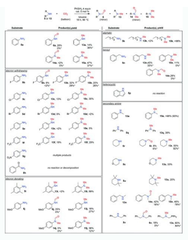
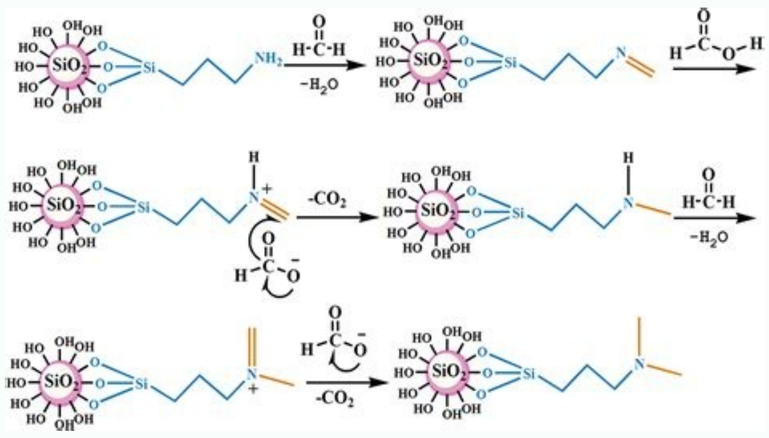
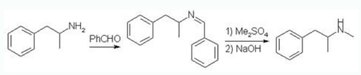
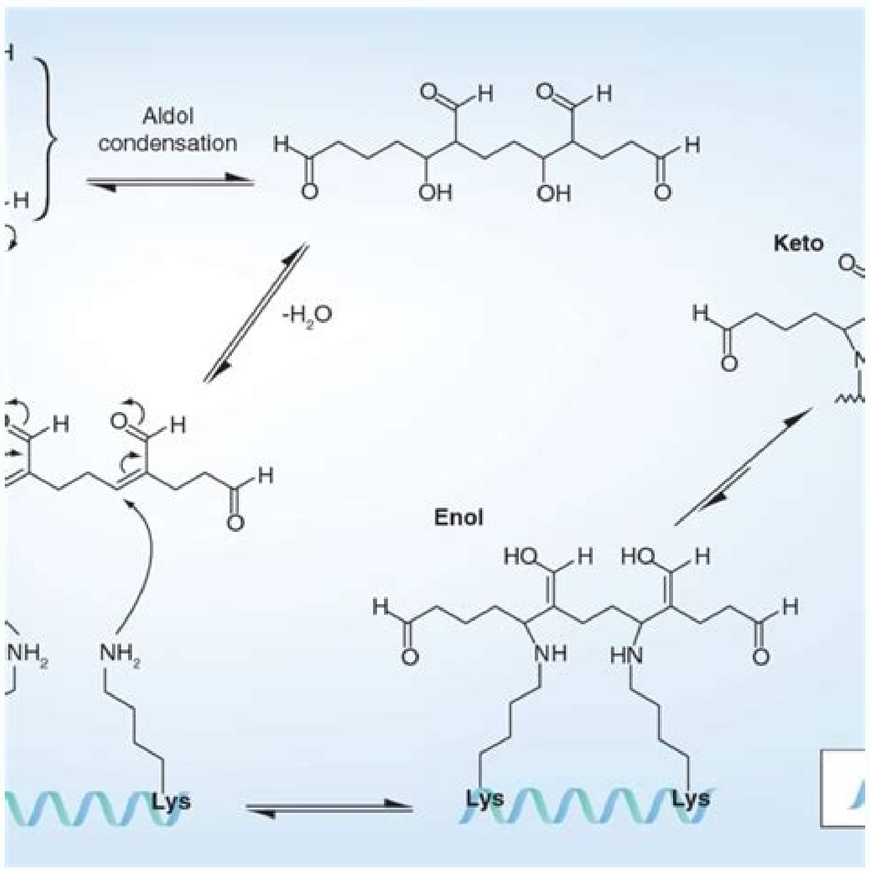
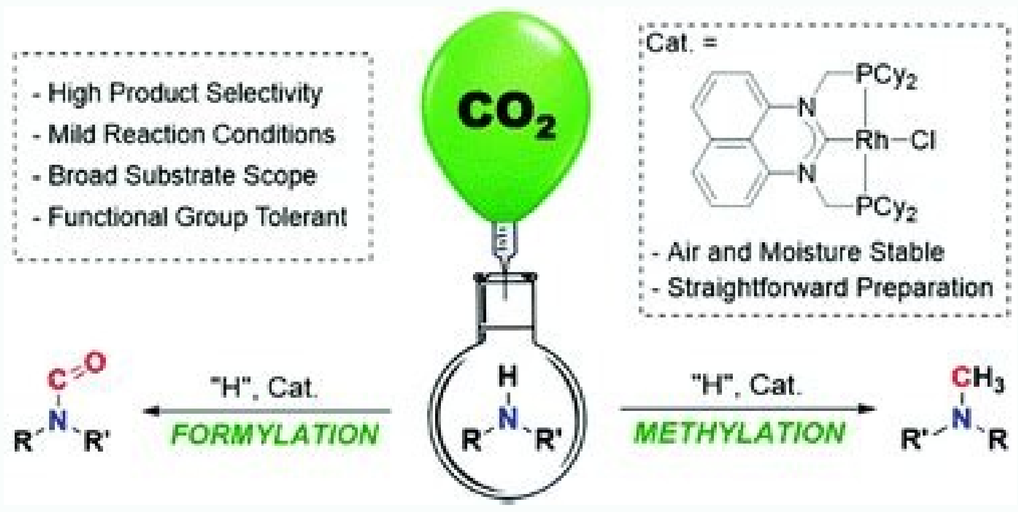
Methylation of primary amines with formaldehyde











Methylamine adalah.

