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PHASE TRANSFER CATALYZED SYNTHESIS OF AMIDES AND ESTERS OF 2,4-DICHLOROPHENOXYACETIC ACID

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Abstract A convenient procedure is reported for the preparation of amides and esters via the reaction of 2,4-dichlorophenoxyacetyl chloride with amines or phenols under the condition of liquid-liquid phase transfer catalysis using polyethylene gtycol-600 as the catalyst. The products have been characterised on the basis of analytical and spectral (IR and H-NMR) data.

2, 4-Dichlorophenoxyacetic acid and its derivatives have found extensive applications in the field of agriculture. Some of them, such as 2,4-D, 2,4-D amine salt, 2, 4-D ester, and Tomacon have been used as herbicides and plant-growth regulators[1-4]。 In view of these observation and in continuation of our earlier work on the synthesis and biological activity of aryloxyacetic acid derivatives[5-9], we report herein a convenient and efficient procedure for the preparation of amides and esters of 2,4-dichlorophenoxyacetic acid under the condition of liquid-liquid phase transfer catalysis using PEG-600 as the catalyst.

The reaction sequence leading to the formation of the title compounds is shown in scheme 1. 2,4-dichlorophenol was allowed to react with monochloroacetic acid in the presence of polyethylene glycol-600(PEG-600) and KI with powdered K_2CO_3 in toluene

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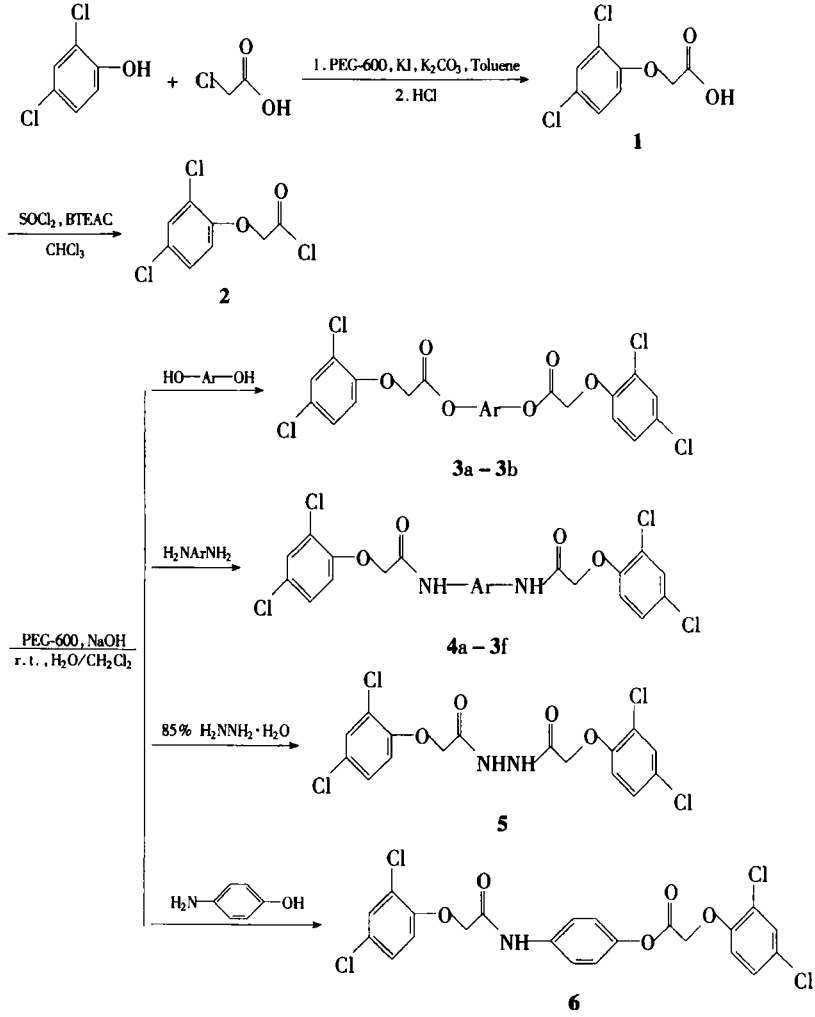
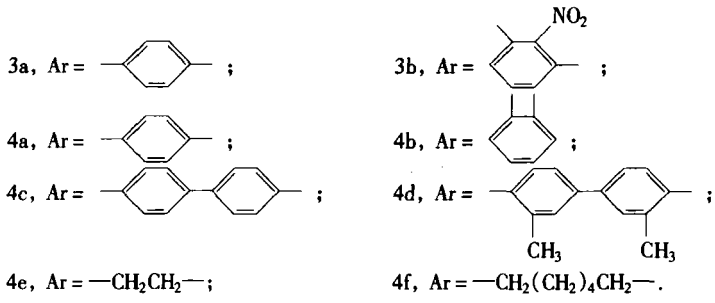
to give potassium 2, 4-dichlorophenoxyacetate, which was acidified with hydrochloric acid to yield 2, 4-dichlorophenoxyacetic acid (1). Compound 1 was treated with an excess of thionyl chloride in the presence of benzyltriethylammonium chloride in chloroform to offer the corresponding acyl chloride (2). Under liquid-liquid phase transfer catalysis condition, using 3mmol% PEG-600 as the catalyst and sodium hydoxide as a base, compound 2 reacted with various amines or phenols in H_2O/CH_2Cl_2 to yield the title compounds in excellent yield.





