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A Versatile Approach to the Solution-Phase Combinatorial Synthesis of Substituted Pyridines: The Cobalt-Catalyzed Cyclotrimerization of Alkynes with a Nitrile

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The cobalt-catalyzed trimerization of two alkynes and one nitrile was exploited to produce solution-phase libraries of pyridines. Upon addition of 2 equiv of a CO scavenger (i.e., an amine-*N*-oxide), the commercially available [$CpCo(CO)_2$] proved to be an attractive catalyst, as the required reaction temperatures, side product formation (i.e., carbocycles), and oxygen sensitivity are moderate. Purification of the reaction mixture was performed with an acidic cation-exchange resin.

Introduction

Compounds which display biological activity are often derived from heterocyclic structures.[1] Pyridine derivatives are among the most common heterocyclic compounds.[2] The pyridine motif is found in various therapeutic agents, including numerous antihistamines, antiseptic, antiarrythmic, antirheumatic, and other pharmaceutical compounds.[3]

To date, the combinatorial generation of pyridines was achieved primarily via the synthesis of dihydropyridines (Hantzsch condensation), followed by an oxidation.[4] However, this route sets severe constraints on the substitution patterns of the pyridines. Indeed, compounds prepared by this method incorporate acyl or carbonyl groups in the 3- and 5-positions. Another access to the pyridine core is achieved via a "3+3" pyridine synthesis of an α,β-unsaturated carbonyl compound and a primary enamine.[5] A three-component solid-phase synthesis of trisubstituted pyridines via a three-step procedure involving a Claisen−Schmidt reaction was recently reported.[6] To the best of our knowledge, the only solution-phase combinatorial synthesis of pyridines has appeared recently: reaction of 3-aminocrotonitrile with chalcones under standard Hantzsch cyclization conditions yields 2,3,4,6-tetrasubstituted pyridines.[7]

We recently launched a research program aimed at the use of transition metal catalysts for the generation of solution-phase libraries.[8,9] For this purpose, we sought a broadly applicable transition metal-catalyzed reaction yielding heterocycles. For combinatorial chemistry, a *three*-component condensation is most attractive, as it allows, by varying the components individually, to generate rapidly very large diversity mixtures.

In the past three decades, the cobalt-catalyzed co-oligomerization between alkynes and nitriles has received considerable attention.[10,11] This method which was introduced by Wakatsuki and Yamazaki[12] was further refined by Bönnemann[13−16] as well as Vollhardt.[17−19] Most often, cobalt-cyclopentadiene derivatives were used as catalysts for the co-oligomerization of alkynes with nitriles to yield substituted pyridines. For most synthetic purposes, this methodology suffers from a major drawback: except for symmetrical alkynes or reaction yielding fused pyridines, regioisomers are produced. Although the regioisomers can complicate analytical and biological evaluation of library mixtures, this route provides access to a wide range of diverse structures.

In this paper, we report the cobalt-catalyzed cyclization of two alkynes and one nitrile to yield 2,4,6- and 2,5,6-trisubstituted pyridines.[20] In contrast to the published combinatorial pyridine syntheses, the method outlined herein does not require any special funtional group to ensure the formation of the pyridine scaffold. The substitution pattern, however, is limited to either the 2,4,6- or the 2,5,6-trisubstituted pyridines. It thus nicely complements the other published methods.

Results and Discussion

The cobalt-catalyzed co-oligomerization of an alkyne and a nitrile, can, in principle, yield four pyridine regioisomers, as depicted in Scheme 2. It is generally accepted that the reaction proceeds via a cobaltacyclopentadiene intermediate.[11] Upon reaction with a nitrile, four possible pyridine regioisomers can result. Although the reasons are not fully understood, it has long been noted that only the pyridines with a 2,4,6- or a 2,5,6-substitution pattern are produced in significant amounts (see Scheme 1).[14]

In the presence of two different alkynes and a single nitrile in a reaction mixture, eight pyridines can be produced. Four of these result from the homocondensation of two identical alkynes and thus bear the same substituents in 2- *and* 4- or 5-position. The remaining four pyridines bear up to three different substituents. Let us call these homo- and hetero-pyridines, respectively (see Scheme 2).

