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CATALYSIS

# Synthesis of Heteroaromatic Carboxylic Acids by Carbonylation of Hetaryl Halides with Catalysts Based on Cobalt Carbonyl Modified with Epoxides

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**Abstract**—A new method for the synthesis of heteroaromatic acids and their derivatives (esters and salts) by carbonylation of the corresponding halides was developed. Hetaryl halides were activated in alcoholic-alkali medium by highly active catalytic systems based on cobalt carbonyl modified with epoxides, developed previously for carbonylation of aryl halides.

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Heteroaromatic acids are widely used in preparative organic chemistry and as a raw material in the production of a wide range of substances, mainly biologically active, and first of all of drugs and plant protection agents [1].

The traditional methods for preparing heteroaromatic acids, used today in the industry and laboratory practice, are diverse. They are based on a set of classical reactions of organic chemistry (alkylation, acylation, oxidation, cyanidation) and have a number of serious disadvantages: multistep synthesis, low selectivity, large consumption of raw materials, and complex process flowsheet. Some of these methods are environmentally unfavorable. Recently, the method of carbonylation of the corresponding halides has come into use for selective (one-step) introduction of the carboxy group into an aromatic core, i.e., for the synthesis of aromatic acids. Preparation of arenecarboxylic acids by carbonylation of aryl halides using cobalt carbonyl complex modified with alkyl halides as a catalyst has been known since the mid-1980s [2–6]:

$$\mathrm{ArHal + CO} \xrightarrow[\mathrm{ROH + B}]{\mathrm{Co(CO)_8 + A}} \mathrm{ArCOOR},$$

where A is an activator (alkyl halide) and B, base.

It was found that alkylcobalt carbonyl complexes $\mathrm{R'Co(CO)_4}$ formed in situ by the reaction of alkyl halides R'X, active in nucleophilic substitution (e.g., methyl iodide or methyl monochloroacetate $\mathrm{ClCH_2COOCH_3}$), with cobalt carbonyl in an alcoholic-alkaline medium can activate comparatively inert aryl halides in carbonylation reactions [2]. In the process, alkyl halides act as cocatalysts (activators) of cobalt carbonyl in aryl halide carbonylation. The reaction proceeds under very mild conditions: CO pressure of 1–3 atm and temperature of 60–65°C. We have shown [3, 4] that benzyl chloride forming the catalytic complex $\mathrm{PhCH_2Co(CO)_4}$ is the best activator (A) among alkyl halides.

Miura et al. [7] found that aryl halide carbonylation can proceed at room temperature and atmospheric pressure of CO, with the system cobalt(II) chloride–methyl iodide is used as a catalyst, but the reaction is slow. To accelerate the reaction in this catalytic system, Nindakova et al. [8] used reducing agents and, in particular, sodium borohydride or sodium naphthalenide. Nindakova et al. [8] believe that elimination of the stage of cobalt carbonyl preparation is an advantage of such an approach. However, in spite of the fact that such systems do not differ in activity from the systems studied in [2–6], additional reducing agents complicate the process.

In 1994, we discovered a new catalytic system for carbonylation of bromobenzene and chloronaphtalene, which consists of cobalt carbonyl, potassium carbonate, and olefin oxide (e.g., ethylene oxide or propylene oxide) [9]:

$$ArHal + CO + CHO^- \xrightarrow[\text{CH}_3\text{OH, } K_2CO_3, 60^\circ C, P_{CO} = 1 \text{ atm}]{Co(CO)_4^-,\ \text{epoxide}} ArCOOCH + Hal^-$$

We found that this catalytic system noticeably surpasses in activity the previously used system based on alkyl halides.

The new catalyst was used to prepare various aromatic carboxylic acids: 4-butylbenzoic, 4-acetylbenzoic, 4,4'-diphenyl- and 4,4'-(diphenyl oxide)dicarboxylic, and 2,6-naphtalenedicarboxylic. It was shown that this system can be successfully used for laboratory and commercial synthesis of a wide range of aromatic carboxylic acids of various structures [10].

