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TDA-1 CATALYSIS IN SMILES REARRANGEMENT OF N-ARYLPHENOXYAMIDES. ACCELERATING EFFECT OF THE 2,4,6-TRICHLORO SUBSTITUTION

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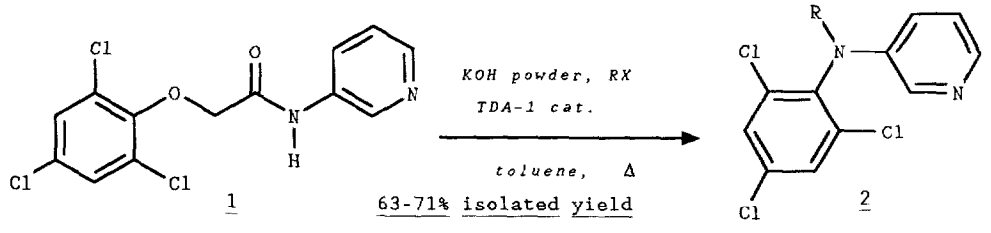
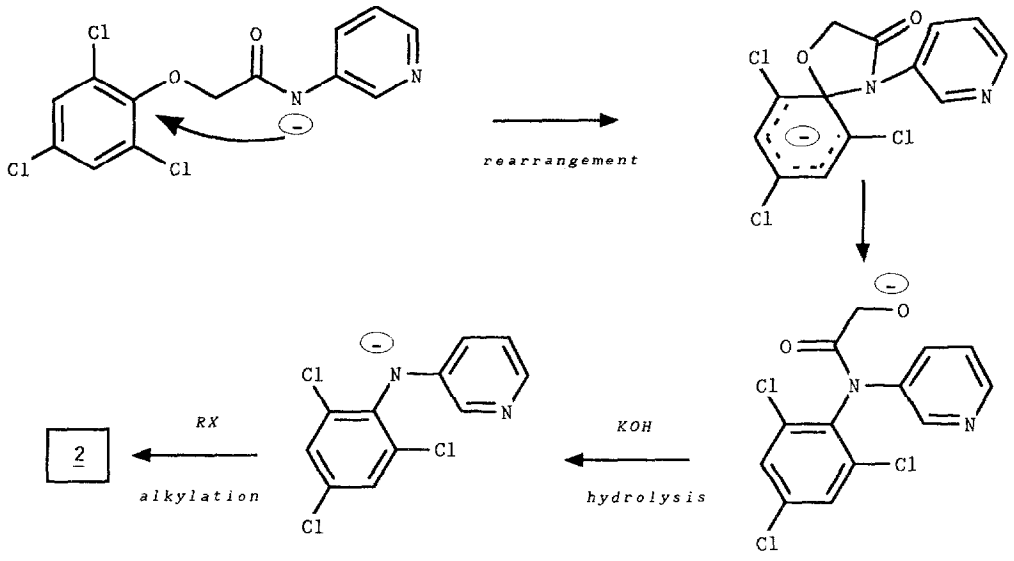
SUMMARY : Attempted N-alkylation of 3-(2,4,6-trichlorophenoxyacetamido) pyridine, with TDA-1 catalysis, yielded surprisingly N-alkylated 3-(2,4,6-trichlorophenylamino)pyridines through a Smiles rearrangement.

TDA-1 [tris(3,6-dioxaheptylamine)] has been shown to be a very efficient solid-liquid phase transfer catalyst [1] . During a study on the N-alkylation of chlorinated phenoxyacetamides , a surprising Smiles rearrangement [2] of 3-(2,4,6-trichlorophenoxyacetamido)pyridine was observed with this catalyst and powdered KOH [3] . Whilst N-alkylation of the sodium salt generated by sodium hydride was slow in polar aprotic solvents like DMSO, DMF or NMP, even at reflux, with lower alkylbromides (ethyl, propyl, butyl, isopropyl and isobutyl), a surprisingly quick reaction took place in toluene in the presence of TDA-1 . Structural analysis (IR and NMR) showed no evidence of an acetamide moiety and mass spectrometry suggested the structure to be a N-alkyl N-(2,4,6-trichlorophenyl) 3-aminopyridine [4,5,6].