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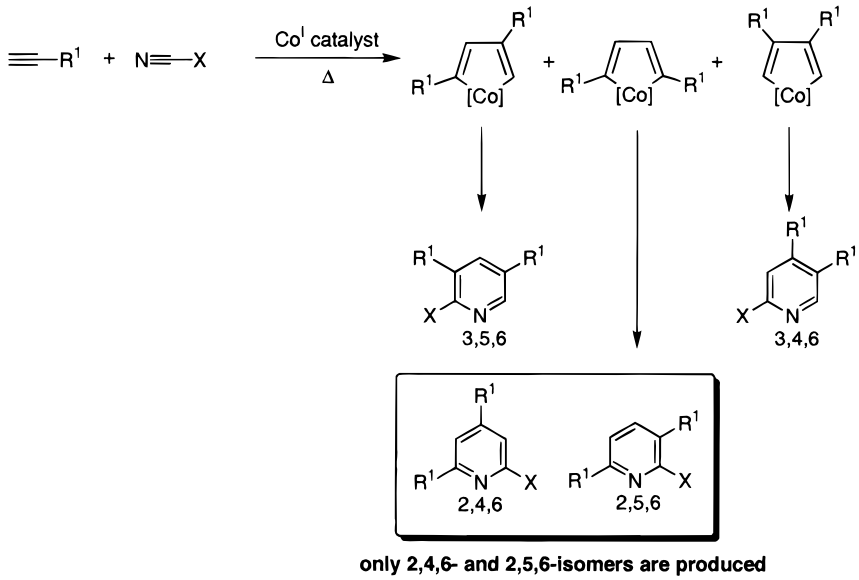
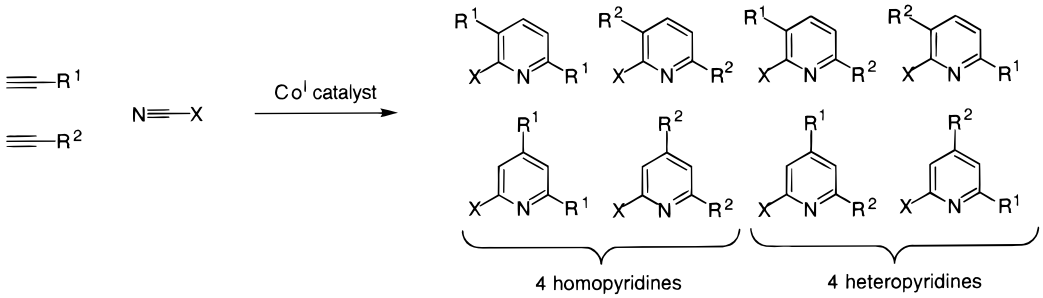
Scheme 1. Addition of a Nitrile to the Three Possible Cobaltacyclopentadiene Intermediates Could Yield Four Pyridine Regioisomers; Only the 2,4,6- and 2,5,6-Isomers Are Formed



Scheme 2. Two Different Terminal Alkynes React with One Nitrile in the Presence of a Cobalt Catalyst To Afford Eight Different Pyridine Derivatives



We tested various well-documented catalytic systems, including $CoCl_2/NaBH_4$ **1**,[13] $[Cp_2Co]$ **2**,[21] [CpCo(COD)] **3**,[22] $[CpCo(C_2H_4)_2]$ **4**,[23] $[CpCo(CO)_2]$ **5**,[24] $[Me_5CpCo(CO)_2]$ **6**,[25,26] and $[Me_5CpCo(allyl)]$ **7**.[27,28] Most of these systems, however, need either high temperature (i.e., >140 °C) (i.e., catalysts **1**−**3, 5, 6**), photochemical irradiation (i.e., catalyst **3**), or handling under rigorous inert conditions (i.e., catalyst **4**, **7**). With a 96-well plate format in mind, we sought a catalytic system which could operate at lower temperature and on a benchtop rather than in a glovebox.

