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3,462,486

METHOD FOR PREPARING 3',4'-DICHLORO-CYCLOPROPANECARBOXANILIDE

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4 Claims

ABSTRACT OF THE DISCLOSURE

Anilides and substituted anilides of lower cycloalkanoic acids are prepared by reacting a lower alkyl ester of the cycloalkanoic acid with a primary aromatic amine in solution in a mutual organic solvent and a molar equivalent amount of an undissolved alkali metal alcoholate, preferably sodium methoxide, ethoxide or propoxide, distilling off the alcohol liberated in the reaction as it is formed, neutralizing the reaction mixture with aqueous acid and recovering the product. Preferred organic solvents include hydrocarbons which form azeotropes with the liberated alcohol. Nitro substituents apparently inhibit the reaction but phenolic hydroxy groups and aliphatic halides do not, merely consuming part of the metal alcoholate reagent.

This application is a continuation of U.S. Ser. No. 265,372, filed Mar. 15, 1963, now abandoned.

DESCRIPTION OF THE INVENTION

The following examples are set forth to illustrate more clearly the principle and practice of this invention to those skilled in the art.

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EXAMPLE I

Part A

One hundred forty parts (1 mol) of methyl 4-chlorobutyrate and thirty-nine parts (1 mol) of freshly prepared sodamide and 500 parts of benzene are charged to a reaction flask equipped with a stirrer, reflux condenser and heating means. The reaction mixture is stirred for thirty-six hours and heated to provide gentle reflux. An analysis of an aliquot of the reaction mixture indicates that methyl cyclopropane-1-carboxylate is formed in close to a 90% yield based upon the methyl 4-chlorobutyrate.

Part B

Fifty-four parts (1 mol) of freshly prepared sodium methoxide and 162 parts (1 mol) of 3,4-dichloro aniline are added to the reaction mixture of Part A. The reaction mixture is stirred for 12 hours while providing sufficient heat to provide gentle reflux. The benzene-methanol azeotrope is slowly removed as formed. After cooling, the reaction mixture is successively washed with dilute hydrochloric acid and water. The organic phase is dried and the benzene is removed by vacuum distillation. The amide thus recovered is recrystallized from ligroin to give N-(3,4-dichlorophenyl) cyclopropane carboxamide which melts at 127-129°. The overall yield based on the methyl 4-chlorobutyrate employed in Part A is 79%.

EXAMPLES II-XXXI

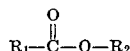
Thirty-one N-substituted amides are prepared by reacting equimolar portions of ester, a primary aromatic amine, and sodium methoxide in benzene following the general procedure described in Example I, Part "B." In each case the amide is obtained in a yield in excess of 60% based on the starting ester. The reactants employed and the amide produced are set forth in following table.

TABLE I

Example	Ester Reactant	Amine Re	Amide	Melting point, ° C.
II	Methyl cyclopropane carboxylate	3-chloroaniline	N-(3-chlorophenyl)cyclopropane-carboxamide	147-149
III	do	4-methoxyaniline	N-(4-methoxyphenyl)cyclopropane-carboxamide	130-132
IV	Methyl methacrylate	3,4-dichloroaniline	N-(3,4-dichlorophenyl)methacrylamide	120-121
V	Ethyl benzoate	Aniline	N-phenylbenzamide	162-163
VI	Methyl 1-methoxycyclopropane-1-carboxylate	3,4-dichloroaniline	N-(3,4-dichlorophenyl)-1-methoxycyclopropanecarboxamide	93-94
VII	Methyl 2-methylcyclopropane-1-carboxylate	do	N-(3,4-dichlorophenyl)-2-methyl cyclopropanecarboxamide	93-94
VIII	Methyl 1-methylcyclopropane-1-carboxylate	do	N-(3,4-dichlorophenyl)-1-methyl cyclopropanecarboxamide	120-122
IX	do	3-chloroaniline	N-(3-chlorophenyl)-1-methyl cyclopropanecarboxamide	118-120
X	do	3-chloro-4-methylaniline	N-(3-chloro-4-methylphenyl)-1-methyl cyclopropanecarboxamide	103-105
XI	do	2-methyl-5-chloroaniline	N-(2-methyl-5-chlorophenyl)-1-methyl cyclopropanecarboxamide	74-76
XII	Ethyl hexanoate	m-Toluidine	N-(3-methylphenyl)hexamide	95-96
XIII	Isopropyl benzoate	do	N-(3-methylphenyl)benzamide	139-140
XIV	Methyl cyclopropane carboxylate	Aniline	N-(phenyl)cyclopropanecarboxamide	110-111
XV	do	3,4-dichloroaniline	N-(3,4-dichlorophenyl)cyclopropanecarboxamide	130-131
XVI	Ethyl propionate	Aniline	Propionanilide	105-107
XVII	do	4-chloroaniline	N-(4-chlorophenyl)propionanilide	139-140
XVIII	do	p-Toluidine	N-(4-methylphenyl)propionanilide	121-123
XIX	do	p-Fluoroaniline	N-(4-fluorophenyl)propionanilide	128-129
XX	do	p-Anisidine	N-(4-methoxyphenyl)propionanilide	89-91
XXI	Methyl propionate	Aniline	Propionanilide	105-107
XXII	Butyl propionate	do	do	105-107
XXIII	Ethyl propionate	2-chloroaniline	N-(2-chlorophenyl)propionanilide	95-96
XXIV	do	3-chloroaniline	N-(3-chlorophenyl)propionanilide	84-86
XXV	do	Alpha-naphthylamine	N-(1-naphthyl)propionanilide	117-118
XXVI	do	Beta-naphthylamine	N-(2-naphthyl)propionanilide	123-124
XXVII	do	p-Bromoaniline	N-(4-bromophenyl)propionanilide	145-146
XXVIII	Ethyl B-(1-pyrrolidyl) isobutyrate	3,4-dichloroaniline	N-(3,4-dichlorophenyl)-B-(1-pyrrolidyl) isobutyramide	78-80
XXIX	do	3-chloroaniline	N-(3-chlorophenyl)-B-(1-pyrrolidyl) isobutyramide	57-59
XXX	Ethyl-2-hydroxy-2-methyl-propionate	Aniline	N-phenyl-2-hydroxy-2-methylpropionanilide	134-135
XXXI	do	5-chloro-2-methylaniline	N-(5-chloro-2-methylphenyl)-2-hydroxy-2-methylpropionanilide	104-106
XXXII	do	3,4-dichloroaniline	N-(3,4-dichlorophenyl)-2-hydroxy-2-methylpropionanilide	132-134

