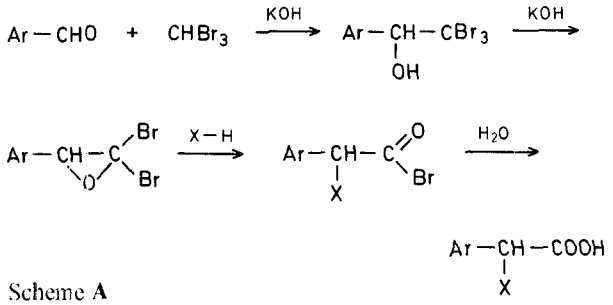
Synthesis of α-Aminoarylacetic Acids from Bromoform, Arylaldehydes, and Ammonia, with Potassium Hydroxide/Lithium Amide Combination as Catalyst

Edward L. Compere, Jr., David A. Weinstein

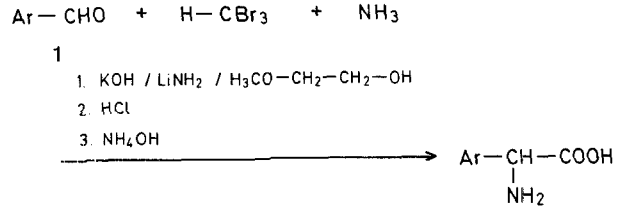
Department of Chemistry, Eastern Michigan University, Ypsilanti, Michigan 48197, U.S.A.

A number of earlier articles have reported the condensation of chloroform (or bromoform) with arylaldehydes to produce either aryltrihalomethyl-substituted methanols or the products of the reaction of such alcohols[2] with base and/or solvent. In the latter cases, α-substituted arylacetic acids are often produced. Thus when arylaldehydes are reacted with bromoform in methanolic potassium hydroxide the result is a "one-batch" preparation of α-methoxyarylacetic acids[3] (X = OCH_3) in yields varying from 1–80%. With an aqueous solvent (dioxan/water, 1:1) α-hydroxyarylacetic acids (X = OH) are formed in excellent yields[4] (≥90%).



Scheme **A**

We report here new solvent/base conditions which allow the preparation of α-aminoarylacetic acids (**2**; X = NH_2); 2-methoxyethanol (methyl cellosolve) containing ammonia is the solvent, and the base is a combination of lithium amide and potassium hydroxide (Scheme **B**).



Scheme **B**

A general mechanism for these related reactions, involves an epoxide intermediate, which undergoes ring opening with solvent (or base) species to produce the various α-substituted acids after hydrolysis; see Scheme **A**.

The evidence for this mechanism has been summarized previously[5]. Other similar syntheses of α-amino acids from arylaldehydes utilize a Perkin type condensation of the aldehydes with hydantoin[6], with acetylglycine[7] (azlactone syntheses), or with rhodamine[8], which provide yields of up to 50%, 65%, and 75%, respectively; however, all of these syntheses involve several steps, with intermediate products isolated, different conditions of reaction required for each reaction step, and the products are α-amino-β-arylpropanoic acids. In our haloform condensation, the yields of α-amino-α-arylacetic acid are 15 to 82% for a series of ten aldehydes, consistently higher than those obtainable by any other "one-batch" procedure starting with aryl aldehydes, including the classical Strecker[9] synthesis.

Table. α-Aminoarylacetic Acids **2** prepared[a]

Ar	Yield [%] of crude **2**[b]	m.p. (dec.)	Lit. m.p. (dec.)[c]	Molecular formula[c]
C_6H_5	59	265–267°[d]	260°	$C_8H_9NO_2$ (151.2)
3-Cl—C_6H_4	83	244–246°[d]	253–254°	$C_8H_8ClNO_2$ (185.6)
4-Cl—C_6H_4	79	270–272°[d]	260–261°	$C_8H_8ClNO_2$ (185.6)
2-F—C_6H_4	37	262–264°	—	$C_8H_8FNO_2$ (169.2)
3-F—C_6H_4	57	260–262°	253°	$C_8H_8FNO_2$ (169.2)
4-F—C_6H_4	54	271–273°	—	$C_8H_8FNO_2$ (169.2)
2-naphthyl	15	282–284°[d]		$C_{12}H_{11}NO_2$ (201.2)
3-H_3C—C_6H_4	52	253–254°[d]	238–241°	$C_9H_{11}NO_2$ (165.2)
4-H_3C—C_6H_4	42	258–260°[d]	257–258°	$C_9H_{11}NO_2$ (165.2)
4-H_3CO—C_6H_4	33	271–273°[d]	264–265°	$C_9H_{11}NO_3$ (181.2)

[a] Reaction of 0.1 mol of arylaldehyde.