Inspired by the Pauson−Khand reaction,[29,30] we focused on $[CpCo(CO)_2]$ **5**. We speculated that, upon addition of a carbon monoxyde scavenger, we should be able to significantly decrease the reaction temperature and thus offer an attractive methodology for the combinatorial synthesis of pyridine libraries. Addition of 2 equiv of an amine *N*-oxide (either *N*-methylmorpholine-*N*-oxide (NMO) or trimethylamine oxide (TMAO)) to $[CpCo(CO)_2]$ **5** proved possible to decrease reaction temperature from ca. 180 °C to ca. 85 °C. A further advantage of this catalyst mixture is that the products resulting from alkyne trimerization (i.e., carbocycles) are produced only in small amounts (<5% vs pyridines), whereas other catalysts often produce larger amounts of benzene derivatives. Oxygen should be avoided as much as possible; however, the use of nitrogen-flushed reagents pipetted on a benchtop proved sufficient to ensure reproducible yields.

Although this reaction can be performed in a wide variety of solvents, including water/methanol mixtures,[31] the solubility of both the catalyst and the starting materials is critical. We found that, for convenience, equimolar amounts of each alkyne are best dissolved in the neat nitrile. After addition of 2−5 mol % of $[CpCo(CO)_2]$ **5** and 5−10 mol % of TMAO cocatalyst, the reaction vessel is sealed and heated with stirring at 85 °C for 16 h. The presence of an excess nitrile (> 5 equiv vs alkynes) favors the formation of the pyridine vs the carbocycles (benzene derivatives), which are invariably produced as side producs (<5% by GC). In the case of solid nitriles or when acetylene is used, the reaction can be carried out in xylene or toluene.

After heating at 85 °C with stirring for 16 h, the reaction mixture is filtered over an acidic cation-exchange resin (DOWEX 50 W X 8). This purification step protonates the basic pyridine compounds and most probably oxidizes the cobalt catalyst while both the carbocycles and the starting materials are eluted as they are not protonated. Elution with an ammonia-containing organic solvent (wet methanol or wet acetonitrile) yields, after evaporation of the volatiles (including trimethylamine produced from TMAO), essentially pure (by GC) pyridines in ca. 50% overall yield. After this simple filtration procedure, we determined that the cobalt content in the solution phase is <3 ppm (by atom absorption spectroscopy). Typical GC spectra of a crude reaction

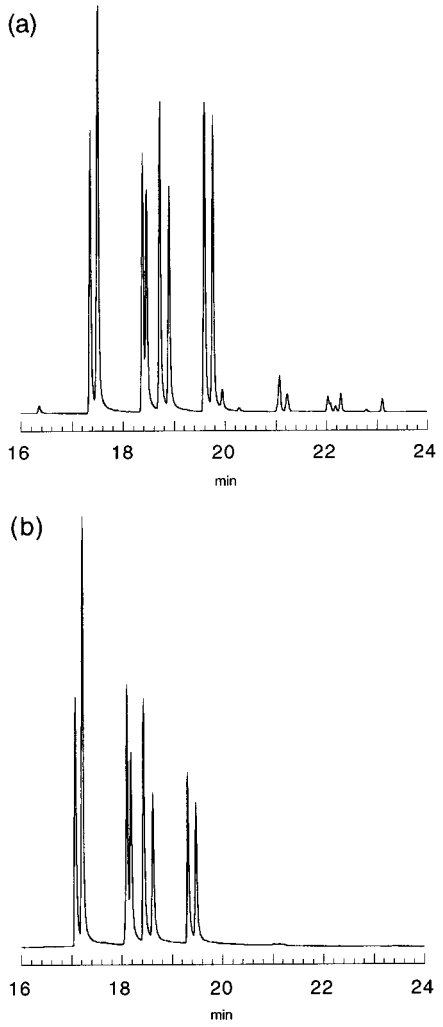


Figure 1. GC spectra of the crude (a) and purified (b) mixture resulting from the reaction between propionitrile (neat, 5 equiv), 1-hexyne (1 equiv), and methylpropargyl ether (1 equiv) in the presence of $[CpCo(CO)_2]$ (0.05 equiv) and TMAO (0.1 equiv). (These products were identified by GC-MS and ^{1}H NMR.)

mixture and after filtration over the acidic cation-exchange resin are depicted in Figure 1.

To test the applicability of this methodology for the generation of solution-phase libraries, we screened 14 alkynes and 10 nitriles that can potentially yield a total of 3920 pyridines. These are listed in Figure 2.