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The ester employed in the invention is not critical and may be an ester formed from either an aliphatic or an aromatic acid. The alcohol from which the ester is formed is not critical, but usually a 1-3 carbon atom alkanol is employed for this purpose. In general, the esters employed will conform to the formula:



wherein R_1 is selected from the group consisting of alkyl groups, cycloalkyl groups, alkenyl groups, aryl groups, alkaryl groups and aralkyl groups, and R_2 is a 1-3 carbon atom alkyl group. Typical esters that may be employed include methyl formate, ethyl acetate, ethyl propionate, methyl benzoate, butyl benzoate, methyl 4-methylbenzoate, methyl beta-phenylacetate, methyl acrylate, ethyl acrylate, methyl methacrylate, methyl 1-methylcyclopropane carboxylate, etc.

The aromatic amine employed in the process must be a primary aromatic amine. In general, the aromatic amines employed will conform to the formula:



wherein R_3 is selected from the group consisting of unsubstituted aryl groups, alkoxy-substituted aryl groups, halo-substituted aryl groups, unsubstituted alkaryl groups, alkoxy-substituted alkaryl groups, and halo-substituted alkaryl groups. Typical amines that can be employed include aniline, the toluidines, o-, m-, and p-ethylanilines, o-, m-, and p-methoxyanilines, o-, m-, and p-chloroanilines, the various polychloro-substituted anilines such as 3,4-dichloroaniline, anilines containing both alkyl and halo substituent groups such as 2-methyl-5 chloroaniline, etc.

The alkali metal alcoholate employed may be an alcoholate of any suitable alcohol, but usually is an alcoholate of a 1-3 carbon atom alkanol. The alkali metal moiety of the alcoholate ordinarily will be lithium, sodium or potassium, but if desired other alkali metals can be employed for this purpose.

The reaction solvent employed will be an organic liquid which is a solvent for both the ester and the amine reactants. Preferably, the solvent employed should be one which will form an azeotrope with the alcohol liberated in the reaction, particularly an azeotrope which will boil below the boiling point of the reaction solvent. The preferred classes of solvents are the unsubstituted alkanes, the unsubstituted aromatic hydrocarbons and the halo-substituted aromatic hydrocarbons. Typical solvents that can be employed include benzene, toluene, chlorobenzene, ethylbenzene, hexane, etc.

The ester reactant, the amine reactant, and the reaction solvent employed should preferably, and in certain limited cases mandatorily, be free of substituent groups which are capable of reacting with the alkali metal alcoholate. For example, aromatic hydroxyl groups are sufficiently acidic to react with the alkali metal alcoholate in preference to the desired reaction between the ester, the aromatic amine, and the alkali metal alcoholate. Where it is desired to prepare a product containing an aromatic hydroxyl group it is essential that the alkali metal alcoholate be employed in a quantity sufficient to react with the hydroxyl group in addition to the molar quantity of alkali metal alcoholate required for the desired reaction. By way of specific example, equimolar quantities of ethyl propionate and p-aminophenol can be reacted in benzene in the presence of 2 molar quantities of sodium methoxide to provide N-(4-hydroxyphenyl) propionamide which melts at 168-169, the desired product being obtained in a yield in excess of 60% based upon the ester reactant. It will be noted that the amide obtained is that predicted and the aromatic hydroxyl group interferes in the reaction only in the sense of requiring the use of an additional quantity of the alkali metal alcoholate.