[b] Infrared spectra of the "crudes" are identical with those of analytical samples.

[c] All products gave satisfactory microanalyses (C ±0.24%, H ±0.22%, N ±0.13%); analyses were by Spang Microanalytical Laboratory, Box 1111, Ann Arbor, Michigan 48109.

[d] In these cases the compounds began to melt at these temperatures, but incompletely; melting was followed by sintering and decomposition indicating color change (these decomposition points were determined using a MEL-TEMP and are uncorrected).

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Various reaction conditions were tested before our general procedure was devised. Solvent systems included: dioxan, liquid ammonia (in addition to methyl cellosolve), and various combinations of these. Base variations included lithium amide and potassium hydroxide separately and in combination with lithium chloride (in varying amounts). Eventually the conditions described below as the "general" procedure produced the optimum results, which are tabulated in the Table.

General Procedure for the Preparation of α-Aminoarylacetic Acids: To a 500 ml three-necked flask, equipped with a pressure equalizing addition funnel, a thermometer, an efficient power stirrer, a nitrogen gas inlet (with drying tube) and a second addition funnel (all being accommodated by the use of two Claisen adaptors) is added lithium amide (0.3 mol), finely powered potassium hydroxide (0.2 mol; fused prior to use), and methyl cellosolve (100 ml; distilled from calcium hydride). This mixture is stirred for 15 min and then liquid ammonia is added dropwise (one drop per sec), from a chilled dropping funnel, for 15 min. This mixture is placed in an ice/water bath and stirred for 0.5 h, it is then flushed with dry nitrogen gas until the flask temperature reached 5°. A mixture of arylaldehyde (0.1 mol; freshly distilled under nitrogen), distilled bromoform (0.125 mol); and methyl cellosolve (10 ml) are placed in an additional funnel and flushed with dry nitrogen. Addition of liquid ammonia is begun again (one drop per three sec) concurrently with addition of the aldehyde/bromoform mixture (one drop per four sec), while maintaining the internal temperature at 0° (±5°). When one third of the aldehyde/bromoform mixture has been added, these additions are interrupted and ground potassium hydroxide (0.055 mol) is spooned in. After 5 min, the addition of the aldehyde/ bromoform and ammonia liquids are resumed. When two thirds of the aldehyde/bromoform mixture has been added, another portion of potassium hydroxide (0.055 mol) is spooned in; after 5 min the addition of the reactants is resumed. When all the aldehyde/bromoform has been added, the ammonia addition is continued for 10 min, and the flask contents are stirred for 6 h (in ice). Sufficient ammonia is added to bring the temperature to 0°, after 10 min water (100 ml) is added and the mixture is allowed to stir overnight. Then water (50 ml) and sodium hydroxide (10 g) are added, the mixture is stirred for 15 min, and then refluxed gently for 2 h. The solution is cooled and extracted several times with 50 ml portions of ether. The aqueous layer is acidified to pH 1 with 6 normal hydrochloric acid and extracted three times with 50 ml portions of ether. The aqueous layer is held at 80° for 15 min to remove residual ether. The solution is adjusted to pH 7 with 6 molar ammonium hydroxide, chilled, and crystallization is induced. The α-aminoarylacetic acid is collected and washed successively with water, ether, and 95% ethanol. Recrystallization is accomplished by dissolving the amino acid in hot 6 molar ammonia solution (adding decolorizing carbon if necessary), filtering, neutralizing with 6 normal hydrochloric acid and cooling. At most two recrystallizations are needed to obtain an analytical sample.

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