We focused first on the synthesis of homopyridines which result from the condensation of two identical alkynes and one nitrile. For screening purposes, 76 reactions (covering all starting materials depicted in Figure 2) were carried out and characterized. Six of these were analyzed and characterized by GC-MS and ^{1}H NMR. Nine reaction mixtures were characterized by GC-MS, five by ^{1}H NMR, and the remaining 55 were analyzed by GC. In 62 cases (82%), both regioisomers were unambiguously identified. In a single case (butyronitrile and 1-hexyne) a single regioisomer was detected by GC. Depending on the substituents, the ratio (R) of the regioisomers varies between $1 < R < 3.6$. In all other cases (18%), no product could be identified. With this methodology, aromatic nitriles gave poor results as no pyridines could be identified. By increasing the temperature to ca. 140 °C, however, these smoothly reacted to afford pyridines bearing an aromatic substituent in 6-position. We thus conclude that this reaction is broadly applicable and tolerates most functional groups. A rough ordering of reactivity of substrates is presented in Figure 2.

To generate diversity, we then focused on reactions derived from two different alkynes and one nitrile, yielding a total of eight pyridines per pool (four homo- and four heteropyridines). We carried out 300 reactions between two different alkynes and one nitrile in a sealed Teflon 96-well plate (Titan PTFE micro titer plates from Radleys (1 mL wells)). Twenty-four wells were analyzed.

Analysis of these mixtures revealed that in many cases less than eight signals were detected by GC. From the relative intensity of the GC signals, however, we suspected that some of the peaks correspond to two regioisomers (see Figure 3a). Using a derivatized cyclodextrin GC column solved this problem in a few cases, yielding a total of eight peaks.

Alternatively, ^{1}H NMR was used to determine both the overall yield (upon addition of 1,3,5-triazine as an internal standard) and the product ratios. Depending on the substitution pattern of the pyridines (2, 4, 6 or 2, 5, 6), either the H^3 and H^5 signals or the H^3 and H^4 signals appear as two singlets or two doublets, respectively (neglecting long-range coupling). The chemical shift (δ in ppm) of these signals can be accurately predicted from increment tables: in most cases $6.5 < \delta < 8.5$. Integration of the 16 signals (24 lines) produced by the eight pyridines gives the relative ratios (R) of the products which again lie in the range $1 < R < 3.6$ (see Figure 3b). However, due to the presence of traces of Co (<3 ppm by AAS), the relevant ^{1}H signals were broadened in some cases, thus hampering the wide use of this method to determine product ratios, as fewer than 24 lines could be unambiguously assigned.

Despite our efforts, the expected eight pyridines could be detected only in five cases. Seven pyridines were detected in six cases. Six pyridines were detected in four cases. On the basis of the experiments with only one alkyne (where both pyridine regioisomers are produced in >80% of the cases) and inspection of the GC chromatograms (see Figure 3 and Supporting Information), we suspect that even when only six or seven peaks are present, all eight pyridines are indeed produced. Combining these, we suggest that in 67% of the cases all eight pyridines are formed. In 21% of the cases, no product could be unambiguously assigned.

Concerning the deconvolution strategy, we propose the following procedure. After screening the pyridine library for a given activity, let us assume that one or several wells each containing eight pyridines have been identified. The active member can be a pyridine which results from the condensation of either one or two alkynes (see Scheme 2, homo- and heteropyridines, respectively). The homopyridines are present in several wells and therefore should easily be identifiable from their occurrence in a given library. If only one well is active, the activity must be caused by one of the four heteropyridines present in that well. For a few model reactions, we have shown that the pyridine regioisomers can be separated either by flash chromatography or preparative HPLC, thus ensuring only a modest deconvolution effort.

