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# Solid Superacid Catalyzed Efficient Synthesis of 2-Diethylaminoethyl Aryloxyacetates

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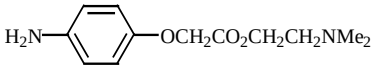
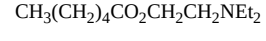
**Abstract:** 2-Diethylaminoethyl aryloxyacetates are prepared efficiently in 75~95% yields by condensation of the corresponding aryloxyacetic acids with 2-diethylaminoethanol in the presence of catalytic amount of solid superacid $SO_4^{2-}/Fe_2O_3$.

**Keywords:** Solid superacid, esterification, diethylaminoethyl aryloxyacetate, catalyst.

2-Dialkylaminoethyl esters have been found to possess many interesting biological activities. For examples, procaine **1** is a well known local anesthetic agent in clinical use, 2-diethylaminoethyl hexanoate **2** promotes the growth of crops[1] and efficiently induces the biosynthesis of β-carotene[2], 2-diethylaminoethyl cyclohexyloxyacetate **3** has anti-acetyl choline activity[3] while 2-dimethylaminoethyl 4-chlorophenoxyacetate hydrochloride **4** displays a range of pharmacological properties such as anti-stress, anti-aging, anesthetic, reducing of pigment accumulation in aged people *etc*[4]. As a consequence, the development of efficient methods for the synthesis of these 2-dialkylaminoethyl carboxylates has attracted considerable attention and several methods for their synthesis have been reported[5]. These reported methods can be grouped into two major categories, *i.e*., direct condensation[5a] of a carboxylic acid or also can gain its acid derivative[5b-c], such as the anhydride or acyl chloride, reacted with 2-dialkylaminoethanol **5**, by transesterification[5d-e] of an alkyl (or aryl) carboxylate with **5**. All these methods, however, have some drawbacks such as the use of harsh reaction conditions and environmental unfriendly reagents [5a], required multi-reaction steps[5d-e] or give low yields of the desired products.




**1**

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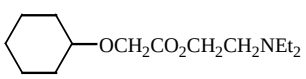


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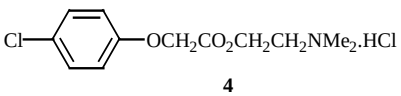


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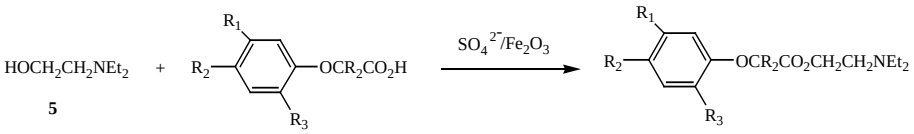
**Scheme 1**




**6** R=$R_1$=$R_2$=$R_3$=H
**7** R=$R_1$=$R_3$=H, $R_2$=Cl
**8** R=$R_1$=H, $R_1$=$R_2$=Cl
**9** R=$CH_3$, $R_1$=$R_2$=$R_3$=H
**10** R=$CH_3$, $R_1$=$R_3$=H, $R_2$=Cl
**11** R=$R_1$=$R_3$=H, $R_2$=Br
**12** R=$R_1$=$R_3$=H, $R_2$=$CH_3$

**13** R=$R_1$=$R_2$=$R_3$=H
**14** R=$R_1$=$R_3$=H, $R_2$=Cl
**15** R=$R_1$=H, $R_1$=$R_2$=Cl
**16** R=$CH_3$, $R_1$=$R_2$=$R_3$=H
**17** R=$CH_3$, $R_1$=$R_3$=H, $R_2$=Cl
**18** R=$R_1$=$R_3$=H, $R_2$=Br
**19** R=$R_1$=$R_3$=H, $R_2$=$CH_3$

**Table 1** Catalytic activity of the solid superacids[a]

| Entry | Solid superacid | Yield (%)[b] |
|---|---|---|
| 1 | $SO_4^{2-}/Fe_2O_3$ | 71 |
| 2 | $SO_4^{2-}/TiO_2$ | 64 |
| 3 | $SO_4^{2-}/SnO_2$ | 59 |

a: All reactions were carried out by reacting 1.0 mmol phenoxyacetic acids with 0.75 mmol 2-diethylaminoethanol **5** in the presence of 10% (Wt of total reactants) of the solid superacids in toluene (8 mL) at 110℃ for 4 h.
b: Isolated yields.

