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PHASE TRANSFER CATALYZED SYNTHESES OF 4-CARBOXYLPHENOXYACETIC ACID DERIVATIVES

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ABSTRACT: A series of new aryl 4-carboaryloxyphenoxyacetates (**3a-e**) and 4-carboanilinophenoxyacetanilides (**3f-s**) are synthesized by the reactions of 4-chloroformylphenoxyacetyl chloride with substituted phenols or aromatic amines via liquid-liquid phase transfer catalysis using PEG-400 as the catalyst.

Aryloxyacetic acid and their derivatives usually possess many important biological activities, studies on the syntheses and biological activities of them have received much attention[1-3]. Our research group has synthesized a large quantity of aryloxyacetic acid derivatives, some of them have been used as plant-growth regulators[4-9]. We now report the preparation of some new aryl 4-carboaryloxyphenoxyacetates and 4-carboanilinophenoxyacetanilides under the

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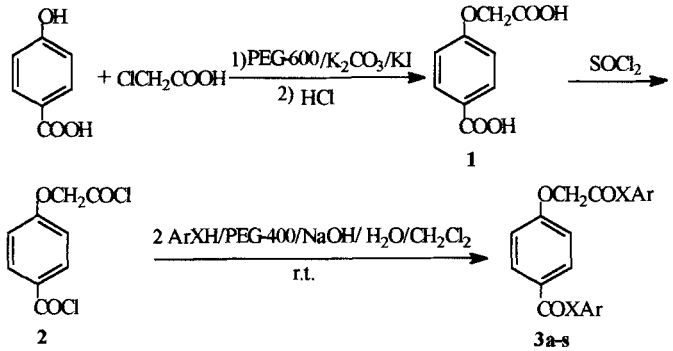
condition of phase transfer catalysis using polyethylene glycol (PEG) as the catalyst.

4-hydroxybenzoic acid is condensed with chloroacetic acid in the presence of anhydrous potassium carbonate, PEG-600 and potassium iodide as phase transfer catalyst to give the corresponding disodium salt, which on acidification with aqueous hydrochloric acid yields 4-carboxylphenoxyacetic acid (**1**). Further, treatment of compound **1** with an excess of thionyl chloride at refluxing temperature of thionyl chloride obtains the corresponding acyl chloride **2**. Under the condition of liquid-liquid phase transfer catalysis, using PEG-400 as the catalyst and aqueous sodium hydroxide as the base, compound **2** is reacted with substituted phenols and aromatic amines respectively to yield the title compounds **3a-s** in good to excellent yields (Scheme).

Two kinds of phase transfer catalysts have been used in this route to prepare title compounds. PEG-600 as the solid-liquid phase transfer catalyst can greatly improve the yield of compound **1** compared with the previous method[10]. PEG-400 as the liquid-liquid phase transfer catalyst has shown an obvious catalytic effect on the acylation reactions of obtaining compound **3**. For example, the yield of compound **3g** can reach 84% under the PEG-400 catalytic condition, in contrast, the yield of **3g** is only 61% in the absence of PEG-400 according to our experiments.

In conclusion, phase transfer catalysis as the new method to prepare title compounds has become an attractive alternative. The obvious advantages of this method compared with previous ones are mild conditions, simple operation, high yields and low cost catalysts.

Scheme



3	X	Ar	3	X	Ar
3a	O	2,6-$(O_2N)_2C_6H_3$	**3k**	NH	4-$CH_3COC_6H_4$
3b	O	2,4-$Cl_2C_6H_3$	**3l**	NH	2-ClC_6H_4
3c	O	4-ClC_6H_4	**3m**	NH	4-$CH_3CONHC_6H_4$
3d	O	1-Naphthyl	**3n**	NH	2-$CH_3OC_6H_4$
3e	O	8-Quinolyl	**3o**	NH	3-$CH_3C_6H_4$
3f	NH	C_6H_5	**3p**	NH	2-$CH_3C_6H_4$
3g	NH	2-$O_2NC_6H_4$	**3q**	NH	2-Thiazolyl
3h	NH	3-$O_2NC_6H_4$	**3r**	NH	4-(2,4-$(O_2N)_2C_6H_3O$)C_6H_4
3i	NH	4-$O_2NC_6H_4$	**3s**	NH	4-(4-$O_2NC_6H_4O$)C_6H_4
3j	NH	4-ClC_6H_4			

EXPERIMENTAL SECTION

IR spectra were recorded using KBr pellets on an Alpha Centauri FTIR spectrophotometer and ^1H NMR spectra on a FT-80A instrument using $(CD_3)_2SO$

as solvent and Me_4Si as internal standard. Elemental analyses were performed on a Carlo-Erba 1106 Elemental Analysis instrument. Melting points were observed in an open capillary tube and uncorrected.

