6-硝基胡椒基酸合成新方法*

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摘　要: 报道了直接以黄樟油为原料, 经硝化和氧化制备 6-硝基胡椒基酸的新工艺。采用调整反应温度和硝酸浓度等因素对硝化反应进行了探讨; 采用正交实验优化了氧化反应参数, 获得了较好的工艺条件。

关键词: 6-硝基胡椒基酸; 黄樟油; 硝化反应; 氧化反应
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1　前言

6-硝基胡椒基酸是一种重要的化工原料, 是合成抗菌药物西洛沙星、米洛沙星、心血管药物奥索利酸、抗癌药物及强心剂的重要中间体, 还可广泛用于香料、染料、纺织品助剂的生产, 具有重要的工业应用价值[1~4]。

合成 6-硝基胡椒基酸的方法多以胡椒醛为原料, 通过硝化、氧化等工艺制取[5~7]。胡椒醛本身由黄樟油或胡椒环经一步或多步反应制取, 而以黄樟油为原料生产胡椒醛的过程有双键位移、控制氧化等步骤。且制取 6-硝基胡椒基酸还要进行硝化、氧化等反应, 生产过程至少有四步反应。该法存在步骤繁琐、工艺要求苛刻、最终收率低等缺点。有鉴于传统工艺的不足, 笔者直接以黄樟油为原料, 通过硝化、氧化两步反应来合成 6-硝基胡椒基酸。对硝化反应和氧化反应中的原料配比、反应温度等因素进行了探讨, 获得了较好的工艺条件。该工艺未见文献报道。

2　实验部分

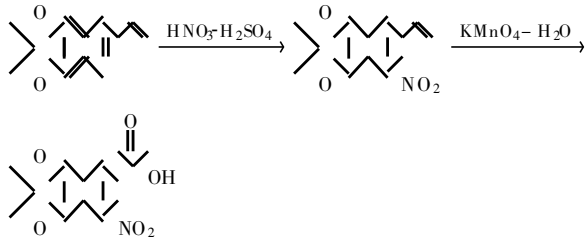
2.1　试剂与仪器

试剂: 黄樟油(95%)、浓硫酸、发烟硝酸、高锰酸钾均为分析纯试剂。

仪器: PE-1710 型红外仪、WRS-1 数字显微熔点仪、LC-CAD 高效液相色谱仪。

2.2　实验步骤

由黄樟油为原料合成 6-硝基胡椒基酸的反应式如下:



2.2.1　黄樟油硝化

在装有冷凝管、温度计、滴液漏斗、搅拌棒的 250 ml 四口烧瓶中, 加入 71.5 g(70 ml, 0.44 mol) 黄樟油, 开动搅拌器, 从滴液漏斗中慢慢滴入由 20 ml 98% 的浓硫酸与 30 ml 95% 的发烟硝酸配成的混酸, 控制反应温度在 40 ℃以下(必要时用水浴冷却)。滴加完毕, 继续搅拌反应 6 h。反应完毕后, 将反应物移入分液漏斗中, 分出下层有机相, 弃去无机相, 有机相用饱和食盐水洗涤两次, 每次用饱和食盐水 50 ml, 再用水洗涤两次, 每次用水 50 ml。将有机相静置过夜, 即析出大块棕红色结晶, 烘干, 称量得 85.0 g, 收率 94.4%, 由 IR 谱图分析, 其吸收峰符合 6-硝基黄樟素的结构特征。用 HPLC 分析其含量为 95.0%。

2.2.2　硝基黄樟油的氧化反应

在装有温度计、滴液漏斗、搅拌棒的 500 ml 三口瓶中加入 5.0 g(0.25 mol) 上述硝基化合物和 25 ml 水, 升温至 70~80 ℃, 搅拌下从滴液漏斗中加入由 12.0 g(0.75 mol) 高锰酸钾于 200 ml 水配成的溶液。控制滴加速度, 在 40~50 min 内滴加完毕, 保持温度 70~80 ℃, 反应 1 h。取下烧瓶将反应物倾入 500 ml 烧杯中, 趁热用 10% KOH 溶液调节反应液的 pH 为 10。趁热过滤, 用热水洗涤滤渣, 合并滤液与洗液, 冷却。用 1∶1 盐酸酸化至 pH 为 1。减压

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浓缩溶液, 至有黄色结晶析出为止。溶液置于冰箱中 6 h, 即有大量针状结晶析出。过滤, 干燥, 产品重 9. 7 g, 收率 96. 0%, mp. 173~ 175 ℃(文献值为 172 ~ 173 ℃) 。由 IR 谱图分析, 其吸收峰符合为 6-硝基胡椒基酸结构特征。由 HPLC 分析含量为 99. 0%。