Scheme 1

The use of phase transfer catalysis, PTC, for nucleophilic substitution reactions is well documented[10], however, PTC reactions at an acyl carbon are much less common, Weber has reported the preparatian of benzoyl cyanide[11]. Illi has used PTC to acylate sterically crowded phenols[12]. Mathias has reported N-acylation reactions under invevse phase transfer catalysis condition[13]. In recent years, we hove focused our attention to PTC nucleophilic acylation reactions and obtained good results[14-16].

Aryloxyacetic acid esters and amides have been made available by reaction of aryloxyacetic acids with substituted phenols or aniline in the presence of concentrated sulfuric acid. However, high temperature and a long reaction times are required for their preparation[17-18]. We have found that phase transfer catalysis offers an attractive alternative for the preparation of the title compounds. Compared with classical method, this procedure has the advantages of mild conditions, simple operation, short reaction times and high yield. The catalyst PEG-600 is inexpensive, relatively nontoxic, high stable and easily available.

Experimental Procedures

IR Spectra were recorded using KBr pellets on an Alpha Centauri FT-IR spectrophotometer and ^{1}H-NMR spectra on a FT-80A instrument, DMSO-d_6 was used as solvent and Me_4Si as internal standard. Elemental analyses were performed on a PE-

2400 CHN instrument. Mps were observed in an open capillary tube and are uncorrected.

Preparation of 2,4-dichlorophenoxyacetic acid(1)

2,4-Dichlorophenol(32.6 g,0.2 mol) was used as received, K_2CO_3(55.2 g,0.4 mol), KI(3.2 g 0.02 mol), PEG-600(7.2 g,0.012 mol), and 120 ml of anhydrous toluene were added to a dry, three-neck, 250 ml round-bottomed flask equipped with a condenser and magnetic stirring bar and stirred at 100℃ for 15 min, and then a solution of monochloroacetic acid(19 g,0.2 mol) in toluene(80 ml) was added dropwise over 30 min. Heating and stirring were maintained for 1.5 hrs. The reaction mixture was cooled to 60℃ and added 150 ml of water, The water layer was separated and acidified with hydrochloric acid, a precipitate formed which was collected by fitration. The solid product was crystallized from benzene to give white crystals; yield 41.5 g(94%); m.p. 138-140℃(lit. m.p. 138℃)[1]

Preparation of 2,4-dichlorophenoxyacetyl chloride(2)

To a dry, three-neck, magnetically stirred, 100 ml round-bottomed flask, equipped with a gas bubbler is added compound **1**(20 g,90.5 mmol), $SOCl_2$(20 ml,276 mmol), chloroform(50 ml) and benzyltriethylammonium chloride(0.55 g, 2.4 mmol). The mixture was refluxed for 4 hrs. The excess thionyl chloride and chloroform distilled off at atmospheric pressure. The product was then distilled at 180 mm from a claisen flask connected directly to a water-cooled receiver, The acyl chloride crystallized out in the receiver in white needle-like crystals; m. p. 44 ~ 45℃ (lit.[19] 44.5 – 45.5℃); yield 18.5 g (85%)

Tipical procedure for the preparation of compound 3a

2,4-Dichlorophenoxyacetyl chloride(1.45 g,6.08 mmol), hydroquinone(0.33 g, 3 mmol), NaOH(0.24 g,6 mmol), PEG-600(0.108 g,0.18 mmol), dichloromethane (20 ml) and water(15 ml) were placed in a round-bottomed flask containing a magnetic stirrer bar. The mixture were stirred at room temperature for 1 hr. Then the orgaic layer was separatcd, water phase was extracted with dichloromethane (5 ml × 2). The

combined organic phase was dried over sodium sulfate(anhydrous) and evaporated. The crude product was crystallized from absolute alcohol to give pure product **3a**.

All the other compounds(**3b**, **4a – 4f**, **5**, **6**) were prepared similarly.

Compound **3a**: 93% yield; m. p. 168 – 169℃; IR(KBr): 1781(C═O)cm^{-1}; ^{1}H-NMR(80 MHz, DMSO-d_6): δ 5.01 (s, 4H, $CH_2 \times 2$), 6.96 – 7.81(m, 10H, Ar—H); Anal. calcd. for $C_{22}H_{14}Cl_4O_6$: C, 51.19; H, 2.73. Found: C, 51.31; H, 2.69.

Compound **3b**: 76% yield; m. p. 153 – 154℃; IR(KBr): 1776(C═O) cm^{-1}; ^{1}H-NMR (80 MHz, DMSO-d_6): δ4.98(s, 4H, $CH_2 \times 2$), 6.89 ~ 7.86(m, 9H, Ar—H); Anal. calcd. for $C_{22}H_{13}Cl_4NO_8$: C, 48.09; H, 2.34; N, 2.49. Found: C, 47.17; H, 2.43; N, 2.51.

