# Efficient and regioselective acetylation of benzene derivatives with Ac₂O in the presence of mercurytetrathiocyanatocobaltate (II)

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**Abstract:** Based on Friedel Crafts acylation, an efficient and facile method for the chemo-selective as well as region-selective acylation of substituted benzene derivatives has been developed by using $Hg[Co(SCN)_4]$ as catalyst. The reaction is highly chemo-selective as well as region-selective as only acetophenones were obtained, whereas the benzophenones are not formed. The present method is very efficient with simple work up gives the products in good to excellent yield. The reaction is carried out using $CHCl_3$ as solvent at room temperature. It is anticipated that the present newly developed method will open a gateway for the chemist to prepare the chemo as well as region-selective acetophenones.

## 1. Introduction

The Friedel-Crafts (FC) acylation reaction of aromatics with acid halides or acetic anhydride is a fundamental and important reaction in organic synthesis.[1-3] The region-selective FC acylation to produce aromatic ketones in chemical industry is a important conversion as they are useful intermediates in the preparation of various synthetic intermediates,[4] chemical feed stocks,[5] pharmaceuticals[6] and fine chemicals.[7] Although, the aromatic ketones have numerous applications in organic synthesis but their conventional methods to produce them has limitations such as complicated synthetic procedures and environmentally hazardous conditions,[8-9] the use of homogeneous catalysts, for example, protic acids,[10] soluble metal halides[11] and substituted anhydrides[12] in stoichiometric amounts and other homogeneous catalysts, i.e., $Ln(OTf)_3$-$LiClO_4$,[13] $LiClO_4$-acyl anhydride complex,[14] $(PhCN)_2PtCl_2/AgSbF6$[15] and $Re$-$Br(CO)_5$.[16]

The industrial application of these homogeneous catalysts is also associated with various shortcomings because of the non-economical reaction process and environmental issues.[17] Therefore, design and development of a highly efficient and economical catalyst system with less environmental disputes is in immense need to overcome these challenges. Certain efforts have been put on for the development of FCR in the recent years for example the synthesis of solid acid catalysts in the solution or gas phase.[18] Various solid acid catalysts i.e., sulfated $ZrO_2$ or $Fe_2O_3$,[19-20] sulfated $Al_2O_3$–

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ZrO$_2$ (or TiO$_2$),[21-22] acidic zeolite,[23] clays,[24] metal oxides,[25] heteropoly acid salts,[26] Nafion[27] etc. are reported. At the present time, researchers have paid attention for synthesis and application of nano-scale metal or metal oxide catalysts for various organic transformations as catalysts in their nanometric regime provide improved reactivity and selectivity.[28-30] The metal based triflates and their nitrogenous analogous are also reported to catalyze the FCR.[31-35]

Many interesting reactions catalyzed by transition metals, or their complexes have been employed for a wide variety of organic transformations.[36-39] The use of transition metal reagents has found considerable applications in organic synthesis and has radically changed the realm of chemical science. Electrophilic Hg(II) salts are important reagents in organic synthesis and there is published literature establishing this fact.[40] Although, Hg(II) salts are toxic but they are very cheap in comparison to other transition metal salts and are one of the soft Lewis acids of the periodic table.[41] Hg(II) salts are reported for the C-C bond formation,[42] Synthesis of Spiro[4.5]decatriene diones from Allenyl Ketones,[43] synthesis of heterocycles.[44] Mercury will form a stable Cobalt (II) Mercury Tetra thiocyanate (Werner complex) which are recently been reported for the organic functional group transformation. Recently, Arifuddin and his co-workers reported the use of transition metal complexes for various functional group transformations.[45-47] The Friedel-Crafts (FC) acylation of aromatic substrates with acid halides and anhydrides is a fundamental and important reaction in organic synthesis. Although the aromatic ketones have tremendous applications, yet conventional strategies to produce such aromatic ketones often suffer from major challenges of complicated synthetic procedures and environmental concerns. In continuation of the ongoing work for the preparation of acetophenones various methods we are employed but could not able to get the required selectivity. Arifuddin et. al., reported regioselective acetylation of phenols and anilines mediated by WTMCs under solvent-free condition.[48] Thus herewith we would like to report our findings when we used this protocol in presence of chloroform as solvent the aromatic acetylation is taken place and the corresponding acetophenones are obtained. Thus, encourage by this result for the synthesis of acetophenones,[49-54] herewith the regioselective acetylation of aromatic compounds with acetic anhydride by using Cobalt (II) Mercury Tetra thiocyanate (Werner complex) Hg[Co(SCN)$_4$][55-57] in good to excellent yield is reported (Scheme 1).
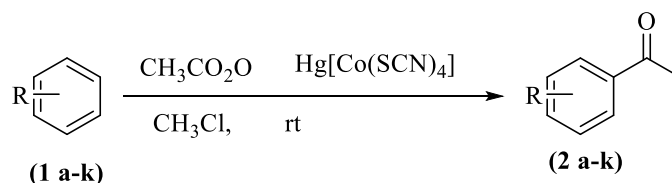