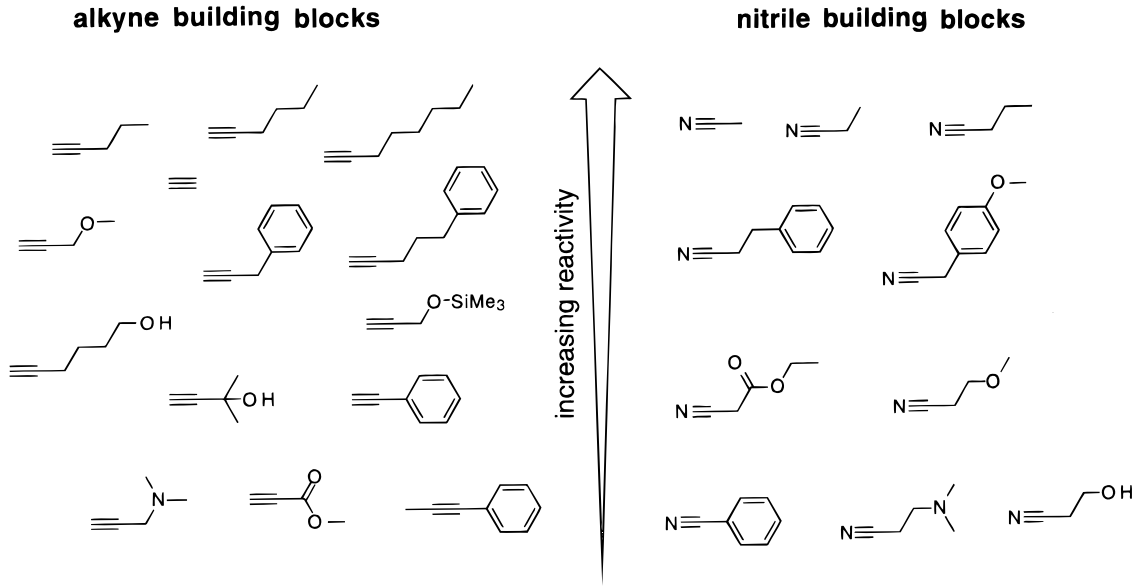


Figure 2. Fourteen alkyne building blocks and 10 nitrile building blocks allow the combinatorial generation of 3920 pyridines.

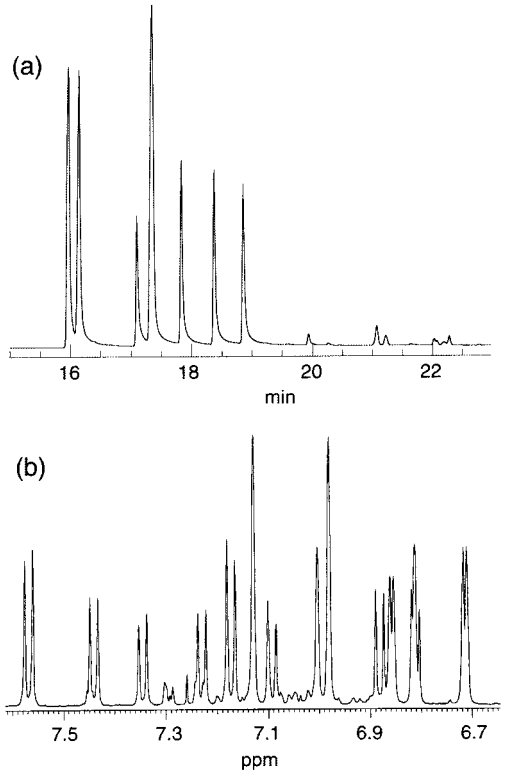


Figure 3. Analysis of the reaction mixture resulting from acetonitrile and methylpropargyl ether and 1-hexyne: (a) seven peaks detected by GC analysis; (b) ^{1}H NMR analysis revealing 16 signals (24 lines).

Conclusion

We have applied the cobalt-catalyzed generation of pyridines to solution-phase combinatorial chemistry. For this purpose, we used [$CpCo(CO)_2$] in combination with an amine *N*-oxide which proved to be a very convenient catalyst for the 96-well plate format. This procedure allows one to work on a benchtop with nitrogen-flushed reagents and requires only modest temperatures to produce analytically pure pyridines mixtures in ca. 50% yield after a simple filtration and elution procedure over an acidic ion-exchange resin. We are currently testing our libraries as inhibitors for various enzymatic reactions including alchohol dehydrogenase and phosphorylation.

Future efforts are directed toward the synthesis of libraries of bipyridines as well as lactones using related methodologies.