It is desirable to develop environmental friendly and one step synthesis for these biologically active dialkylaminoethyl esters. In comparison with stoichimetric or other convention condensational reagents such as concentrate sulfuric acid, in general, the superacids have several advantages. They can be easily recovered by simple filtration, are much less corrosive to the reaction vessels and have less industrial wastes since they are used in catalytic amounts and can be reused[6a-b]. For the preparation of 2-dialkylaminoethyl carboxylic esters, the use of solid superacids has one particular advantage in that the catalyst does not form amine salt with the aminoethanol, which will otherwise reduce the reactivity of the alcohol partner in the esterification reaction. In this paper we report a general, green and one step efficient method for the synthesis of 2-diethylaminoethyl aryloxyacetates using $SO_4^{2-}/Fe_2O_3$ as the solid superacid catalysts **(Scheme 1).**

To screen a suitable solid superacid for current research, three solid superacid catalysts were prepared according to literature method[7] by impregnating sulfate anion on $Fe_2O_3$, $TiO_2$ and $SnO_2$ solid, respectively. Among these three solid superacid catalysts $SO_4^{2-}/Fe_2O_3$ was found to give best results under identical but un-optimized conditions for the formation of 2-diethylaminoethyl phenoxyacetate 13 **(Table 1)**.

The $SO_4^{2-}$ content in the $SO_4^{2-}/Fe_2O_3$ solid superacid catalyst was determined to be 2.21% by ICP-AES(IRIS Intrepid II XPS). Using $SO_4^{2-}/Fe_2O_3$ as the catalyst, optimized reaction conditions were examined by reacting 2-diethylaminoethanol with phenoxyacetic acid. The best results were obtained in the case the reaction was carried out with a ratio of the aminoalcohol to aryloxyacetic acids 0.75:1(mol) in the presence of 3-4% of the catalyst (Wt of total reactants) in xylene at 140℃ for 6 h.

**Table 2** $SO_4^{2-}/Fe_2O_3$ catalyzed synthesis of 2-diethylaminoethyl aryloxyacetates[a]

| Entry | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|---|---|---|---|---|---|---|---|
| Aryloxyacetic acid | 6 | 7 | 8 | 9 | 10 | 11 | 12 |
| 2-Diethylaminoethyl aryloxyacetates[b] | 13 | 14 | 15 | 16 | 17 | 18 | 19 |
| Yield (%)[c] | 78 | 90 | 85 | 84 | 95 | 75 | 80 |

a: All reactions were carried out by reacting 1.0 mmol aryloxyacetic acids with 0.75 mmol 2-diethylaminoethanol **5** in the presence of 3% (Wt of total reactants) $SO_4^{2-}/Fe_2O_3$ in xylene (8 mL) at 140℃ for 6 h.
b: Products were fully characterised[8].
c: Isolated yields.

Under the optimized conditions seven 2-diethylaminoethyl aryloxyacetates **13-20** were prepared in 75%~95% yields, respectively **(Table 2)**, by condensation of the corresponding aryloxyacetic acids with 2-diethylaminoethanol. The yields were much higher then that of the conventional methods, using concentrated sulfuric acid as the dehydrating agent[5a].

In conclusion we have developed an efficient and environmental friendly method for the preparation of biologically active 2-diethylaminoethyl aryloxyacetates using solid superacid $SO_4^{2-}/Fe_2O_3$ as the catalyst. This method has advantages over the traditional ones in that: (i) the amount of the catalyst was small and the catalyst can be recovered; (ii) the work-up procedure is simple; (iii) by this method the amine salts did not form; (iv) the waste is less acidic so the corrosion to the reaction vessel is less. It can be expected that this method should be found its application in the preparation of other useful 2-diethylaminoethyl aryloxyacetates. The reliability and reusability of the catalyst, however, remains to be further examined.