At the same time, the synthesis, using this catalytic system, of aromatic carboxylic acids with a complex structure containing heterocyclic substituents has not been studied. At the same time, the exclusively high selectivity of the new catalytic system can become especially useful in the case of difficultly available and expensive heterocyclic compounds. Taking into account the fact that a number of various heteroaromatic halides can be prepared comparatively simply (by direct introduction of halogen into the aromatic core or by substitution with halogen of hydroxy group often formed in synthesis of the heterocycle), the use of cobalt carbonyl as an inexpensive and readily available catalyst of oxo synthesis, as applied to carbonylation of hetaryl halides, seemed very attractive from the practical and theoretical viewpoints. At the same time, this question required special consideration, because the majority of the heterocyclic compounds can potentially react as ligands and affect the catalytic properties of the cobalt complex.

First of all, we examined the possibility of using carbonylation to prepare acids derived from a nitrogen-containing heterocycle. It is well known that pyridine can form complexes with cobalt carbonyl, acting as a base ligand [11]. Therefore, it was necessary to check to what extent the catalytic activity of the carbonyl-base-propylene oxide system is preserved in the presence of the pyridine compound. We found that 2-chloropyridine undergoes carbonylation. Some important conclusions follow from this fact: (1) The system preserves the catalytic activity under the above conditions, i.e., in the presence of the potential heterocyclic ligand. (2) Hetaryl halides can undergo carbonylation. (3) As in usual reactions of nucleophilic substitution, halopyridine is more active than the corresponding halobenzene, i.e., the activating effect of the pyridine ring is preserved. This allows preparation of pyridinecarboxylic (and, apparently, also quinolinecarboxylic) acids by carbonylation of the corresponding hetaryl chlorides, which are substantially more readily available than the corresponding hetaryl bromides.

The synthesis of various quinolinecarboxylic acids, which are difficult to prepare by other methods, is of particular practical interest. We studied carbonylation of a series of halides containing tetrahydroquinoline (**I**), quinoline (**IV**, **V**), tetrahydroqiunazoline (**II**), and tetrahydroquinoxaline (**III**) rings:

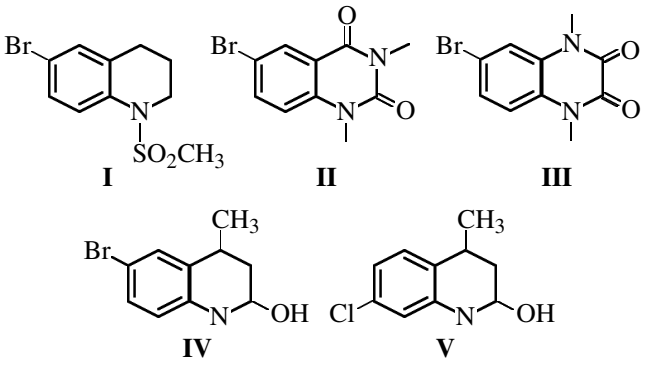



**Table 1.** Carbonylation of hetaryl halides containing fused nitrogen-containing heterocycles ($T$ = 61–63°C, $P_{CO}$ = 1 atm, reaction time 6 h)

| Substrate | Substrate concentration, M | Molar ratio substrate : cobalt carbonyl : propylene oxide : potassium carbonate | Substrate conversion* | Product yield** |
|---|---|---|---|---|
| | | | % | |
| **I** | 0.34 | 100 : 1 : 100 : 310 | 91 | 86 (95) |
| **II** | 0.27 | 92 : 1 : 111 : 310 | 87 | 86 (99) |
| **III** | 0.27 | 15 : 1 : 41 : 74 | 89 | 49 |
| **IV** | 0.2 | 22 : 1 : 107 : 40 | 23 | – |
| **V** | 0.34 | 65 : 1 : 91 : 196 | 85 | 81 (95) |

* From the volume of carbon monoxide taken up.