Chemical reaction Eschweiler–Clarke reaction Named after Wilhelm Eschweiler Hans Thacher Clarke Reaction type Substitution reaction Identifiers Organic Chemistry Portal eschweiler-clarke-reaction RSC ontology ID RXNO:0000376 The Eschweiler–Clarke reaction (also called the Eschweiler–Clarke methylation) is a chemical reaction whereby a primary (or secondary) amine is methylated using excess formic acid and formaldehyde.[1][2][3][4] Reductive amination reactions such as this one will not produce quaternary ammonium salts, but instead will stop at the tertiary amine stage. It is named for the German chemist Wilhelm Eschweiler (1860–1936) and the British chemist Hans Thacher Clarke (1887-1972). Mechanism The first methylation of the amine begins with imine formation with formaldehyde. The formic acid acts as a source of hydride and reduces the imine to a secondary amine. The driving force is the formation of the gas carbon dioxide. Formation of the tertiary amine is similar, but slower due to the difficulties in iminium ion formation. From this mechanism it is clear that a quaternary ammonium salt will never form, because it is impossible for a tertiary amine to form another imine or iminium ion. Chiral amines typically do not racemize under these conditions.[5] Altered versions of this reaction replace formic acid with sodium cyanoborohydride. See also Leuckart–Wallach reaction References ^ Eschweiler, W. (1905). "Ersatz von an Stickstoff gebundenen Wasserstoffatomen durch die Methylgruppe mit Hülfe von Formaldehyd". Ber. 38: 880–882. doi:10.1002/cber.190503801154. ^ Clarke, H. T.; Gillespie, H. B.; Weisshaus, S. Z. (1933). "The Action of Formaldehyde on Amines and Amino Acids". Journal of the American Chemical Society. 55 (11): 4571. doi:10.1021/ja01338a041. ^ Moore, M. L. (1949). "The Leuckart Reaction". Org. React. 5: 301–330. doi:10.1002/0471264180.or005.07. ISBN 0471264180. ^ Icke, R. N.; Wisegarver, B. B.; Alles, G. A. (1945). "β-Phenylethyldimethylamine". Organic Syntheses.; Collective Volume, vol. 3, p. 723 ^ Farkas, Eugene; Sunman, Cheryl J. (1985). "Chiral synthesis of doxpicomine". J. Org. Chem. 50 (7): 1110. doi:10.1021/jo00207a037.) Retrieved from " Hongli Wang,a Yongji Huang,a Xingchao Daia and Feng Shi *a Author affiliations The selective N-monomethylation of amines is an important topic in fine chemical synthesis. Herein, for the first time, we described a selective N-monomethylation reaction of amines with paraformaldehyde and H2 in the presence of a CuAlOx catalyst. A variety of amines, including primary aromatic amines, benzylamine and cyclohexylamine, as well as secondary amines, have been shown to be compatible with this reaction. You have access to this article Please wait while we load your content... Something went wrong. Try again? Supplementary information PDF (3798K) Article type Communication First published 26 Apr 2017 Chem. Commun., 2017,53, 5542-5545 H. Wang, Y. Huang, X. Dai and F. Shi, Chem. Commun., 2017, 53, 5542 DOI: 10.1039/C7CC02314F To request permission to reproduce material from this article, please go to the Copyright Clearance Center request page. If you are an author contributing to an RSC publication, you do not need to request permission provided correct acknowledgement is given. If you are the author of this article, you do not need to request permission to reproduce figures and diagrams provided correct acknowledgement is given. If you want to reproduce the whole article in a third-party publication (excluding your thesis/dissertation for which permission is not required) please go to the Copyright Clearance Center request page. Read more about how to correctly acknowledge RSC content. Tweet Share Fetching data from CrossRef. This may take some time to load. Loading related content Clipboard, Search History, and several other advanced features are temporarily unavailable. The .gov means it’s official. Federal government websites often end in .gov or .mil. Before sharing sensitive information, make sure you’re on a federal government site. The site is secure. The https:// ensures that you are connecting to the official website and that any information you provide is encrypted and transmitted securely. Display options Format AbstractPubMedPMID A simple transition metal-free procedure using formal dehyde for the N,N-dimethylation and N-methylation of primary and secondary anilines is reported. The reaction showed limitations on sterically hindered and electron-withdrawing anilines, but is successful on amines with electron-donating substituents. Formaldehyde acts as both the reducing agent and the carbon source in the reaction. Ruthenium-catalyzed alkylation of indoles with tertiary amines by oxidation of a sp3 C-H bond and Lewis acid catalysis. Wang MZ, Zhou CY, Wong MK, Che CM. Wang MZ, et al. Chemistry. 