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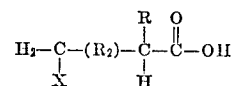
In contrast to the situation involving aromatic hydroxyl groups as described in the paragraph above, aliphatic hydroxyl groups in no way interfere with the desired reaction. Aliphatic halogen atoms have an effect similar to aromatic hydroxyl groups in that the halogen atoms react with the alkali metal alcoholate in preference to the desired reaction. By using an excess of the alkali metal alcoholate it is possible to prepare N-aryl substituted amides, but the aliphatic halogen atom of the initial reactant may be converted to an alkoxy group.

For reasons which are not fully understood, nitro groups appear to completely inhibit the desired reaction regardless of the quantity of the alkali metal alcoholate employed.

The reaction can be carried out by simply heating the ester, the amine and the alkali metal alcoholate in the reaction solvent. Temperatures as low as 30-40° C. are suitable, but the rate of reaction can be increased substantially by carrying out the reaction at higher temperatures. The yield of the desired N-aryl substituted amide can be improved by carrying out the reaction under reflux and removing the alcohol liberated in the reaction from the reaction zone as an azeotrope with the reaction solvent. Mild agitation is preferably provided as the alkali metal alcoholate is a solid which does not dissolve in the reaction solvent.

In a preferred embodiment of the invention, N-aryl substituted amides of lower cycloalkanoic acids are prepared by an integrated two-step process that can be carried out without recovering or separating any of the intermediate products. In the first step of the reaction, an ester of a halo-substituted alkanolic acid is reacted with either an alkali metal amide such as sodamide or an alkali metal alcoholate in a suitable solvent to form an ester of a lower cycloalkanoic acid. Thereafter, an alkali metal alcoholate is added to the reaction mixture from the first step and the amide is prepared as previously described.

The halo-alkanoic acid moiety of the ester employed in the first step of the process described in the paragraph above conforms to the formula:



wherein X is a halogen atom of the group consisting of chlorine, bromine and iodine, R is selected from the group consisting of hydrogen, alkyl radicals and aryl radicals, and R_2 is an alkylene group whose carbon chain linking the beta and omega carbon atoms of the haloalkanoic acid contains 1-4 carbon atoms. Suitable haloalkanoic acids conforming to the above formula include 4-chlorobutanoic acid, 1-methyl-4-bromobutanoic acid, 1,3-dimethyl-5-iodopentanoic acid, 1-ethyl-7-bromoheptanoic acid, 1-phenyl-4-chlorobutanoic acid, etc.

Many of the N-substituted amides that can be prepared by the process of the invention are known compounds which have known utilities. Certain of the N-aryl substituted amides of lower cycloalkanoic acids have utility as herbicides as described in copending applications Ser. No. 180,306, filed Mar. 16, 1962, now abandoned, and Ser. No. 180,310, filed Mar. 16, 1962, now U.S. Patent 3,246,975, both of which applications are assigned to the assignee of the present application. Other of the amides described in the examples are believed to be new chemical compounds not previously reported in the scientific literature. These new compounds all have herbicidal activity. The N-aryl substituted amides of acrylic and methacrylic acid can be polymerized to form homopolymers or copolymers with a wide variety of comonomers such as acrylonitrile, alkyl acrylates, alkyl methacrylates, vinyl chloride, styrene, and other vinyl or vinylidene monomers.

The above descriptions and particularly the examples are set forth for purposes of illustration only. Many variations and modifications thereof will be obvious to

those skilled in the art and can be made without departing from the spirit and scope of the invention herein described.

What is claimed is:

1. The method of preparing 3',4'-dichlorocyclopropanecarboxanilide comprising heating an alkyl ester of cyclopropanecarboxylic acid in which the alkyl group has from 1 to 3 carbon atoms with 3,4-dichloroaniline in a mutual organic solvent selected from the group consisting of unsubstituted alkanes, unsubstituted aromatic hydrocarbons and halo-substituted aromatic hydrocarbons in the presence of one mole of an alkali metal alcoholate per mole of ester, said alkali metal alcoholate being present in the form of an undissolved solid, removing the alcohol liberated in the reaction as it is formed, neutralizing the resulting reaction mixture with aqueous acid and recovering 3',4'-cyclopropanecarboxanilide.

2. The method of preparing 3',4'-dichloro-1-methylcyclopropanecarboxanilide comprising heating an alkyl ester of 1-methylcyclopropanecarboxylic acid in which the alkyl group has from 1 to 3 carbon atoms with 3,4-dichloroaniline in a mutual organic solvent selected from the group consisting of unsubstituted alkanes, unsubstituted aromatic hydrocarbons and halo-substituted aromatic hydrocarbons in the presence of one mole of an alkali metal alcoholate per mole of ester, said alkali metal alcoholate being present in the form of an undissolved solid, removing the alcohol liberated in the reaction as it is formed, neutralizing the resulting reaction mixture with aqueous

acid and recovering 3',4'-dichloro-1-methylcyclopropanecarboxanilide.

3. The method of claim 1 wherein the ester employed is methyl cyclopropanecarboxylate, and the alkali metal alcoholate is sodium methoxide.

4. The method of claim 2 wherein the ester employed is methyl 1-methylcyclopropanecarboxylate and the alkali metal alcoholate is sodium methoxide.

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71—95, 118; 260—326.3, 408, 468, 558, 562