Gram-Scale Ketone Synthesis by Direct Reductive Coupling of Alkyl Iodides with Acid Chlorides

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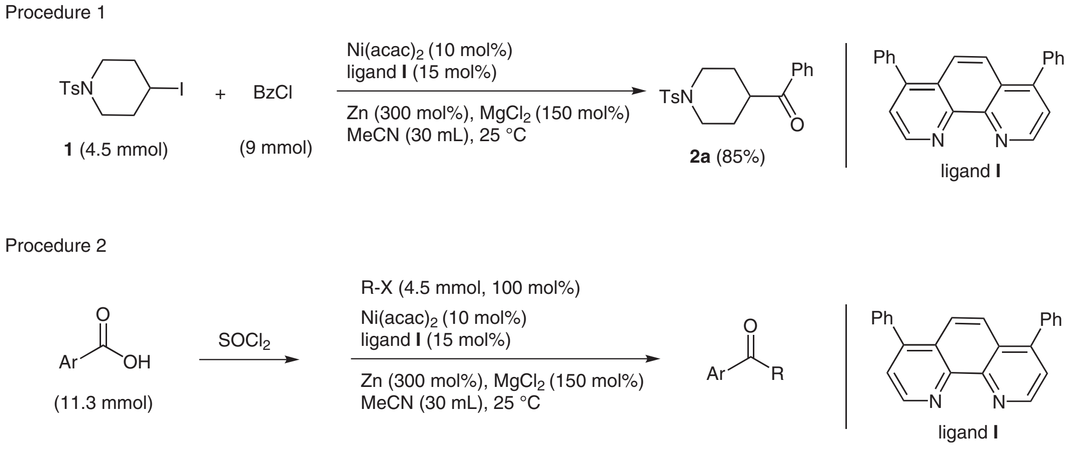
Received: 30.04.2013; Accepted after revision: 06.06.2013

PSP No 253

Abstract: Alkyl aryl ketones were prepared on a gram scale by the nickel-catalyzed reductive coupling of alkyl iodides with aroyl chlorides. When scaled up 30-fold, this reaction shows a comparable coupling efficiency to the previously reported reaction performed under small-scale conditions. The mild and convenient reaction conditions show excellent tolerance to a range of functional groups and provide the ketones in good to excellent yields.

Key words: nickel, catalysis, ketones, halides, reductions



Scheme 1 Procedures for the nickel-catalyzed reductive coupling of alkyl iodides with aroyl chlorides

The ketone group is a fundamental organic functional group that is well documented in various textbooks. The transition-metal-catalyzed coupling of alkyl organometallic reagents with acid derivatives represents a major recent advance in the synthesis of ketones.[2] We recently reported an efficient nickel-catalyzed procedure for the synthesis of alkyl aryl ketones by direct coupling of alkyl halides with aroyl chlorides or anhydrides that avoids the need for prior formation of an alkylated organometallic nucleophile.[3–5] Our preliminary mechanistic studies indicated that the formation of organozinc compounds in situ is not necessarily involved in the reaction.[3,4] The reaction, which occurs under mild conditions, tolerates a broad range of functional groups and generally gives the ketones in high yields. Furthermore, it uses relatively cheap bis(acetylacetonato)nickel(II) and commercially available 4,7-diphenyl-1,10-phenanthroline, making it a practical method for ketone synthesis. In particular, the reductive coupling protocol is amenable to the preparation of alkyl ketones bearing active β-leaving groups that would otherwise be difficult to prepare from conventional alkylated organometallic nucleophiles, because conversion of those alkyl halides into the corresponding organometallic reagents would result in severe β-elimination.[6] Previously, we had only performed the reactions on a small scale (0.15 mmol of alkyl halide as the limiting reactant). For practical applications, larger-scale preparations are important, so we examined the synthesis of alkyl aryl ketones on a gram scale, representing a 30-fold scale-up of our original reactions.