2010 May 17;16(19):5723-35. doi: 10.1002/chem.200902387. Chemistry. 2010. 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RSC Adv. 2019 Sep 26;9(52):30570-30574. doi: 10.1039/c9ra06144d. eCollection 2019 Sep 23. RSC Adv. 2019. PMID: 35530231 Free PMC article. N-Dimethylation and N-Functionalization of Amines Using Ru Nanoparticle Catalysts and Formaldehyde or Functional Aldehydes as the Carbon Source. Liu J, Song Y, Wu X, Ma L. Liu J, et al. ACS Omega. 2021 Aug 26;6(35):22504-22513. doi: 10.1021/acsomega.1c01961. eCollection 2021 Sep 7. ACS Omega. 2021. PMID: 34514223 Free PMC article. MeSH terms Substances Cite Format: AMA APA MLA NLM United States Patent Office 3,210,349 Patented Oct. 5, 1965 METHYLATION OF PRIMARY AND SECONDARY AMINES USING A SMALL STOICHKOMETRIC EXCESS OF FORMALDEHYDE AND ADDING A SMALL STOICHIOMETRIC EXCESS OF FORMIC ACID LAST Norman B. Godfrey, Austin, Tex., assignor to Jefferson Chemical Company, Inc., Houston, Tex., a corporation of Delaware No Drawing. Filed Nov. 6, 1961, Ser. No. 150,153 7 Claims. (Cl. 260-247) This invention relates to the method for the preparation of tertiary amines. More particularly, this invention relates to a method for the methylation of a primary or a secondary amine. One of the methods that is widely used for the methylation of primary or secondary amines is the Eschweiler-Clarke modification of the Leuckart reaction (Organic Reactions," volume V, page 307), wherein the amine to be methylated is mixed with a 100% to 300% molar excess of formic acid to provide a corresponding formate salt, followed by a reaction of the formate salt with formaldehyde for a period of eight to twelve hours. Prior workers have considered it necessary, and it has been the customary practice, to utilize the procedure just outlined in methylating amines, even though very large excesses of reactants are required. It has now been surprisingly discovered that by violating the above teaching of the prior art, a much more etfective process for the methylation of amines is possible. Briefly, and in accordance with the present invention, a primary or secondary amine is mixed with a small stoichiometric excess of formaldehyde and thereafter, a small stoichiometric excess of formic acid (based on the amine) is slowly added to the resultant mixture with agitation at a temperature in the range of 50 C. to 110 C., whereby a completely methylated amine is formed. The starting materials for the present invention include formic acid, formaldehyde and a primary or secondary amine. Preferably, the formic acid is employed as a concentrated 85% to 95% aqueous solution. Formaldehyde may be employed in aqueous solution (e.g., formalin), as paraformaldehyde, etc. The amines to be utilized, in accordance with the present invention, are primary or secondary amines of the general formula: wherein R is a saturated hydrocarbon group and R is hydrogen or a saturated hydrocarbon group. The hydrocarbon group may be alkyl or aralkyl and may be substituted with alkoxy or tertiary amine groups. Preferably, the amine will contain from 2 to 20 carbon atoms. Also, R and R taken together, may represent a carbocyclic or saturated heterocyclic ring. Examples of suitable amines include methylamine, dimethylamine, and homologs thereof, such as n-hexylamine, di-n-propylamine, etc., morpholine, etc., Z-aminoethanol, 2,2'-iminodiethanol, 2-(2-aminoethoxy)ethanol, 4-(2-aminoethy1) morpholine. In accordance with the present invention, from about 1 to about 1.2 (perferably 1.1) mols of formaldehyde per equivalent of replaceable amino hydrogen (1 equivalent per mol of secondary amine, 2 equivalents per mol of primary amine) are mixed with the amine to be methylated as a first step. External cooling may he applied during this step if desired in order to moderate the exothermal heat of reaction. As a second step, from about 1 to about 1.2 (preferably about 1.1) mols of formic acid per equivalent of replaceable amino hydrogen are added slowly with agitation. Reaction occurs exothermally at temperatures in the neighborhood of to C., accompanied by vigorous evolution