**Scheme 1.** Regio-selective acetylation of aromatic compounds with acetic anhydride by using Hg[Co (SCN)$_4$]

## 2. Experimental

### 2.1. Chemical Material and Apparatus

All the solvents were distilled and dried before use. The chemicals purchased from commercial vendors and were used without any further purification. The reactions were monitored by using TLC on Silica gel 60 plates, with a typical ratio of petroleum ether: ethyl acetate (8:2) as mobile phase. Melting points were determined with a hot-plate microscope apparatus and are uncorrected. The $^1$H-NMR and $^{13}$C-NMR spectra were recorded on Varian-400 NMR spectrometer at 400MHz/ 100MHz using CDCl$_3$ and TMS as solvent and internal standard, respectively. DIP Mass Spectrum was recorded on Agilent- G6160 A infinity lab LC/MSD/IQ mass spectrometer.

### 2.2. Chemistry

### 2.2.1. General Procedure for the Friedel-Crafts Acylation

*Preparation of 4-hydoxyacetophenone (2a)*: A solution of acetic anhydride (1 mmol), phenol (1 mmol) and Hg[Co (SCN)$_4$] (1 mmol) in chloroform was stirred at room temperature for 90 minutes After completion of the reaction as indicated by TLC, the reaction mixture was filtered and solvent

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was evaporated under reduced pressure. The residue was diluted in water (20 mL) and extracted with ethyl acetate (20 mL X 3). The organic layer was dried over $Na_2SO_4$ and concentrated under reduced pressure. The crude product was purified over column chromatography by using silica gel 100-200 mesh and 20% hexane / EtOAc as eluent to obtain the 4-hydroxyacetophenone in 90% yield. All the other acetophenones are prepared by following the same method (Table 2). All the compounds are known, and they are confirmed by their M.P, Mass, $^1$H-NMR and $^{13}$C-NMR spectral analysis and comparison with the literature values. The Mass, $^1$H-NMR and $^{13}$C-NMR spectral data are given in supplementary information file.

## 3. Results and Discussion

There are numerous known methods reported for the Friedel-Crafts acylation, newer methods continue to attract attention for their experimental simplicity and effectiveness. We have been interested in the development of methods for Friedel-Crafts acylation that (a) would avoid the use of added acids and bases, (b) are easy to perform, and (c) are economical for application to large-scale preparations. In continuation of ongoing work to develop the novel synthetic protocols for the various organic functional group transformations, now it is discovered that $Hg[Co(SCN)_4]$ catalyzed very efficiently the chemo as well as regioselectivity Friedel-Crafts acylation of aromatic compounds with acetic anhydride as acylating agent. $Hg[Co(SCN)_4]$ were prepared following the method described in Advanced Practical Inorganic Chemistry.[58]

To optimize the best reaction condition initially acetylation of phenol is taken as model reaction. To get the best optimized reaction conditions for the acetylation of phenol (**1a**) with acetic anhydride the best results various combinations of solvents were tested in the presence $Hg[Co(SCN)_4]$. When THF / $Hg[Co(SCN)_4]$ is used (rt /24 h) no reaction was observed. When DMF/ $Hg[Co(SCN)_4]$ is used at the same conditions no reaction was observed. Similar results were obtained with benzene / $Hg[Co(SCN)_4]$ / shaking or toluene / $Hg[Co(SCN)_4]$ / shaking and EtOAc / $Hg[Co(SCN)_4]$ shaking with EtOH / $Hg[Co(SCN)_4]$ / rt / 24 h, MeOH/ $Hg[Co(SCN)_4]$ / rt / 24 h reaction conditions were used as solvent. Interestingly, when the reaction was carried out in halogenated solvent such as DCM (dichloromethane) and Chloroform ($CHCl_3$) the reaction is enormously increased (Table 1, entries 7 and 8) in short reaction. This might be due to the polar nature of halogens and chelating properties of halogens with acetic anhydride. When the reaction was carried out in the albescence of $Hg[Co(SCN)_4]$, no reaction was observed as the starting material are recovered (Table 1, entry 9).

