The Halogen-Metal Interconversion Reaction and Its Application to the Synthesis of Nicotinic Acid Labeled With Isotopic Carbon[1]

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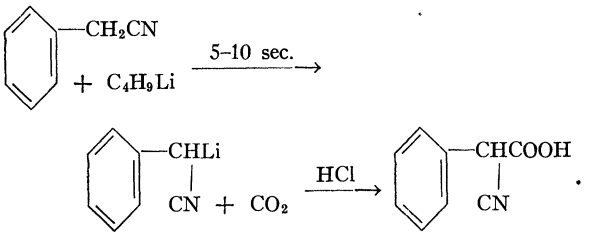
The halogen-metal interconversion reaction is essentially a double decomposition reaction between an organoalkali compound (usually a metal alkyl) and an aryl halide:

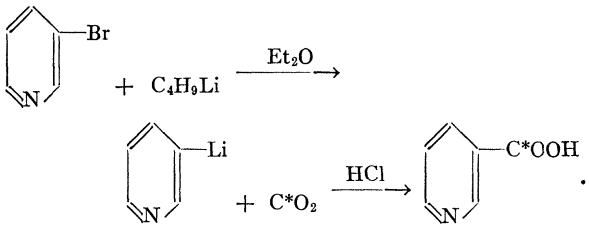
$$R\text{–}X + R'\text{–}M \leftrightharpoons R\text{–}M + R'\text{–}X.$$

Gilman, Langham, and Moore (*1*) made an extensive study of the application of the above reaction to the preparation of a number of unusual organolithium compounds. The extremely short reaction times required permit the preparation of organometallic compounds having additional functional or reactive groups, a feat not possible in the usual Grignard preparation. Like the Grignard reaction, however, these reactions yield carboxylic acids when carbonated with CO_2.

The extreme rapidity of the exchange reaction is not confined to the halogen-metal interconversion alone but may be evidenced in special cases of the hydrogen-metal exchange. For example, if benzyl cyanide is treated with n-butyl lithium, a 55 per cent yield of phenylcyanoacetic acid results from carbonation within 5–10 seconds. The reaction proceeds according to the following equation:

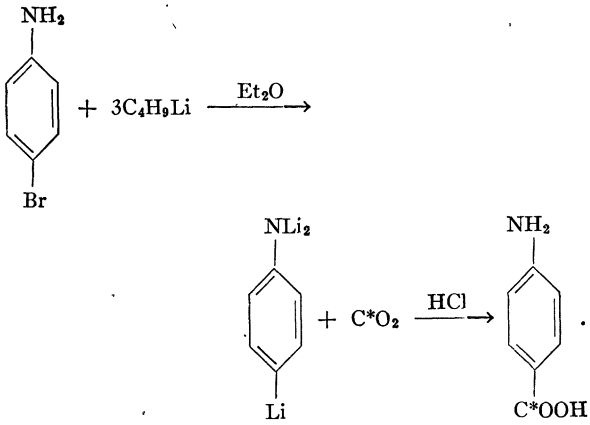


Using n-butyl lithium and 3-bromopyridine according to the method reported by Gilman and Spatz (*2*), 3-pyridyl lithium was prepared. The reaction was scaled down to the millimol level and carbonation effected with $C^{13}O_2$ and $C^{14}O_2$, generated by treating the respective isotopic barium carbonates with concentrated H_2SO_4. Isotope-labeled nicotinic acid (3-pyridine carboxylic acid) resulted according to the following reactions:



A reaction employing *21* millimols of $BaC^{13}O_3$ resulted in an *82* per cent crude yield of nicotinic acid having a C^{13} content of 0.9 isotopic per cent. When the reaction was repeated using 0.8 millimol of $BaC^{14}O_3$, the crude yield of C^{14}-labeled nicotinic acid was *62* per cent. The material had a specific activity of approximately 8 microcuries/mg.

The interconversion reaction between n-butyl lithium and p-bromoaniline (*3*) is being employed for the synthesis of p-aminobenzoic acid labeled with isotopic carbon according to the following reactions:



A reaction using 3 millimols of ordinary $BaCO_3$ has resulted in a 21 per cent yield of p-aminobenzoic acid of high purity.

References

1. GILMAN, HENRY, LANGHAM, WRIGHT, and MOORE, FRED W. *J. Amer. chem. Soc.*, 1940, **62**, 2327.
2. GILMAN, HENRY, and SPATZ, S. M. *J. Amer. chem. Soc.*, 1940, **62**, 446.
3. GILMAN, HENRY, and STUCKWISCH, C. G. *J. Amer. chem. Soc.*, 1941, **63**, 2844.

Analytical Determination of Basic Groups in Amino Acids and Proteins

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In the course of work upon proteins, it has been found that the basic groups of amino acids (except arginine and histidine) or of proteins can be determined rapidly and simply.

The sample (0.2 gram of amino acid or 2 grams of protein) is dissolved at room temperature in 100 ml. of 0.05 N $Ca(NO_3)_2$ solution saturated with $Ca(OH)_2$. An excess of solid $Ca(OH)_2$ (0.5 gram) is added, and the mixture is shaken repeatedly during two hours. It is then filtered and protected from the air to avoid carbonation. An aliquot is titrated with standard HCl (0.05 N). A blank containing no amino acid or protein is prepared at the same time and carried through simultaneously with the sample. The difference between sample and blank represents the basic groups in the sample and may be expressed as the per cent of basic nitrogen in the sample. Results on pure amino acids are accurate to within 1.5 per cent error.

This method has some advantages over the Sorensen method, particularly with regard to proline and hydroxyproline, which can be titrated accurately by the present method.

A similarly simple method of determining the acid groups of amino acids and proteins has been sought, but completely satisfactory results have not been obtained. Use of picric acid has given the best results to date.

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