R= a: ethyl; b: n-propyl; c: i-propyl; d: n-butyl; e: i-butyl

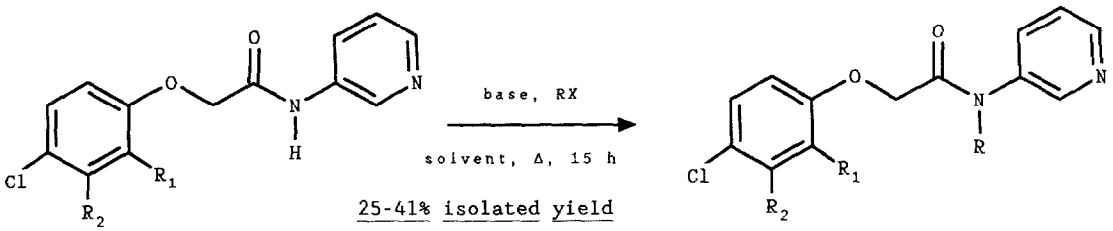
Undoubtedly, these products arise from a very fast Smiles rearrangement, followed by hydrolysis of the amide function and N-alkylation of the resulting amine.



Smiles rearrangement of phenoxyacetamides of this type has been shown to occur, but the need for strong electron withdrawing groups and alpha substitution [7] or presence of an alkoxide anion in close vicinity [8] has been stressed. On the other hand, halogen activation has been demonstrated in the more classical Smiles rearrangement of α-aminodiarylethers, where the cyclic transition state is favored by the second aromatic ring.

To investigate the effect of the halogens, control experiments have been carried out on less chlorinated phenoxyacetamides. 2,4,6-Trichloro substitution on the phenyl ring was essential for the Smiles pathway to occur. Mono and dichloro-derivatives gave clean N-alkylation of the acetamide using potassium carbonate as a base (to depress the competing amide hydrolysis occurring with KOH) in toluene/acetonitrile (**3** and **4**) or using sodium hydride in dimethylsulfoxide (**5**), but at a very slow rate and heating for several hours was necessary [9].

A kinetic study showed the dramatic effect of 2,4,6-trichloro substitution which gave a complete rearrangement of the sodium salt of **1** in xylene at room temperature (2 h). The sodium salt of the 3,4-dichloro



reaction conditions:

-Proc.A: *K_2CO_3, toluene/acetonitrile 4:1, TDA-1 0.1 eq., 100°*

-Proc.B: *NaH, DMSO, 100°*

3 : R_1,R_2= H ; 4 : R_1= H, R_2= Cl ; 5 : R_1= Cl, R_2=H

derivative **4** needed 60° for the rearrangement to start and 75 h at 90° to go to completion whilst the 2,4-dichloro derivative **5**, as its sodium salt, started to react at 90° and was completely transformed after 70 h at 110°. In no case did any reaction occur without the TDA-1 catalyst.

These results show the powerful activation of the TDA-1 catalyst and the peculiar effect of a 2,4,6-trichloro substitution. A related activation occurs in the reactivity of hexachlorobenzene towards a variety of nucleophiles [10] . Extension of this rearrangement could provide an easy access to the otherwise difficultly obtained N-(2,4,6-trichlorophenyl) N-aryl amines [11].