Preparation of 4-carboxylphenoxyacetic acid (1)

A suspension of 4-hydroxybenzoic acid (27.6g, 0.2mol), anhydrous potassium carbonate (55.2g, 0.4mol), PEG-600 (3.6g, 6mmol) and potassium iodide (0.17g, 1mmol) in 90ml of toluene was stirred for 15 minutes at 100℃, then a solution of monochloroacetic acid (18.9g, 0.2mol) in 30ml of toluene was added dropwise within 0.5h. The mixture was stirred for another 1.5h at 105-110 ℃. After cooled to 60℃, water was added to the mixture until the solid was dissolved, then the organic layer was removed and water layer was acidified with hydrochloric acid to PH=3.The separated solid was recrystallized from acetic acid to give compound **1** (36.5g, 93% yield). m.p.279-280℃. Cacld.for $C_9H_8O_5$: C,55.51; H,4.11. Found: C,55.47, H,4.14. IR (KBr):3300-2400(COOH), 1738(C=O), 1244(C-O-C), 1600, 1505(Ar). ^1H NMR (DMSO-d_6): 4.76(s,2H,OCH_2), 6.92-8.16(m,4H,ArH), 12.91(s,1H,COOH).

Preparation of 4-chloroformylphenoxyacetyl chloride (2)

4-carboxylphenoxyacetic acid (**1**) (19.6g, 0.1mol) and thionyl chloride (50ml) were refluxed on a water-bath for 6h. The excess of thionyl chloride was removed by distillation under the reduced pressure and the resulting solid was

Table 1 Physical and analytical data for **3a-s**

3	m.p. (℃)	Yield (%)#	Molecular formula	C	H	N
				Found (Calcd.)		
3a	183-184	75	$C_{21}H_{12}N_4O_{13}$	47.42 (47.74)	2.25 (2.29)	10.35 (10.60)
3b	134-135	82	$C_{21}H_{12}Cl_4O_5$	51.74 (51.88)	2.43 (2.47)	
3c	184-185	88	$C_{21}H_{14}Cl_2O_5$	59.89 (60.45)	3.72 (3.38)	
3d	145-146	89	$C_{29}H_{20}O_5$	77.45 (77.69)	4.42 (4.50)	
3e	153-154	85	$C_{27}H_{18}N_2O_5$	71.80 (71.83)	4.11 (4.24)	6.02 (6.21)
3f	223-224	98	$C_{21}H_{18}N_2O_3$	72.61 (72.82)	5.22 (5.24)	8.03 (8.09)
3g	267-268	84	$C_{21}H_{16}N_4O_7$	57.64 (57.80)	3.67 (3.70)	12.68 (12.84)
3h	266-267	96	$C_{21}H_{16}N_4O_7$	57.65 (57.80)	3.69 (3.70)	12.60 (12.84)
3i	293-294	80	$C_{21}H_{16}N_4O_7$	57.80 (57.80)	3.68 (3.70)	12.71 (12.84)
3j	246-247	84	$C_{21}H_{16}Cl_2N_2O_3$	60.51 (60.74)	3.72 (3.88)	6.71 (6.75)
3k	302-303	74	$C_{25}H_{22}N_2O_5$	69.68 (69.75)	5.08 (5.14)	6.50 (6.51)
3l	208-209	80	$C_{21}H_{16}Cl_2N_2O_3$	60.63 (60.74)	3.74 (3.88)	6.62 (6.75)
3m	355-356	83	$C_{25}H_{24}N_4O_5$	65.11 (65.21)	5.14 (5.25)	12.11 (12.17)
3n	204-205	82	$C_{23}H_{22}N_2O_5$	67.88 (67.97)	5.38 (5.46)	6.81 (6.89)
3o	172-173	81	$C_{23}H_{22}N_2O_3$	73.69 (73.78)	5.84 (5.92)	7.31 (7.48)
3p	198-199	86	$C_{23}H_{22}N_2O_3$	73.64 (73.78)	5.87 (5.92)	7.37 (7.48)
3q	247-248	83	$C_{15}H_{12}N_6O_3S_2$	49.93 (49.99)	3.22 (3.36)	15.50 (15.55)
3r	271-272	84	$C_{33}H_{22}N_6O_{13}$	57.69 (57.78)	3.02 (3.12)	11.73 (11.83)
3s	220-221	79	$C_{33}H_{24}N_4O_9$	63.74 (63.87)	3.85 (3.90)	8.91 (9.03)

Based on ArXH (X=O, NH)