After the optimized reaction condition in hand we focused to check the generality of the reaction by taking different substituted aromatic compounds which is depicted in Scheme-2 and the results are presented in the Table-2 and spectral data is given in Table-3. The results of the present findings revealed that the electron donating groups on aromatic ring yielding is higher than with-drawing groups on aromatic ring. It is noteworthy to note that the major difference between the earlier reported method by Arifuddin et. al.,[43] is that the previous work required the use of $H_3PO_4$ as a co-catalyst, while this work reports the use of chloroform as a solvent which is the key to this system.
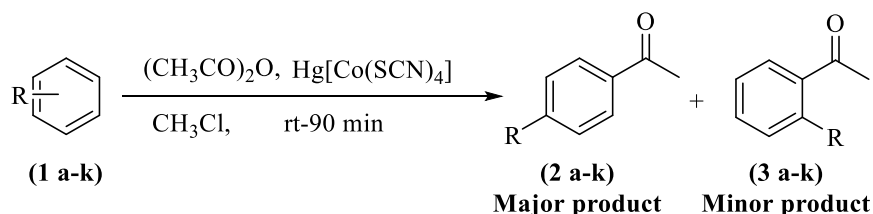


**Scheme 2.** Generality and regio-selectivity of the present optimized FCR

**Table 1.** Optimization of 4-hydroxyacetophenone formation from phenol catalyzed by Hg[Co (SCN)$_4$]

| S. No | Solvent | Reaction condition | Yield % |
|-------|---------|--------------------|---------|
| 1 | THF | Hg[Co (SCN)$_4$] / shaking for 24 hr | NR |
| 2 | DMF | Hg[Co (SCN)$_4$] / shaking for 24 hr | NR |
| 3 | Benzene | Hg[Co (SCN)$_4$] / shaking for 24 hr | NR |
| 4 | Toluene | Hg[Co (SCN)$_4$]/ shaking for 24 hr | NR |
| 5 | EtOAc | Hg[Co (SCN)$_4$] / shaking for 24 hr | NR |
| 6 | Ethanol | Hg[Co (SCN)$_4$] / shaking for 24 hr | NR |
| 7 | DCM | Hg[Co (SCN)$_4$]/ shaking for 120 min | 38 |
| **8** | **Chloroform** | **Hg[Co (SCN)$_4$] / shaking for 90 min** | **90** |
| 9 | Chloroform | Without Hg[Co(SCN)$_4$]/ Reflux, 24 hr | NR |

Note: * NR= No reaction

Surprisingly, this protocol was only effective with acetic anhydride as a reagent and the use of benzoic anhydride failed to deliver the desired product. For example when the efforts are made to synthesize the 4-hydroxybenzophenone from the phenol by employing the benzoic anhydride (PhCO)$_2$O for the benzoylation reaction by using Hg[Co (SCN)$_4$] as catalyst it was observed that benzophenones were not obtained where as a thick dark black mass is obtained which was not separable (Scheme-3). We cannot at this stage put forward any hypothesis as to why the benzoylation reaction does not occur under the same conditions (Scheme 3).

**Table 2.** Hg[Co (SCN)$_4$] catalyzed chemo- and regioselective Friedel-Crafts acylation.

| S. No | Starting material (1a-k) | Major Product (2a-k) | Reaction time (min) | Yield (%) |
|-------|--------------------------|----------------------|---------------------|-----------|
| 1 | Phenol (**1a**) | 4-Hydroxyacetophenone (**2a**) | 90 | 90 |
| 2 | Toluene (**1b**) | 4-Methylacetophenone (**2b**) | 90 | 93 |
| 3 | Anisole (**1c**) | 4-Methoxyacetophenone (**2c**) | 90 | 92 |
| 4 | Chlorobenzene (**1d**) | 4-Chloroacetophenone (**2d**) | 90 | 90 |
| 5 | Bromobenzene (**1e**) | 4-Bromoacetophenone (**2e**) | 90 | 87 |
| 6 | Fluorobenzene (**1f**) | 4-Fluorrocetophenone (**2f**) | 90 | 88 |
| 7 | 1, 3-Dichlorobenzene (**1g**) | 2, 4-Dichloroacetophenone (**2g**) | 90 | 85 |
| 8 | Naphthalene (**1h**) | 1-acetylnaphthalene (**2h**) | 90 | 87 |
| 9 | 3-Nitrobenzene (**1i**) | 3-Nitroacetophenone (**2i**) | 90 | 75 |
| 10 | 1, 2-Methylenedioxybenzene (**1j**) | 3, 4-(Methylenedioxy) acetophenone (**2j**) | 90 | 80 |
| 11 | 2-Nitrotoluene (**1k**) | 4-Methyl-3-Nitroacetophenone (**2k**) | 90 | 78 |
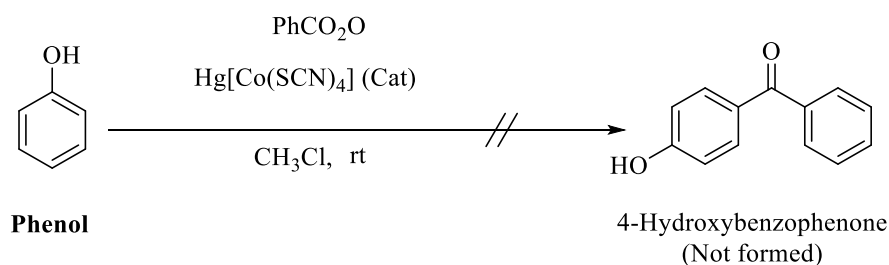