of carbon dioxide gas. Toward the end of the formic acid addition, the rate normally slackens; and external heating may be resumed. When gas evolution stops, the tertiary amine reaction product may be recovered by any suitable means, such as distillation. Optionally, a strong base such as sodium or potassium hydroxide may first be added to the crude reaction product mixture in order to neutralize any unreacted formic acid and to cause separation into an aqueous phase and an organic phase containing essentially all the tertiary amine product. The invention will be further illustrated by the following examples, which are given by way of illustration and not as limitation on the scope of this invention. Example I Morpholine (86 grams) and 36.3% formaldehyde solution (91 grams) were mixed in a stirred reaction flask. Formic acid (56 grams, 85% strength) was added dropwise to the spontaneously refluxing mixture, which was then heated under reflux until gas evolution ceased. Total reaction time was two hours. Sodium hydroxide (25 grams) was dissolved in the reaction mixture, which was then distilled. The distillate, collected over the range of 88 to 99 C., contained N-methylmorpholine in 92.5% yield, together with co-distilling water. Example Il Dipropylamine (202 grams) was mixed with 37.8% formaldehyde solution (175 grams) as above. Formic acid (56 grams, 85%) was added dropwise during one hour. The mixture was refluxed for another 1% hours, until gas evolution had nearly ceased. Potassium hydroxide (50 grams) was dissolved in the reaction mixture, which separated into two layers. The upper layer was dried with solid potassium hydroxide and distilled, giving a 67% yield of methyldipropylamine boiling in the range 114.5 to 115 C. Example 111 Paraformaldehyde (50 grams) was added to pyrrolidine (102.7 grams) with stirring and cooling in an ice bath. Formic acid (86.2 gram-s, 85%) was added dropwise to 50 to 60 C. during 1% hours. The mixture was refluxed another two hours. Sodium hydroxide (20 grams) was dissolved in the reaction mixture, the layers were separated, and the upper layer was distilled. An 82% yield of N-methylpyrrolidine was obtained, boiling at 73.5 to 745 C. Example IV Hexylamine (102.4 grams) and formaldehyde solution (178.5 grams, 37.8%) were mixed as above, then treated dropwise with formic acid (119 grams, 85 Addition required 3 /2 hours, and refluxing, another hour. The yield of N,N-dimethy1hexylamine (boiling point 148 C.) was Example V Formic acid (119.4 grams, Was added to a mixture of 4-(2amin0ethyl)morpholine (130.1 grams) and formaldehyde (178.7 grams, 37.8%) in one hour at 75 to C. The reaction was completed by heating at reflux temperature for 2 /2 hours. The yield of 4-(2-dirnethylaminoethyl)morpholine (boiling range 565 to 57 C./2 mm.) was 61%. What is claimed is: 1. In a method for the rnethylation of an amine selected from the group consisting of primary and secondary amines by treating said amine with formic acid and formaldehyde, the improvement which comprises mixing said amine with a small stoichiometric excess of formaldehyde, adding a small stoichiometric excess of formic acid to the resultant mixture with agitation, at a temperature within the range of about 50 to about 110 0., whereby a methylation reaction is spontaneously initiated which results in the evolution of carbon dioxide and maintaining said reaction mixture at said reaction temperature until the evolution of carbon dioxide substantially ceases. 2. A method as in claim 1 wherein from about 1 to about 1.2 mols of formaldehyde and from about 1 to about 1.2 mols of formic acid are employed per replaceable amino hydrogen in the amine feed stock. 3. A method as in claim 2 wherein the amine is morpholine and the product is N-methylmorpholine. 4. A method as in claim 2 wherein the amine feed stock is dipropylamine and the product is methyl-dipropylamine. 5. A method as in claim 2 wherein the amine feed stock is pyrrolidine and the product is N-methylpyrrolidine. 5 stock is 4-(2-aminoethyl)morpholine and the product is 4-(Z-dimethylaminoethyl)morpholine. References Cited by the Examiner UNITED STATES PATENTS 1/45 Kirby 260-583 1/57 Erickson 260583 OTHER REFERENCES Clarke et al.: J. Am. Chem. Soc., vol. 55, pp. 4571-87 References Cited by the Applicant UNITED STATES PATENTS 2,636,032 4/53 Weston et a1. NICHOLAS S. RIZZO, Primary Examiner. LEON ZITVER, Examiner.

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