3 结果与讨论

3. 1 硝化反应

硝化反应是放热反应, 硝酸-浓硫酸混酸滴加速度不宜过快。混酸硝化体系中, 高温有利于发生以硝酸作为氧化剂的氧化反应和多硝化反应。反应温度和时间对硝化反应的影响如下:

反应温度(℃)	10	10	20	20	30	40	40	50	60
反应时间(h)	5	6	5	6	5	6	5	6	6
收率(%)	75	76	88	89	93	94	95	95	95

以上结果可见, 当温度升至 40 ℃, 反应时间为 5 h, 收率达到最高。随后升高温度与延长反应时间, 收率没有明显提高的趋势。

硝化反应中, 起作用的是硝酰正离子。保证反应体系中硝酸达到一定浓度以产生足够的硝酰正离子是硝化反应中至关重要的因素。就黄樟素而言, 由于烷氧基和烷基对苯环的推电子作用, 使环上电子云密度增大, 硝化反应容易进行。硝酸浓度对硝化反应的影响结果如下:

硝酸浓度(%)	65	70	75	80	85	90	95	98
收率(%)	0	10	25	50	65	80	94	90

由以上可见, 硝酸浓度为 95% 时, 黄樟素的硝化反应收率最高。

3. 2 氧化反应

芳烃侧链烷基的氧化可选用硝酸、重铬酸钾-硫酸、高锰酸钾等。笔者选用 10% ~ 40% 的各种浓度的硝酸作氧化剂, 6-硝基黄樟素的转化率很低。选用重铬酸钾-硫酸作氧化剂, 所得产物的选择性很差, 产物中除了有 6-硝基胡椒基酸之外, 还有 6-硝基胡椒醛等杂质。选择饱和高锰酸钾溶液作氧化剂, 原料的转化率和产品的选择性都较好, 在初步试验的基础上, 设计了一个三因素三水平的 L_9 实验, 实验结果见表 1。

表 1 6-硝基黄樟素氧化反应实验结果

序号	配比*	反应时间 (h)	温度 (℃)	产物熔点 (℃)	收率 (%)
1	3∶6	1	60	162	52
2	3∶6	1. 5	回流	164	47
3	3∶6	2	75	163	56
4	3∶10	2	75	171	96
5	3∶10	1	60	170	92
6	3∶10	1. 5	回流	170	93
7	3∶14	1	回流	168	85
8	3∶14	1. 5	60	165	88
9	3∶14	2	75	169	95

* 配比为硝化黄樟素与高锰酸钾的摩尔比, 收率由 HPLC 归一化法分析得出。

由表 1 结果中的不同水平的极差分析可知, 由高锰酸钾作为氧化剂时, 反应温度对氧化反应影响较大。

4 结论

1) 以黄樟油为原料, 通过硝化、氧化两步反应, 可制取 6-硝基胡椒基酸。两步反应总收率可达 89. 3% 。

2) 硝化反应中, 硝酸浓度为 95% , 温度为 990 ℃, 反应时间为 5 h, 收率达到最高。

3) 氧化反应中, 由高锰酸钾作为氧化剂, 硝化黄樟素与高锰酸钾的摩尔比为 3∶10, 反应时间为 2 h, 反应温度为 75 ℃, 氧化收率最高, 产物纯度也较高。

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ABSTRACTS

The Progress on the Studies of Molecular Imprinting Technique in Chiral Drug Separation and Clinical Drug Analysis. *LIU Hui-jun, etc (College of Chemistry and Chemical Engineering, Hunan University, Changsha Hunan 410082, China).* J. fine chem. intermediates, 2003, 33(6): 1~ 5

The synthesic methods of molecular imprinted polymer (MIP) were presented, and the molecular recognizable theory of MIP was reviewed in the paper. The research progress on applications of MIP in chiral drug separation and clinical drug analysis in the recent years was expounded.

Key words: molecular imprinting technology; molecular imprinted polymer; recognizable theory; chiral separation; drug analysis.

The Development of Study on Hydrodynamics of Vapor-liquid-liquid Three-phase Distillation. *JIANG Zhuo-liang, etc (Hunan Haili Engineering Consultation Co., Ltd. Changsha Hunan 410007, China).* J. fine chem. intermediates, 2003, 33(6): 6~ 8

The development of study on hydrodynamics of vapor-liquid-liquid three-phase distillation from trays was introduced. Flow regimes and liquid-liquid mixing phenomena on the trays, and a lot of parameters affecting hydrodynamics were discussed. A great deal of viewpoints and suggestions having been put forward in the paper are significant important for optimizing design of distillation tower.