**Scheme 3.** Representation of benzoylation reaction (Not working)

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**Table 3.** Hg[Co (SCN)$_4$] catalyzed chemo and regio-selective Friedel-Crafts acylation spectral data

| S. No | Major Product (2a-k) | $^1$H-NMR (CDCl$_3$) | $^{13}$C-NMR (CDCl$_3$) | Mass Obtained (calculated) | M.P $^0$C Obtained (Reported) |
|---|---|---|---|---|---|
| 1 | **2a** | δ 7.99 - 7.87 (m, 2H), 7.68 (s, 1H), 7.00 - 6.90 (m, 2H), 2.59 (s, 3H). | 198.07, 160.94, 131.12, 129.84, 115.45, 26.30 | 137.00 [M+1]$^+$ (136.05) | 133-134 (132-135) |
| 2 | **2b** | δ 7.85 (d, J = 8.2 Hz, 2H), 7.25 (d, J = 7.9 Hz, 2H), 2.57 (s, 3H), 2.40 (s, 3H). | 196.76, 163.43, 130.54, 130.26, 113.63, 55.41, 26.30 | 135.00 [M+1]$^+$ (134.07) | Low melting solid (22-24) |
| 3 | **2c** | δ 7.94 (d, J = 8.9 Hz, 2H), 6.93 (d, J = 8.9 Hz, 2H), 3.87 (s, 3H), 2.55 (s, 3H). | 197.87, 143.85, 134.64, 129.20, 128.49, 26.51, 21.59 | 151.00 [M+1]$^+$ (150.07) | 36-37 (36-40) |
| 4 | **2d** | δ 7.91 (d, J = 8.5 Hz, 2H), 7.43 (d, J = 8.2 Hz, 2H), 2.55 (s, 3H). | 196.81, 139.54, 135.39, 129.70, 128.86, 26.53 | 177.90 ([M+Na]$^+$ (154.02) | Low melting solid (14-18) |
| 5 | **2e** | δ 7.81 (d, J = 8.5 Hz, 2H), 7.59 (d, J = 8.5 Hz, 2H), 2.58 (s, 3H). | 196.98, 135.77, 131.84, 129.79, 128.26, 26.49 | 239.20 [M+1 +H$_2$O+Na]$^+$ (197.97) | 107-109 (108-110) |
| 6 | **2f** | δ 8.12 (t, 2H), 7.18 (d, J = 8.5 Hz, 2H), 3.87 (s, 3H), 2.58 (s, 3H). | 196.50, 167.01, 164.47, 133.55-133.52 (d), 130.96-130.87 (d), 115.73-115.52 (d), 26.52 | 160.80 [M+Na]$^+$ (138.50) | Low melting solid (4-5) |
| 7 | **2g** | δ 7.28 (dd, 1H), 7.43 (s, 1H), δ 7.59 (dd, 1H),2.64 (s, 3H). | 198.94, 137.69, 137.14, 132.50, 130.68, 130.52, 127.32, 30.66 | 188.80 (187.90) | 32-33 (33-35) |
| 8 | **2h** | δ 8.74 (d, J = 8.2 Hz, 1H), 7.92 (n, 3H), 7.54 (m 3H), 2.73 (s, 3H). | 201.85, 135.41, 133.94, 133.01, 130.10, 128.64, 128.37, 128.03, 126.41, 125.97, 124.29, 29.95 | 171.10 (170.07) | Low melting solid (9-11) |
| 9 | **2i** | δ 8.78 (s, 1H), 8.43 (d, J = 7.3 Hz, 1H), 8.30 (d, J = 7.7 Hz, 1H), 7.71 (t, J = 8.0 Hz, 1H), 2.71 (s, 3H). | 195.62, 148.38, 138.17, 133.73, 129.87, 127.34, 123.14, 26.67 | 166.10 [M+1]$^+$ (165.04) | 75-76 (76-78) |
| 10 | **2j** | δ 7.55 (dd, J = 8.1, 1.7 Hz, 1H), 7.43 (d, J = 1.7 Hz, 1H), 6.85 (d, J = 8.1 Hz, 1H), 6.04 (s, 2H), 2.54 (s, 3H). | 196.18, 151.72, 148.12, 132.06, 124.71, 107.92, 107.76, 101.80, 26.39 | 164.90 (164.05) | 85-86 (87-89) |
| 11 | **2k** | δ 8.51 (d, J = 1.7 Hz, 1H), 8.08 (dd, J = 8.0, 1.8 Hz, 1H), 7.48 (d, J = 8.0 Hz, 1H), 2.66 (d, J = 8.9 Hz, 7H). | 195.54, 149.29, 138.59, 136.05, 133.30, 131.94, 124.60, 26.56, 20.61 | 179.90 (179.06) | 57-58 (57-61) |