** Preparation yield (in parenthese, taking into account isolated unchanged substrate); the same for Table 2.

**Table 2.** Influence of reaction conditions on carbonylation of hetaryl halide **I** ($T$ = 63°C, $P_{CO}$ = 1 atm, reaction time 4 h)

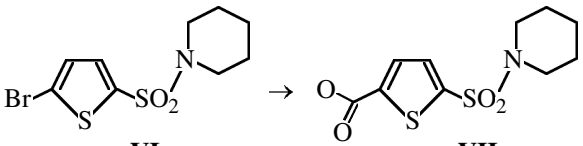
| Substrate concentration, M | Molar ratio substrate : cobalt carbonyl : propylene oxide : potassium carbonate | Substrate conversion* | Product yield |
|---|---|---|---|
| | | % | |
| 0.17 | 50 : 1 : 50 : 130 | 87 | 83 (95) |
| 0.34 | 100 : 1 : 100 : 310 | 91 | 86 (95) |
| 0.69 | 200 : 1 : 200 : 600 | 28 | 26 (93) |
| 0.34 | 200 : 1 : 200 : 635 | 52 | 51 (98) |
| 0.34 | 194 : 1 : 200 : 620 | 52 | 52 (100) |
| 0.34 | 190 : 1 : 190 : 600 | 75 | 71 (95) |
| 0.34 | 194 : 1 : 400 : 620 | 68 | 64 (94) |
| 0.48 | 200 : 1 : 200 : 600 | 78 | 75 (96) |

* From $^1$H NMR data.

The results obtained are listed in Table 1. As seen, all the hetaryl bromides studied readily undergo carbonylation with the catalytic system suggested. Moreover, chlorine derivatives of quinoline can also be, as expected, substrates in carbonylation. With the carbonylation of **I** as an example, we examined the influence of the reactant, catalyst, and activator concentrations on the reaction yield (Table 2).

The data obtained show that the method suggested is suitable for preparing heteroaromatic carboxylic acids.

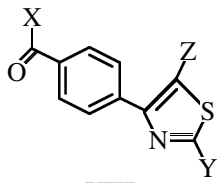
To check whether the activity of the catalytic system is preserved with sulfur-containing heterocycles as substrates, we studied carbonylation of 2-bromo-5-(piperidyl-1-sulfo)thiophene **VI**:



**VI** **VII**

We found that the substrate conversion in 4 h reached 94%, and the yield of isolated acid **VII** was 79%.