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8. General procedure for the synthesis of 2-diethylaminoethyl aryloxyacetates: To a flask fitted with reflux condenser and a calcium drying tube was added sequentially 2-diethylaminoethanol (5, 88 mg, 0.75 mmol), an aryloxyacetic acid (1.0 mmol), $SO_4^{2-}/Fe_2O_3$ (3% Wt of total reactants) and xylene (8 mL). The mixture was heated at 140℃ for 6 h. After cooling, the resultant mixture was filtered and washed with xylene (2 mL). The combined filtrates were washed with saturated aqueous $Na_2CO_3$ solution (2 x 2 mL). The xylene layer was further washed with water (2x2 mL) and brine (2 mL), dried over $Na_2SO_4$. The solvent was removed under reduced pressure and the crude product was purified by silica gel flash column chromatography gradiently eluting with ethyl acetate in petroleum ether to give the desired 2-diethylaminoethyl aryloxyacetates.

2-Diethylaminoethyl phenyloxyacetate **13**: 173 mg (78%) as a pale yellow partial crystalline liquid. IR(LF): ν 3063, 3039, 1762, 1737(s, C=O), 1596, 1495, 1446, 1263,1192, 754 and 691 $cm^{-1}$; $^1$H-NMR($C_6D_6$, δppm): 7042-7.04 (m, 5H, Ph-), 4.18 (s, 2H, $OCH_2CO_2$), 3.92 (t, 2H, *J* 6.2Hz, $-CO_2CH_2-$), 2.24 (t, 2H, *J* 6.2Hz, $-CH_2N=$), 2.13 [q, 4H, *J* 7.1Hz, $-N(CH_2)_2-$] and 0.69 (t, 6H, *J* 7.1Hz, 2 x $-CH_3$); *m/z* (ESI): 252 [100%, $(M+1)^+$].

2-Diethylaminoethyl (4-chlorophenyloxy)acetate **14**: 192 mg (90%) as a pale yellow partial crystalline liquid. IR (LF): ν 3099, 3067, 1761 (s, C=O), 1592, 1491, 1448, 1381, 1278, 1199, 1079, 1009, 826 and 642 $cm^{-1}$; $^1$H-NMR($C_6D_6$, δppm): 7.26-6.85(m, 4H, Ph ), 4.60 (s, 2H, $OCH_2CO_2$), 4.38 (t, 2H, *J* 6.1Hz, $-CO_2CH_2-$), 2.73 (t, 2H, *J* 6.1Hz, $-CH_2N=$), 2.56 [q, 4H, *J* 7.2Hz, $-N(CH_2)_2-$] and 1.04 (t, 6H, *J* 7.2Hz, 2 x $-CH_3$); *m/z* (ESI): 286.8 [100%, $(M+1)^+$], 288.5[35%, $(M+2)^+$].

2-Diethylaminoethyl (2, 4-dichlorophenyloxy)acetate **15**: 204 mg (85%) as a pale yellow partial crystalline liquid. IR(LF): ν 3068, 3032, 1759 (s, C=O), 1598, 1489, 1441, 1239, 1202, 880, 803, 719 and 640 $cm^{-1}$; $^1$H-NMR($C_6D_6$, δppm): 7.16- 6.80 (m, 4H, Ph ), 4.68 (s, 2H, $OCH_2CO_2$), 4.26 (t, 2H, *J* 5.9Hz, $-CO_2CH_2-$), 2.74 (t, 2H, *J* 5.9Hz, $-CH_2N=$), 2.58 [q, 4H, *J* 7.3Hz, $-N(CH_2)_2-$] and 1.05 (t, 6H, *J* 7.3Hz, 2 x $-CH_3$); *m/z* (ESI): 320 (41.8%, $M^+$), 321 [21%, $(M+1)^+$] and 322.8[100%, $(M+2)^+$].

