One-Pot Synthesis of Substituted Aniline-*N*,*N*-diacetic Acids

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Substituted aniline-*N*,*N*-diacetic acids are synthesized by reaction of substituted anilines with *n*-butyllithium and sodium chloroacetate in good yields.

Primary alkyl amines readily react with two equivalents of alkyl halide to form tertiary alkylamines.[1] By this fashion, ethylenediamine with haloacetic acid yields ethylenediamine tetraacetic acid, which is an excellent chelating reagent. In the case of arylamines, even under more vigorous conditions or in the presence of a catalyst, alkylation with haloacetic acids or their esters yields only *N*-arylglycines.[2]

Herein, we report a one-pot process to prepare substituted aniline-*N*,*N*-diacetic acids (**6a–g**) from anilines and sodium chloroacetate by using *n*-butyllithium as base. The title compounds are potential ligands or surfactants. In this reaction, *n*-BuLi deprotonates amine **1** to form lithium amide **2**,[3] which reacts with sodium chloroacetate to form *N*-arylglycinate **3**. Compound **3** undergoes rapid transmetalation with lithium amide **2**.

The rapid proton exchange most probably is facilitated by aggregation of the lithium amides[5] with formation of aniline **1** and the amide **4**. The latter further reacts with another sodium chloroacetate to yield diacetic acid sodium salt. The crystaline needles of products **6** obtained from routine work-up procedure are already analytically pure.

Table. Substituted Aniline-*N*,*N*-diacetic Acids **6a**–**g**

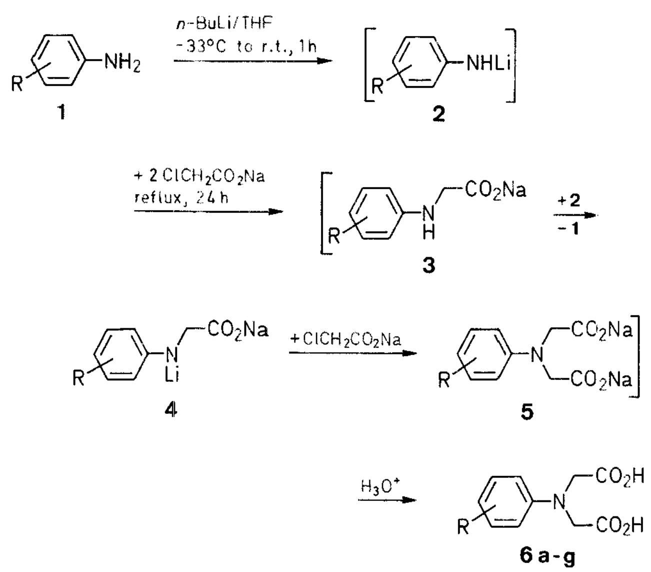
Product	mp (°C)	Yield[a] (%)	Molecular Formula[b]	IR[c] ν(cm^{-1})	^{1}H-NMR (CD_3COCD_3)[d] δ, J(Hz)
6a	198–200	56	$C_{10}H_{11}NO_4$ (209.2)	3470 (OH) 1730 (C=O)	4.39 (s, 4H, CH_2); 6.70 (m, 3H); 7.30 (m, 2H)
6b	182–184	78	$C_{10}H_{10}BrNO_4$ (288.1)	3420 (OH) 1710 (C=O)	4.42 (s, 4H, CH_2); 6.72 (d, 2H, J = 9.2); 7.48 (d, 2H, J = 9.2)
6c	195–196	84	$C_{10}H_{10}ClNO_4$ (243.6)	3400 (OH) 1700 (C=O)	4.43 (s, 4H, CH_2); 6.75 (d, 2H, J = 9.4); 7.35 (d, 2H, J = 9.4)
6d	224–225	80	$C_{10}H_{10}ClNO_4$ (243.6)	3450 (OH) 1720 (C=O)	4.45 (s, 4H, CH_2); 6.80 (m, 3H); 7.34 (t, 1H, J = 7.8)
6e	197–198	60	$C_{11}H_{13}NO_4$ (223.2)	3400 (OH) 1870, 1700 (C=O)	2.32 (s, 3H, CH_3); 4.38 (s, 4H, CH_2); 6.63 (d, 2H, J = 8.8); 7.15 (d, 2H, J = 8.8)
6f	150–151	72	$C_{11}H_{13}NO_5$ (239.2)	3500 (OH) 1750 (C=O)	3.83 (s, 3H, OCH_3); 4.33 (s, 4H, CH_2); 6.69 (d, 2H, J = 9.2); 6.97 (d, 2H, J = 9.2)
6g	169–170	70	$C_{11}H_{13}NO_5$ (239.2)	3200 (OH) 1760, 1700 (C=O)	3.83 (s, 3H, OCH_3); 4.33 (s, 4H, CH_2); 6.40 (m, 3H); 7.25 (t, 1H, J = 8.3)
7	161–163	75	$C_9H_{11}NO$ (165.2)	3340 (OH) 1720 (C=O)	2.28 (s, 3H, CH_3); 4.01 (s, 2H, CH_2); 6.66 (m, 2H); 7.12 (d, 2H, J = 7.0)
8	178–179	63	$C_{10}H_{12}N_2O_4$ (224.2)	3200 (OH) 1730 (C=O)	4.01 (s, 2H, CH_2); 4.11 (s, 2H, CH_2); 6.66–6.98 (m, 4H)

