaline solids were dissolved in water, acidified to pH 6 and concentrated. Extraction with methylene chloride yielded compound 18 (20 mg). b) Without TDA-1: Compound 17 (0.5 g, 4 mmol) was treated under the same conditions used in a) but in absence of TDA-1. After concentration of toluene the residue was washed with hexane/ether and compound 19 (540 mg, 70%) was isolated as a white product, which slowly rearranged to 1-benzyloxy-2 (1H) pyridone on standing or by heating at 100 .

2,3-Dimethoxypyridine N-oxide (20) a) By oxidation with MCPBA: To a solution of 2,3-dimethoxypyridine (1.4 g, 10 mmol) in methylene chloride (25 ml) was added a solution of MCPBA (2.6 g, 1.5 mmol) in methylene chloride (25 ml). The reaction was allowed to stir at room temperature for 7 days and methylene chloride removed in vacuo. The residue was basified with 5% aqueous sodium carbonate and extracted with methylene chloride. The organic solution was dried over anhydrous sodium sulfate and evaporated. The residue was purified by column chromatography using methylene chloride to remove the pyridine and methylene chloride/ethanol 9:1 to isolate compound 20 (200 mg, 13%) which crystallized by treatment with ice-cold hexane-ether. b) By treatment with sodium methoxide and DMF: To a solution of sodium methoxide (4.3 mmol) in absolute methanol (2 ml) and dry DMF (2 ml) was added compound 14 (0.5 g, 3.1 mmol). The reaction was stirred at room temperature for 17 hr. Water (10 ml) was added and extracted several times with methylene chloride. The organic solution was dried over anhydrous sodium sulfate and concentrated in vacuo. The residue was purified by column chromatography as in a) and compound 20 (200 mg, 42%) was isolated.

2-Benzyloxy-3-methoxypyridine N-oxide (21). Compound 14 (0.5 g, 3.1 mmol) was treated under the same conditons used in 14 a) but using benzene as solvent at room temperature. After 22 hr, the organic solution was filtered, dried and concentrated. ^{1}H NMR spectrum of the crude showed the signals of compound 21 and the absence of compound 16. Purification by column chromatography on silica gel using methylene chloride/ethanol 98:2 gave a mixture of compound 16 (120 ml) and compound 21 (280 mg) which rapidly rearranged to 16 after evaporation of solvent in vacuo at room temperature. The rearrangement was not avoided even keeping the sample in the refrigerator.

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