Experimental Section

General Considerations. Starting materials were purchased from Fluka AG or Aldrich and were used without further purification. Trimethylamine-*N*-oxide (TMAO) was dehydrated by repeated dissolution in benzene and azeotropic evaporation of the water−benzene mixture. The catalyst precursors were prepared according to literature procedures: $CoCl_2/NaBH_4$ **1**,[13] [Cp_2Co] **2**,[21] [CpCo(COD)] **3**,[22] [$CpCo(C_2H_4)_2$] **4**,[23] [$CpCo(CO)_2$] **5**,[24] [$Me_5CpCo(CO)_2$] **6**,[25,26] and [Me_5CpCo(allyl)] **7**.[27,28] All solvents and solid materials were flushed with nitrogen prior to use. Gas chromatography (GC) was performed on a Hewlett-Packard 5890 gas chromatograph equipped with a split-mode capillary injection system and flame ionization detector using a HP Ultra2 capillary column (10 m × 0.33 mm, 100 kPa column head pressure, helium flow, split ratio 1:20, temperature program: from 40 to 270 °C with 6 °C/min and 270 °C for 20 min) or a cyclodextrin column (150% heptakis-[2,3-di-*O*-acetoxy-6-*O*-(*tert*-butyldimethylsilyl)]-β-cyclodextrin in OV-1701, 10 m × 0.3 mm, 20 kPa column head pressure, helium as carrier gas, split ratio 1:20, temperature program: 40 to 200 °C at 2 °C/min and 200 °C for 50 min). GC-MS spectra were recorded on a CarloErba 5300 Mega Series using an HP Ultra2 capillary column (12 m × 0.25 mm, 90 kPa column head pressure, helium as carrier gas, split ratio 1:5, temperature program: 40 °C for 1 min and 6 °C/min to 280 °C and 280 °C for 30 min). Atom absorption spectroscopy was performed on a Perkin-Elmer Zeeman atom absorption spectrometer 4100ZL using a cobalt lamp (242.5 nm).

Typical Reaction Procedures. Solid Nitriles and/or Acetylene. A 1 M xylene solution containing the nitrile (5 mmol) and both alkynes (1 mmol each) was flushed with

nitrogen for 15 min. The catalyst [$CpCo(CO)_2$] **5** (0.05 mol) and TMAO (0.1 mmol) were added successively; the reaction mixture was sealed and heated at 85 °C during 16 h.

Liquid Nitriles. Both alkynes (1 mmol each) were dissolved in the neat nitrile (≥5 mmol) and flushed with nitrogen for 15 min. The catalyst [$CpCo(CO)_2$] **5** (0.05 mol) and TMAO (0.1 mmol) were added successively; the reaction mixture was sealed and heated at 85 °C during 16 h.

Workup. (1) Extraction. The reaction solution was acidified with 2 N HCl and extracted with Et_2O. The aqueous solution was made basic with 2 N NaOH and extracted with Et_2O. The organic phase was dried with Na_2SO_4 and evaporated to dryness. Column chromatography on SiO_2 (mostly hexane/diethyl ether) was applied for purification and separation of the library members.

(2) Ion-Exchange Chromatography. Alternatively, the reaction mixture was filtered through an acidic DOWEX-(50 W X 8) resin plug and washed with aqueous methanol until the filtrate was colorless. Elution with aqueous methanol (or acetonitrile) containing NH_3 yielded, after evaporation of the volatiles, essentially pure pyridine mixtures which were characterized by GC, GC-MS, or NMR.

Yield and Ratio Determination. (1) GC. HP Ultra 2 column: Tetradecan (R_t = 15.8 min) was used as internal standard for the determination of the overall yield. The ratios between pyridine regioisomers were obtained by integration of the corresponding peaks (assuming that both regioisomers give the same response with an FID detector).

(2) ^{1}H NMR. 1,3,5-Triazine was used as internal standard (δ = 9.21 ppm) for the ^{1}H NMR determination of yields and product ratios. Depending on the substitution pattern of the pyridines (2, 3, 6 or 2, 4, 6), either the H^4 and H^5 signals or the H^3 and H^5 signals appear as two singlets or two doublets, respectively (neglecting long-range coupling). The chemical shift (δ in ppm) of these signals can be accurately predicted from increment tables: in most cases $6.5 < \delta < 8.5$. Integration of the 24 lines (16 signals) produced by the eight pyridines gives the relative ratios of the products.

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Supporting Information Available. Purification and characterization (^{1}H and ^{13}C NMR, MS) of single pyridine regioisomers and regioisomeric mixtures and crude GC spectra of pools of pyridines. This material is available free of charge via the Internet at http://pubs.acs.org.

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