Preparation of 4-(4-carboxyphenyl)thiazoles **VIII**

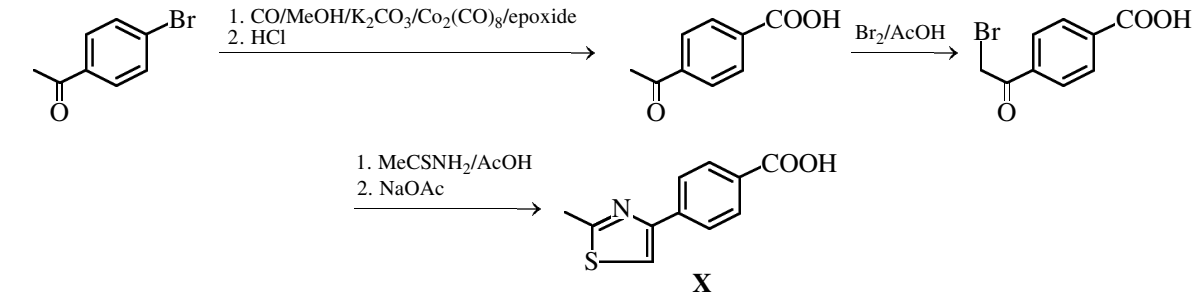


**VIII**

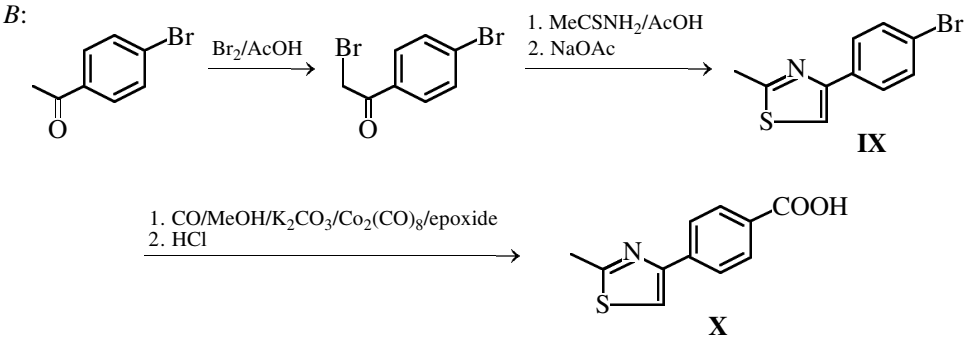
is of great interest. At present, such derivatives are studied as biologically active substances, e.g., potential COX-2 inhibitors [12]. Preparation of these derivatives involves the use of expensive starting compounds, 4-acylbenzoic acids, whereas carbonylation of aryl halides would allow the use of the substantially less expensive 4-bromoacylbenzenes.

The synthesis of 4-(2-methylthiazol-4-yl)benzoic acid **X** from 4-bromoacetophenone by carbonylation can be performed along two pathways:

*A*:

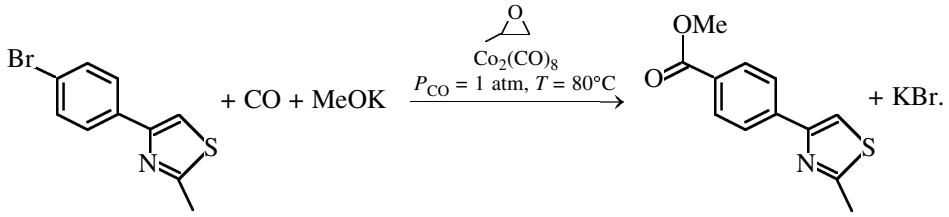


**X**




Pathway *A* involves carbonylation of aryl halide (4-bromoacetophenone) described in [10]. Pathway *B* includes the stage of carbonylation of halide **IX**, which required preliminary examination.

Carbonylation of 4-(4-bromophenyl)-2-methylthiazole **IX** catalyzed by the cobalt complex readily occurs in methanol with potassium carbonate as a base:




Analysis of the reaction mixture showed a high selectivity of carbonylation of this substrate and good preparation yield (Table 3).

Thus, we can synthesize **X** by two methods (*A* and *B*). The preparation yields are compared in Table 4. The data obtained show that the presence of thiazole fragment in the aryl halide molecule does not prevent carbonylation. Carbonylation after heterocycle formation (but not in the early stage of the synthesis) improves the overall parameters of the process.

As can be seen from the above data, the efficient catalytic system $Co(CO)_4$–propylene oxide–$K_2CO_3$ in metanol, developed previously for aryl halide carbonylation, can also be successfully used in the selective synthesis of various heteroaromatic carboxylic acids with a good yield and high selectivity under very mild

**Table 3.** Results of carbonylation of 4-(4-bromophenyl)-2-methylthiazole **IX** at various molar ratios of reactants

| Molar ratio **IX** : $Co_2(CO)_8$ : propylene oxide : $K_2CO_3$ | Reaction time, h | Substrate conversion* | Product yield** |
|---|---|---|---|
| | | % | |
| 73 : 1 : 137 : 160 | 8.0 | 95 | 93 |
| 80 : 1 : 90 : 170 | 6.0 | 93 | 92 |
| 152 : 1 : 170 : 330 | 6.0 | 86 | 84 |

* Conversion is determined by NMR analysis of the reaction mixture.