Key words: hydrodynamics; three-phase distillation; tray

The Research Progress on Preparation of Amino Acid by Oxidative Dehydrogenation of the Alkanolamine(s) in Catalyst. *YE Hong-ping, etc. (The chemical engineering institute of university of Xiang Tan, Xiangtan Hunan 411105, China).* J. fine chem. intermediates, 2003, 33(6): 9~ 13

The research on the amino acid by dehydrogenation alkanolamine(s) in catalyst was recommended. The catalysts adopted were especially introduced the such as, sort of catalyst, the preparation method, and the mechanism of dehydrogenation. The factors influencing the yield of the reaction were analysed, and the methods of separation and sublimation result were also introduced.

Key words: alkanolamine(s); catalyse; amino acid; mechanism of reflection and separation

The Technique Progress and Application of P-phenylphenol. *JIANG Biao. (Hunan Research Institute of Chemical Industry, Changsha Hunan 410007, China).* J. fine chem. intermediates, 2003, 33(6): 14~ 16

The main applications of P-phenylphenol and some important production processes were presented in the article. Some proposals on developing P-phenylphenol were forward based on comparing to the main production processes.

Key words: P-phenylphenol; sulfonation; alkaline fusion; application

Preparing Technology on Microcapsule. *CHEN Jian-shan, etc (Central-south Forestry University, Zhuzhou Hunan 412006, China).* J. fine chem. intermediates, 2003, 33(6): 17~ 19

Methods and theories of the preparation of microcapsule were reviewed. Some approaches methods, such as heterocoagulation, emulsion polymerization etc., and the research progress was introduced in detail.

Key words: microcapsule; heterocoagulation; emulsion polymerization; interface & insitu polymerization

The Study on Synthesis of Cationic Etherification Agent "CHPTMA" under Aqueous Process. *YANG Jian-zhou, etc (College of Chemistry & Chemical Engineering, Shanxi University of Science & Technology, Xianyang Shanxi 712081, China)* J. fine chem. intermediates, 2003, 33(6): 20~ 22

The synthesis of 3-chloro-2-hydroxypropyl trimethylammonium chloride (CHPTMA) under aqueous process at room temperature was discussed. Trimethylamine hydrochloride (TMAHC) was firstly prepared from trimethylamine (Industrial grade) and hydrochloric acid (w= 36%), then epichlorohydrin (EPIC) was dropped in it. The effects of the reaction temperature, drop time of EPIC, total reaction time, pH, catalyst, reaction medium, and molar ratio of EPIC and TMAHC on yield of CHPTMA were studied.

Key words: 3-chloro-2-hydroxypropyl trimethyl ammonium chloride; etherification agent; synthesis; aqueous process

A Novel Synthesis of 2-(2, 4-Dichlorophenoxy) Triethylamine. *HE Jian-ling. (Department of Chemical Engineering of Yancheng Institute of Technology, Yancheng Jiangsu 224003, China)* J. fine chem. intermediates, 2003, 33(6): 23~ 24

A novel synthesis of 2-(2, 4-dichlorophenoxy) triethylamine was investigated. 2-(2, 4-dichlorophenoxy) triethylamine was prepared by phase transfer catalyst from 2, 4-dichlorophenol. The yield of reaction was above 80%. The effects of some factors such as reactants ratio, catalysts, reacting time and temperature etc, were discussed. The structure of product was confirmed by elemental analysis, IR and ^{1}HNMR.

Key words: 2, 4-dichlorophenol; Bu_4NBr; 2-(2, 4-dichlorophenoxy) triethylamine

A New Synthesic Method of 6-Nitro-1, 3-Benzodioxide Acid. *YANG Guang-zhao, etc (College of Chemistry, Xiangtan University, Xiangtan Hunan 411105, China).* J. fine chem. intermediates, 2003, 33(6): 25~ 26

A new method including the nitration and oxidation of synthesis of 6-Nitro-1, 3-benzodioxide acid was introduced. The raw material is safrole. In the process of nitration, the synthesis temperature and the nitric acid concentration was tested. The optimum conditions of oxidation were studied by the way of orthogonal experimental design.

Key words: 6-Nitro-1, 3-benzodioxide acid; Safrole; nitration; oxidation

The Initial Study on the Fluorodenitration to Prepare Fluoroaromatic Compounds. *YE Fang-qing, etc (School of Chemical Engineering, Nanjing University of Science and Technology,*