(2-Diethylaminoethyl)-(2-methy-2-phenyloxy)propionate **16**: 168 mg (84%) as a light brown liquid. IR(LF): ν 3038, 3032, 1738 (s, C=O), 1594, 1490, 1381, 1284, 1234, 1178, 1142, 1091, 831 and 668 $cm^{-1}$; $^1$H-NMR($C_6D_6$, δppm): 7.22-6.86 (m, 5H, Ph ), 4.24 (t, 2H, *J* 6.3Hz, $-CO_2CH_2-$), 2.68 (t, 2H, *J* 6.3Hz, $-CH_2N=$), 2.53 [q, 4H, *J* 7.1Hz, $-N(CH_2)_2-$] 1.60 [s, 6H, $-(CH_3)_2CO_2-$]and 0.99 (t, 6H, *J* 7.3Hz, 2 x $-CH_3$); *m/z* (ESI): 279 (100%, $M^+$), 281 [6%, $(M+2)^+$].

2-Diethylaminoethyl [2-methy-2-(4-chlorophenyloxy)propionate **17**: 225 mg (95%) as a light brown liquid. IR(LF): ν 3107, 3071, 1739 (s, C=O), 1590, 1488, 1382, 1284, 1237, 1178, 1142, 1091, 831 and 668 $cm^{-1}$; $^1$H-NMR($C_6D_6$, δppm): 7.19-6.82 (m, 4H, Ph), 4.23 (t, 2H, *J* 6.3Hz, $-CO_2CH_2-$), 2.67 (t, 2H, *J* 6.3Hz, $-CH_2N=$), 2.53 [q, 4H, *J* 7.1Hz, $-N(CH_2)_2-$] 1.59 [s, 6H, $-(CH_3)_2CO_2-$]and 1.00 (t, 6H, *J* 7.3Hz, 2 x $-CH_3$); *m/z* (ESI): 313 (100%, $M^+$), 315 [44%, $(M+2)^+$].

2-Diethylaminoethyl (4-bromophenyloxy)acetate **18**: 187 mg (75%) as a light brown liquid. IR(LF): ν 3091, 3071, 1760 (s, C=O), 1615, 1589, 1557, 1443, 1382, 1286, 1233, 1186, 1068, 822 and 611 $cm^{-1}$; $^1$H-NMR($C_6D_6$, δppm): 7.36-6.81(m, 4H, Ph), 4.62 (s, 2H, $OCH_2CO_2$), 4.34 (t, 2H, *J* 5.8Hz, $-CO_2CH_2-$), 2.86 (t, 2H, *J* 5.8Hz, $-CH_2N=$), 2.69 [q, 4H, *J* 7.2Hz, $-N(CH_2)_2-$] and 1.07 (t, 6H, *J* 7.2Hz, 2 x $-CH_3$); *m/z* (ESI): 330 (6.7%, $M^+$), 332[6.7%, $(M+2)^+$].

2-Diethylaminoethyl (4-methylphenyloxy)acetate **19**: 167 mg (80%) as a light brown liquid. IR(LF): ν 3035, 1758 (s, C=O), 1611, 1512, 1451, 1382, 1289, 1189, 1081and 814 $cm^{-1}$; $^1$H-NMR($C_6D_6$, δppm): 7.08-6.81(m, 4H, Ph), 4.61 (s, 2H, $OCH_2CO_2$), 4.29 (t, 2H, *J* 6.0Hz, $-CO_2CH_2-$), 2.76 (t, 2H, *J* 5.8Hz, $-CH_2N=$), 2.60[q, 4H, *J* 7.1Hz, $-N(CH_2)_2-$] and 2.28 (s, 3H, Ar-$CH_3$), 1.0 (t, 6H, *J* 7.1Hz, 2 x $-CH_3$); *m/z* (ESI): 266 [100%, $(M+1)^+$], 267[13%, $(M+2)^+$].

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