Table 2 ^{1}H NMR spectral data for **3a-s**

3	δ
3a	5.11(2H,s,CH_2), 7.12-8.14(10H,m,Ar)
3b	5.21(2H,s,CH_2), 7.32-7.81(10H,m,Ar)
3c	5.01(2H,s,CH_2), 7.04-8.02(12H,m,Ar)
3d	5.18(2H,s,CH_2), 7.26-8.12(18H,m,Ar)
3e	5.16(2H,s,CH_2), 7.28-8.13(16H,m,Ar)
3f	4.80(2H,s,CH_2), 7.10-7.84(14H,m,Ar), 10.04(1H,s,NH), 10.10(1H,s,NH)
3g	4.86(2H,s,CH_2), 7.24-8.21(12H,m,Ar) , 10.24(1H,s,NH), 10.32(1H,s,NH)
3h	4.84(2H,s,CH_2), 7.31-8.71(12H,m,Ar) , 10.14(1H,s,NH), 10.25(1H,s,NH)
3i	4.92(2H,s,CH_2), 7.25-8.34(12H,m,Ar) , 10.58(1H,s,NH), 10.67(1H,s,NH)
3j	4.81(2H,s,CH_2), 7.20-7.81(12H,m,Ar) , 10.12(1H,s,NH), 10.23(1H,s,NH)
3k	2.54(6H,s,CH_3), 4.84(2H,s,CH_2), 7.27-7.92(12H,m,Ar) , 10.24(1H,s,NH), 10.31(1H,s,NH)
3l	4.76(2H,s,CH_2), 7.23-7.72(12H,m,Ar) , 10.01(1H,s,NH), 10.21(1H,s,NH)
3m	2.14(6H,s,CH_3), 4.81(2H,s,CH_2), 7.28-8.02(12H,m,Ar) , 10.12(1H,s,NH), 10.24(1H,s,NH) , 10.56(1H,s,NH) , 10.61(1H,s,NH)
3n	3.82(6H,s,CH_3),4.82(2H,s,CH_2), 7.35-8.12(12H,m,Ar) , 10.42(1H,s,NH), 10.50(1H,s,NH)
3o	2.26(6H,s,CH_3),4.78(2H,s,CH_2), 7.13-8.02(12H,m,Ar) , 9.98(1H,s,NH), 10.01(1H,s,NH)
3p	2.28(6H,s,CH_3),4.77(2H,s,CH_2), 7.15-8.04(12H,m,Ar) , 10.02(1H,s,NH), 10.04(1H,s,NH)
3q	4.81(2H,s,CH_2), 7.40-8.12(8H,m,Ar) , 10.51(1H,s,NH), 10.54(1H,s,NH)
3r	4.83(2H,s,CH_2), 7.38-8.51(18H,m,Ar) , 10.54(1H,s,NH), 10.61(1H,s,NH)
3s	4.81(2H,s,CH_2), 7.32-8.42(20H,m,Ar) , 10.08(1H,s,NH), 10.14(1H,s,NH)

Table 3 IR spectra data of **3a-s** (ν_{max} ,cm^{-1})

3	NH	C=O	Ar-O
3a		1758, 1714	1173, 1154
3b		1798, 1716	1156, 1133
3c		1785, 1722	1162, 1124
3d		1783, 1728	1150, 1130
3e		1756, 1728	1173, 1161
3f	3391, 3053	1664, 1651	
3g	3366, 3303	1706, 1677	
3h	3356, 3087	1677	
3i	3372, 3330	1704, 1658	
3j	3386, 3346	1669	
3k	3363, 3310	1670, 1658	
3l	3437, 3381	1703, 1658	
3m	3384, 3363	1704, 1674	
3n	3447, 3390	1684	
3o	3403, 3367	1673, 1658	
3p	3287, 3274	1681, 1636	
3q	3227	1696	
3r	3380, 3148	1670, 1645	
3s	3393, 3382	1678	

recrystallized from chloroform, and the crystal of compound **2** was given (21.2g, 91% yield). m.p. 85.5-86.5℃. Cacld. For $C_9H_6Cl_2O_3$: C,46.38; H,2.59. Found: C,46.42; H,2.56. IR (KBr): 1804 (C=O), 1602, 1502 (Ar), 1212 (C-O-C). ^1H NMR (DMSO-d_6): 5.02 (s,2H,OCH_2), 6.90-8.16 (m,4H,ArH).

General procedure for preparation of compound 3

To a suspension of 4-chloroformylphenoxyacetyl chloride (0.58g, 2.5mmol), substituted phenol or aniline (5mmol), PEG-400 (0.1g, 0.25mmol) in 20ml of dichloroethane, a solution of sodium hydroxide (0.2g, 5mmol) in 10ml of water was added. The mixture was stirred for 1h at room temperature, then the organic layer was separated, and the water phase was extracted with methylene chloride (5mlx2). The resulting organic phase was dried over anhydrous sodium sulfate. After removal of solvent, the crude product was recrystallized from ethanol or acetic acid, and compound **3** was given. The physical, elemental and spectral data are summarized in Table 1-3.

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