** Yield of isolated 4-(2-methylthiazol-4-yl)benzoic acid **X** after carbonylation, base hydrolysis, and acidification of the reaction mixture.

**Table 4.** Comparison of the yields in the synthesis of 4-(2-methylthiazol-4-yl)benzoic acid **X** synthesis by methods *A* and *B*

| Reaction step | Product yield, % of theory | |
|---|---|---|
| | pathway *A* | pathway *B* |
| Bromination of acetyl group | 76 | 79 |
| Formation of heterocycle by reaction with thioacetamide | 78 | 94 |
| Carbonylation* | 74 | 84 |
| Total product yield based on *p*-bromoacetophenone | 44 | 62 |

* Equal conditions and reactant ratios for 4-bromoacetophenone and 4-(4-bromophenyl)-2-methylthiazole; without taking the probable recycle of the substrate into consideration.

conditions both in laboratory practice and on the commercial scale for production of raw materials required for fine chemistry.

## EXPERIMENTAL

The carbonylation reactions were studied at CO atmospheric pressure in ordinary temperature-controlled glass apparatus with vigorous stirring in a CO atmosphere. The reaction products were analyzed by GLC and $^1$H NMR. The identification of products was based on data of $^1$H and $^{13}$C NMR spectroscopy and mass spectrometry.

The mass spectra were recorded on an MKh-1321 mass spectrometer using direct sample inlet and ionization by electron impact (70 eV); the temperature of the ionization chamber was 200°C.

GLC analysis was performed on a Chrom-5 chromatograph with a flame ionization detector; the carrier gas was argon, flow rate 20–30 ml min$^{-1}$. Glass columns, 3 mm in diameter and 2500 mm long, were packed with SF-30 (10%) on Chromaton N-Super (80–100 mesh). The vaporizer and column temperature was 200°C.

The NMR spectra were recorded on a Bruker DPX 300 spectrometer [operating frequency 300.130 ($^1$H) and 75.03 ($^{13}$C) MHz]; solvent: 2 : 1 (by volume) mixture of $CCl_4$ with deuterated dimethyl sulfoxide.

A 2-l round-bottomed flask equipped with a power-driven stirrer, reflux condenser, thermometer, gas-feeding tube, and dropping funnel was purged with CO and charged with 200 g (1.4 mol) of $K_2CO_3$, 1200 ml of methanol, and 0.5 mol of a substrate. The reaction mixture was purged with CO under stirring for 0.5 h. Then, in a CO flow, 2.4 g of octacarbonyldicobalt (7 mmol) was added, and the temperature of the reaction mixture was elevated to 62°C. Then, the required amount of propylene oxide and 15–20 ml of methanol were added from a dropping funnel over a period of 10 min. After that, the temperature of the reaction mixture was elevated to 64°C, and the reaction was performed for 6 h at this temperature. Then the CO flow was stopped, the reaction mixture was cooled, 56 g of KOH (1 mol) was added, and methanol was distilled off at atmospheric pressure with stirring for several hours. After methanol distillation, water and diethyl ether were added into the reaction mixture, the organic phase was separated, and the aqueous phase was acidified with concentrated hydrochloric acid to pH 4–5 and kept until the acids precipitated. The precipitate was filtered off and dried.

## CONCLUSIONS

(1) A new method was developed for synthesis of heteroaromatic acids and their derivatives by carbonylation of the corresponding hetaryl halides using highly active catalytic systems based on cobalt carbonyl, modified with epoxides.

(2) It was demonstrated that carbonylation of hetaryl halides proceeds under very mild conditions (CO pressure 1 atm) in alcohols in the presence of bases.

(3) It was shown that hetaryl halides with various structures, containing pyridine, quinoline, tetrahydroquinoline, tetrahydroquinazoline, thiophene, or thiazole fragments can be substrates in the above synthesis.

(4) A series of previously unknown heteroaromatic acids were synthesized.

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