Mechanistically, it seems that Hg[Co(SCN)$_4$] could be chelating with acetic anhydride and aromatic ring via Hg$^{2+}$ ion and facilitating the acyl ion for the electrophilic attack on the aromatic ring selectively. Furthermore, it is also postulated that chloroform reacts slowly in air to generate HCl as a

by-product and the trace amounts of acid may be the key reason for chloroform to act as an effective solvent for this reaction.

After getting the selective results for the preparation of acetophenones with Hg[Co(SCN)4] we focused to study the efficiency of the present protocol in comparison of the present protocol with selected previously known protocols and other Werner complexes were examined and we summarized the results in the Table 4. Friedel-Crafts acylation of phenol (**1a**) is completed in less than 90 minutes at room temperature in 90% isolated yield using the present protocol to produce 4-hydroxyacetophenone (**2a**). Most of the other protocols listed either takes longer time for completion; require prior preparation of the catalyst support or use of toxic solvents with generally reduced isolated yields (entries 1 and 2). The variety of Werner metal complexes such as $[Co(NH_3)_5Cl]Cl_2$, $Cu[(NH_3)_4]SO_4$, $Mn(acac)_3$, $Ni[(NH_3)_6]Cl_2$, as catalyst corresponding acetylated product (entries 3-6) and it is found that the $Hg[Co(SCN)_4]$ is only giving the desired products. Thus the present protocol seems to be better and selective.

**Table 4.** Comparison of 4-hydroxyacetophenone from phenol catalyzed by Hg[Co (SCN)$_4$] with other known catalysts.

| S. No | Reaction condition | Yield % | reference |
|-------|--------------------|---------|-----------|
| 1 | $Sc(OTf)_3$-$LiClO_4$/ $MeNO_2$/$50^0C$/ 60 min | 90 | Lit.[59] |
| 2 | Graphite/benzene/reflux/ 480 min | 89 | Lit.[60] |
| 3 | $[Co(NH_3)_5Cl]Cl_2$/ shaking for 24 hr | 10 | - |
| 4 | $Cu[(NH_3)_4]SO_4$/ shaking for 24 hr | 10 | - |
| 5 | $Mn(acac)_3$/ shaking for 24 hr | Not determined | - |
| 6 | $Ni[(NH_3)_6]Cl_2$/ shaking for 24 hr | 30 | - |
| 7 | $Hg[Co (SCN)_4]$ / shaking for 90 min | 90 | - |

Note: * NR= No reaction

## 4. Conclusion

In conclusion an efficient and facile method for the synthesis of acetophenones (**2a-k**) has been developed by using $Hg[Co(SCN)_4]$ as catalyst in chloroform. Furthermore, the reaction is highly regioselective as well as chemo-selective as only 4-hydroxyacetophenones were obtained whereas benzophenones are not formed. The present method is very efficient with simple work up and gives the products in good to excellent yield. The reaction is carried out using $CHCl_3$ as solvent. Thus, it is anticipated that the present newly developed method will open a gateway for the chemist to prepare the chemo as well as regioselective acetophenones.

## Acknowledgements

## Supporting Information

Supporting information accompanies this paper on http://www.acgpubs.org/journal/organic-communications

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