[a] Yield of isolated pure product based on *n*-BuLi.

[b] Satisfactory microanalyses obtained: C ±0.23, H ±0.17, N ±0.20, Cl ±0.16.

[c] Recorded on a JASCO-302 infrared spectrophotometer.

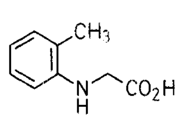
[d] Recorded on a JEOL FX-100 spectrometer.



1–6	R	1–6	R
a	H	**e**	4-CH_3
b	4-Br	**f**	4-MeO
c	4-Cl	**g**	3-MeO
d	3-Cl		

Attempt to improve the yield of the title compounds by increasing the mole ratio of *n*-BuLi to aniline **1** were unsuccessful. Presumably *n*-BuLi reacts with sodium chloroacetate through lithium halogen exchange[4] to form $LiCH_2CO_2Na$. This method also fails for amines containing heteroatoms in addition to that of the amino group (i.e. aminopyridines or nitroanilines). During the reaction of these compounds, the color of the solution became purple to red, which resulted in recovery of the starting materials after aqueous work up.

Under same reaction condition, *o*-methylaniline and *o*-phenylenediamine afford *N*-(*o*-tolyl)glycine (**7**) and *N*,*N*'-(*o*-phenylenediamine)-diacetic acid (**8**), respectively. The resistance of the monosubstituted glycines to the further reaction might be due to steric reasons.



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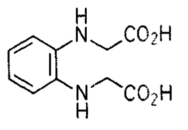

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Substituted Aniline-*N*,*N*-diacetic Acid (6a) from Aniline (1a); Typical Procedure:

To a three-necked flask equipped with condenser containing freshly distilled aniline (**1a**; 1.46 mL, 16 mmol) and dried THF (30 mL) under inert atmosphere is slowly added a 1.64 M solution of *n*-BuLi in hexane (10 mL, 16.4 mmol) at −33°C. After stirring at that temperature for another 1 h, the solution is allowed to warm to room temperature, and stirring is continued for an additional 1 h. During this period, the colorless, clear solution changes to yellow and finally becomes cloudy and light yellow. Then dried sodium chloroacetate (7.63 g, 32 mmol) is added (moderate exothermic reaction). After heat evolution has subsided, the mixture is refluxed for 24 h. For work-up, THF is removed and the residue is dissolved in water (20 mL). The aq. solution is extracted with CH_2Cl_2 (4 × 30 mL) to remove unreacted aniline. The water layer is acidified with conc. HCl (3 mL) to pH 4. The solution is kept in a refrigerator for 6 h. Upon filtration, white needles of **6a** are obtained; yield: 0.96 g (56% based on *n*-BuLi).

Aniline-*N*,*N*-diacetic Acid (6a) from *N*-Phenylglycine:

This reaction is carried by the same procedure as above for, except that *N*-phenylglycine is used instead of aniline and the ratio of *N*-phenylglycine to *n*-BuLi is 1:2. After work-up, needles of **6a** are obtained; yield: 1.21 g (71%).

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