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3-AMINO-2-ARYLPROPANOIC ACIDS BY ELECTROPHILIC SUBSTITUTION OF 2-ARYLETHYLAMINES AT THE BENZYLIC POSITION

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<u>Summary</u>: A reaction sequence consisting of N-pivaloylation, lithiation at the benzylic position, carboxylation and deprotection allows to convert 2-arylethylamines into 3-amino-2-arylpropanoic acids with good yields.

When treated with butyllithium in diethyl ether or hexane, N,N-dimethylaniline ^[1] and N,N-dimethylbenzylamine ^[2] slowly undergo hydrogen/lithium exchange at an *ortho* position. The metalation promoting effect vanishes with increasing distance between the complexing group and the reaction center. Actually, only 7% of the *ortho* substituted derivative were obtained after N,N-dimethyl-2-phenylethylamine had been submitted to consecutive metalation with butyllithium and trapping with benzophenone ^[3]. The principal reaction pathway was postulated to be a lithiation at the benzylic position followed by β -climination of lithium dimethylamide and subsequent polymerization of the resulting styrene. However, N,N-dimethyl-2-methyl-2-phenylpropylamine as a substrate gave only a slightly increased yield (17%) of the *ortho* derivative ^[3].



We wish to report now that the deprotonated N-pivaloylamino [4] moiety provides more powerful and more specific neighboring group assistance to metalation than does the dimethylamino group. In this way, perfect control over the reaction outcome can be achieved :

- With *tert*-butyllithium as the metalating reagent, clean metalation at the benzylic position takes place. The introduction of methoxy substituents into the aromatic ring does not alter this regioselectivity (see Table), while N,N-dimethyl- or N-(trimethylsilyl)-2-(4-alkoxyphenyl)ethylamines are invariably attacked at an aromatic position ^[5].
- The organometallic intermediates are stable towards elimination. They efficiently react with electrophiles, in particular with carbon dioxide (see Table).

• After carboxylation, the N-pivaloyl moiety can be removed by acid hydrolysis. Thus, 2-arylethylamines can be indirectly converted into 3-amino-2-arylpropanoic acids with good yields (see Table).

$$X \xrightarrow{COOH} CH_2 - CH_2 - NH_2 \rightarrow X \xrightarrow{COOH} CH_2 - CH_2 - CH_2 - NH - CO - R \rightarrow X \xrightarrow{COOH} CH_2 - NH_2 - CH_2 - NH_2 \xrightarrow{COOH} CH_2 - NH_2 \xrightarrow{CO} CH_2 - NH_2 \xrightarrow{CO} CH_2 - CH_2$$

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Table. Synthesis of 3-(N-pivaloylamino)-2-arylpropanoic acids ^{a)} and 3-amino-2-arylpropanoic acid hydrochlorides ^{a)} : yields and melting ranges ^{b)}.

x - K			х сн-сн ₂ -N-C-С(СН ₃) ₃		х"- х. х	
X.,	X,	х	yield	melting range	yield	melting range
н	н	н	72%	147 - 148 °C ^{el}	76 %	228 - 229°C ^{g)}
н	н	осн3	77% ^{c}}	179 - 180 °C ^{el}	53%	212 - 213 °C ^{h1}
н	осн₃	н	77% ^{d1}	138 - 139 °C ^{f1}	76%	227 - 228 °C ⁱ¹
осн3	н	н	79 %	132 - 133 °C ^{el}	63 %	214 - 215°C ¹¹
осн _з	0CH3	н	78%	168 - 169 °C ^{e)}	57%	232 - 233 °C ^{il}

(a) Standard working procedures : A 1.5 M solution of tert-butyllithium (30 mmol) in pentane was added to the 2-aryl-N-pivaloylethylamine (10 mmol) in tetrahydrofuran (50 mL) at -75 °C. After 3 h at -50 °C the mixture was poured on dry ice. The organic layer was extracted with water (1×30 and 2×5 mL). Upon acidification of the aqueous phase the 3-(N-pivaloyl)-2-arylpropanoic acid precipitated. It was either immediately collected or isolated by extraction with dichloromethane. The products (3 mmol) were suspended in 20% hydrochloric acid (12 mL) heated 8 h under reflux. The hot solution was filtered; upon cooling the 3-amino-2-arylpropanoic acid hydrochlorides settled out. (b) The hydrochlorides melt under decomposition. (c) Metalation during 6 h at -75 °C. (d) Metalation during 3 h at -75 °C. (e) Crystallized from ethyl acetate. (f) Crystallized from toluene. (g) Crystallized from ethanol. (h) Crystallized from a mixture of isopropanol and diethylether. (i) Crystallized from aqueous ethanol.

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