General procedure for synthesis of N-alkyl N-(2,4,6-trichlorophenyl) 3-aminopyridines from 3-(2,4,6-trichlorophenoxyacetamido)pyridine:

A mixture of powdered KOH (2.3 g, 36 mM) ,TDA-1 (0.1 ml, 3 mM) and 3-(2,4,6-trichlorophenoxyacetamido)pyridine (3.0 g, 9 mM) in dry toluene (50 ml) at 50°, is treated with a toluene solution of the alkyl bromide (18 mM), heated to reflux until the starting material has disappeared on TLC (0.5 to 1.5 h), diluted with water (300 ml), extracted with ethyl acetate (2x100 ml), concentrated under vacuum and the oily residue purified by column chromatography using a 3:1 CH_2Cl_2/CH_3CN solvent mixture. The purified compound is recristallized in Heptane.

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References and Notes

1) G. SOULA *J. Org.Chem.* (1985) **50**, 3717
2) For a review on SMILES rearrangement see: W.E. TRUCE, E.M. KREIDER, W.W. BRAND *Org. React.* (1970) **18**, 99
3) R.A.W. JOHNSTONE, M.E. ROSE *Tetrahedron* (1979) **35**, 2169
4) These new compounds were identical with authentic samples prepared by arylation of 3-acetamidopyridine with bromobenzene followed by hydrolysis, chlorination and subsequent alkylation.
5) All compounds **2** gave satisfactory structural analysis (IR, ^{1}NMR, MS) ; yields have not been optimized: **2b** Yield: 63%; mp: 89°(heptane); NMR: ^{1}H ($CDCl_3$): $C\underline{H}_3$-CH_2-CH_2: 0.96 (3p,t); CH_3-$C\underline{H}_2$-CH_2: 1.68 (2p,m); CH_2-$C\underline{H}_2$-N: 3.52 (2p,t); Py-H: 6.68 (1p,m) 7.08 (1p,dd) 7.68 (1p,d) 8.04 (1p,d); Ph-H: 7.48 (2p,s) **2c** Yield: 70%; oil; NMR: ^{1}H ($CDCl_3$): $C\underline{H}_3$-CH: 1.28 (6p,d); CH_3-$C\underline{H}$-N: 4.24 (1p,m); Py-H: 6.76 (1p,m) 7.12 (1p,dd) 7.92 (1p,d) 8.04 (1p,dd); Ph-H: 7.48 (2p,s). MS: (CI/NH_3) M+1 at m/z: 315 (3^5Cl). **2d** Yield: 67%; mp: 57°(heptane); NMR: ^{1}H ($CDCl_3$): $C\underline{H}_3$-CH_2: 0.96 (3p,t); CH_3-$C\underline{H}_2$-$C\underline{H}_2$-CH_2: 1.68 (4p,m); CH_2-$C\underline{H}_2$-N: 3.52 (2p,t); Py-H: 6.68 (1p,m) 7.08 (1p,dd) 7.68 (1p,d) 8.04 (1p,dd); Ph-H: 7.48 (2p,s). **2e** Yield: 71%; mp: 74°(heptane); NMR: ^{1}H ($CDCl_3$): $C\underline{H}_3$-CH: 1.00 (6p,d); CH_3-$C\underline{H}$-CH_2: 2.00 (1p,m); CH-$C\underline{H}_2$-N: 3.44 (2p,d); Py-H: 6.72 (1p,m) 7.08 (1p,dd) 7.92 (1p,d) 8.04 (2p,dd); Ph-H: 7.48 (2p,s).
6) These products , and related compounds with different aromatic substitution show a strong fungicidal effect on a wide range of plant pathogenic microorganisms. Synthesis and biological results will be published elsewhere.