Compoumd **4a**: 98% yield; m. p. 241 – 242; IR (KBr): 3359 (N—H), 1678 (C═O)cm^{-1}; ^{1}H-NMR(80 MHz, DMSO-d_6): δ 4.80(s, 4H, $CH_2 \times 2$), 7.09 – 7.86 (m, 10H, Ar—H), 10.18(s, 2H, NH × 2); Anal. calcd. for $C_{22}H_{16}Cl_4N_2O_4$; C, 51.39; H, 3.14; N, 5.45. Found: C, 51.36; H, 3.27; N, 5.59.

Compound **4b**: 96% yield; m. p. 216 – 217℃; IR (KBr): 3364 (N—H), 1679 (C═O) cm^{-1}; ^{1}H-NMR(80 MHz, DMSO-d_6): δ 4.85(s, 4H, $CH_2 \times 2$), 7.07 – 7.72(m, 10H, Ar—H), 9.95(s, 2H, NH × 2); Anal. cacld. for $C_{22}H_{16}Cl_4N_2O_4$: C, 51.39; H, 3.14; N, 5.45. Found: C, 51.73; H, 3.18; N, 5.41.

Compound **4c**: 99% yield; m. p. > 250℃; IR (KBr): 3385 (N—H), 1686 (C═O) cm^{-1}, ^{1}H-NMR(80 MHz, DMSO-d_6): δ 4.89 (s, 4H, $CH_2 \times 2$), 7.13 – 7.79 (m, 14H, Ar—H), 10.07(s, 2H, NH × 2); Anal. calcd, for $C_{28}H_{20}C_{14}N_2O_4$: C, 56.97; H, 3.42; N, 4.75. Found: C, 56.83; H, 3.52; N, 4.86.

Compound **4d**: 98% yield; m. p. > 245℃; IR (KBr): 3387 (N—H), 1691 (C═O) cm^{-1}; ^{1}H-NMR(80 MHz, DMSO-d_6): δ 4.86(s, 4H, $CH_2 \times 2$), 7.10 – 7.76(12H, Ar—H), 2.13(s, 6H, $CH_3 \times 2$), 10.16(s, 2H, NH × 2); Anal. calcd. for $C_{30}H_{24}Cl_4N_2O_4$: C, 58.27; H, 3.91; N, 4.53. Found: C, 58.35; H, 3.96; N, 4.38.

Compound **4e**: 84% yield; m. p. 251 – 252℃; IR (KBr): 3324 (N—H), 1689 (C═O) cm^{-1}; ^{1}H-NMR(80 MHz, DMSO-d_6): δ 3.19 – 3.29(m, 4H, $NCH_2 \times 2$),

4.57(s,4H,$OCH_2 \times 2$),7.06 - 7.57 (m,6H,Ar—H),8.03(s,2H,NH × 2); Anal. calcd. for $C_{18}H_{16}Cl_4N_2O_4$: C,46.38; H,3.46; N,6.01. Found: C,46,52; H,3.41; N, 6.18.

Compound **4f**: 92% yield; m. p. 160 - 161℃; IR (KBr): 3324 (N—H), 1688 (C═O) cm^{-1}; ^{1}H-NMR(80 MHz, DMSO-d_6): δ 1.13 - 1.54 (m,8H, $CH_2 \times 4$), 3.06(t,4H, $NCH_2 \times 2$, J = 5 Hz),7.06 - 7.62(m,6H, Ar—H),8.04(s,2H, NH × 2); Anal. calcd. for $C_{22}H_{24}Cl_4N_2O_4$; C,50.59; H,4.63; N,5.38. Found: C,50.63; H, 4.81; N,5.42.

Compound **5**: 83% yield; m. p. 217 - 218℃; IR (KBr): 3221 (N—H), 1658 (C═O) cm^{-1}; ^{1}H-NMR(80 MHz, DMSO-d_6): δ 4.82(s,4H, $CH_2 \times 2$),7.07 - 7.82 (m, 6H, Ar—H), 10.02(s, 1H, NH), 10.05(s, 1H, NH); Anal. calcd. for $C_{16}H_{12}Cl_4N_2O_4$: C,43.86; H,2.76; N,6.39. Found: C,43.92; H,2.71; N,6.45.

Compound **6**: 72% yield; m. p. 159 - 160℃; IR (KBr): 3216 (N—H), 1774 (C═O),1669(C═O) cm^{-1}; ^{1}H-NMR (80 MHz, DMSO-d_6): δ 4.86(s,2H, CH_2),5.01(s,2H, CH_2),6.87 - 7.79(m,10H, Ar—H),9.86(s,1H, NH); Anal. cald. for $C_{22}H_{15}Cl_4CO_5$: C,51.29; H,2.94; N,2.72. Found; C,51.33; H,3.18; N, 2.59.

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