7) R. BAYLES, M.C. JOHNSON, R.F. MAISEY, R.W. TURNER *Synthesis* (1977) 31,33
8) W.R. BAKER *J. Org. Chem.* (1983) **48**, 5140
9) All spectral data (IR, NMR) of compounds **3** , **4** and **5** were in agreement with the expected structures. Yields were not optimized as the slow alkylation reaction was always interrupted after 15h of heating. Physical data of some characteristic representatives are given below. **3b** Yield: 39% (Proc. A); mp: 78°; NMR: ^{1}H ($CDCl_3$): $C\underline{H}_3$-CH_2: 0.88 (3p,t); CH_3-$C\underline{H}_2$: 1.56 (2p,m); CH_2-$C\underline{H}_2$-N: 3.68 (2p,t); O-$C\underline{H}_2$-CO: 4.36 (2p,s); Ph-H: 6.64 (2p,d) 7.20 (2p,d); Py-H: 7.40 (1p,m) 7.56 (1p,m) 8.52 (1p,dd) 8.68 (1p,dd). **3d** Yield: 41% (Proc. A); mp: 96°; NMR: ^{1}H ($CDCl_3$): $C\underline{H}_3$-CH_2: 0.88 (3p,t); CH_3-$C\underline{H}_2$: 1.32 (2p,m); CH_2-$C\underline{H}_2$-CH_2: 1.50 (2p,m); CH_2-$C\underline{H}_2$-N: 3.72 (2p,t); O-$C\underline{H}_2$-CO: 4.36 (2p,s); Ph-H: 6.64 (2p,d) 7.14 (2p,d); Py-H: 7.40 (1p,m) 7.52 (1p,m) 8.48 (1p,d) 8.62 (1p,d). **4b** Yield: 32% (Proc. A); mp: 82°; NMR: ^{1}H ($CDCl_3$): $C\underline{H}_3$-CH_2: 0.92 (3p,t); CH_3-$C\underline{H}_2$: 1.56 (2p,m); CH_2-$C\underline{H}_2$-N: 3.70 (2p,t); O-$C\underline{H}_2$-CO: 4.36 (2p,s); Ph-H: 6.62 (1p,dd) 6.82 (1p,d) 7.30 (1p,d); Py-H: 7.42 (1p,m) 7.58 (1p,m) 8.54 (1p,d) 8.62 (1p,d). **4d** Yield: 34% (Proc. A); mp: 106°; NMR: ^{1}H ($CDCl_3$): $C\underline{H}_3$-CH_2: 0.88 (3p,t); CH_3-$C\underline{H}_2$-$C\underline{H}_2$-CH_2: 1.40 (4p,m); CH_2-$C\underline{H}_2$-N: 3.72 (2p,t); O-$C\underline{H}_2$-CO: 4.36 (2p,s); Ph-H: 6.64 (1p,dd) 6.80 (1p,d) 7.28 (1p,d); Py-H: 7.44 (1p,m) 7.56 (1p,m) 8.52 (1p,m) 8.72 (1p,m). **5a** Yield: 37% (Proc. B); mp: 98°; NMR: ^{1}H ($CDCl_3$): $C\underline{H}_3$-CH_2: 1.16 (3p,t); CH_3-$C\underline{H}_2$-N: 3.80 (2p,q); O-$C\underline{H}_2$-CO: 4.48 (2p,s); Ph-H: 6.74 (1p,d) 7.14 (1p,dd) 7.36 (1p,d); Py-H: 7.48 (1p,m) 7.60 (1p,m) 8.56 (1p,d) 8.68 (1p,d). **5e** Yield: 37% (Proc. B); mp: 98°; NMR: ^{1}H ($CDCl_3$): $C\underline{H}_3$-CH: 0.92 (6p,d); CH_3-$C\underline{H}$-CH_2: 1.80 (1p,m); CH-$C\underline{H}_2$-N: 3.60 (2p,d); O-$C\underline{H}_2$-CO: 4.48 (2p,s); Ph-H: 6.72 (1p,d) 7.12 (1p,dd) 7.32 (1p,d); Py-H: 7.40 (1p,m) 7.60 (1p,m) 8.52 (1p,d) 8.64 (1p,d).
10) A.L. ROCKLIN *J. Org. Chem.* (1956) **21**, 1478
11) For another access to such compounds see: A.W. CHAPMAN *J.Chem.Soc.* (1929) 569.

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