First, we examined the reaction of 4.5 mmol of 4-iodo-1-tosylpiperidine (**1**; 4.5 mmol) with 9 mmol of benzoyl chloride in the presence of 10 mol% of bis(acetylacetonato)nickel(II), 15 mol% of 4,7-diphenyl-1,10-phenanthroline (ligand I), 1.5 equivalents of magnesium(II) chloride,

SYNTHESIS 2013, 45, 2234–2240
Advanced online publication: 11.07.2013
DOI: 10.1055/s-0033-1339297; Art ID: SS-2013-Z0322-PSP

and three equivalents of zinc powder. The desired ketone **2a** was obtained in 85% yield (Scheme 1, Procedure 1; Table 1, entry 1). This yield is slightly lower than that of the corresponding small-scale reaction using 0.15 mmol of **1**, which gave a 90% yield of the ketone. Reducing the loading of the nickel precatalyst and ligand to half the previous values resulted in a significant decrease in the yield to 66%; however, the use of 12 mol% of the ligand instead of 15 mol% gave the ketone in 89% yield, which may be important in practical terms.

Next we examined the coupling efficiency of other aroyl chlorides with a variety of alkyl iodides. The results are summarized in Table 1. In general, the efficiencies of the coupling reactions of secondary alkyl iodides remained high when performed on a gram scale. Coupling of iodide **1** with 4-*tert*-butylbenzoyl chloride (entry 2), 4-fluorobenzoyl chloride (entry 3), or 3-methoxybenzoyl chloride (entry 4) gave the corresponding ketones **2b**–**d** in excellent yields. Pivaloyl chloride was also compatible with the reaction conditions (entry 5), giving ketone **2e** in 60% yield, which was 10% more than the corresponding reaction performed on a small scale.

Other cyclic secondary iodides were also effective reactants, giving products in **3**–**8** in good to excellent yields (entries 6–11, respectively). The alkyl substrates containing active β-H atoms or β-*tert*-butyl(dimethyl)siloxy groups proved to be compatible with the coupling procedure, giving ketones **5a** and **6** in 69% and 90% yield, respectively (entries 8 and 9). We also obtained good yields from our gram-scale procedure with cyclohexyl iodide and *exo*-2-iodobicyclo[2.2.1]heptane (entries 10 and 11), suggesting that alkyl iodides without polar substituents are also effective coupling partners. Open-chain secondary alkyl iodides gave the corresponding ketones **9**–**12** in high yields (entries 12–15). However, a lower yield (35%) was obtained when 2-furoyl chloride was employed as the coupling partner (entry 16). Primary alkyl iodides displayed moderate to good reactivities to give ketones **13**–**19** (entries 17–23). Whereas 1-iodobutane (entry 17) and 3-iodopropyl 4-methoxybenzoate (entry 18) gave comparable yields to those obtained from the corresponding small-scale reactions, 2-iodo-1,1-dimethoxyethane and 3-iodo-1-phenylpropan-1-one gave moderate yields that were much lower than those obtained from small-scale reactions (entries 19 and 20). The low yield of ketone **18** obtained from 1-iodo-2,2-dimethylpropane (entry 21) might be the result of the presence of the sterically demanding *tert*-butyl group. Benzyl bromide was also less effective as a coupling partner in large-scale reactions; coupling reactions with benzoyl chloride or 2-phenylacetyl chloride gave the corresponding ketones **19a** and **19b** in 40% and 76% yield, respectively (entries 22 and 23).

Table 1 Scope and Limitations of Ketone Preparation by Procedure 1

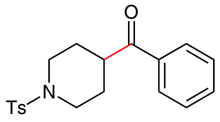
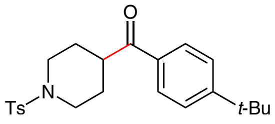
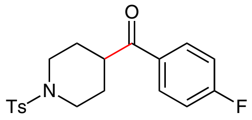
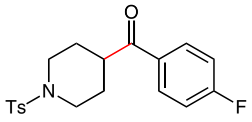
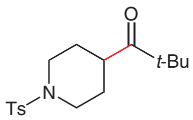
Entry[a]	Product	Small-scale yield[b] (%)	Large-scale yield[c] (%)
1	 **2a**	90	85
2	 **2b**	90	90
3	 **2c**	77	90
4	 **2d**	89	90
5	 **2e**	50	60

Table 1 Scope and Limitations of Ketone Preparation by Procedure 1 (continued)

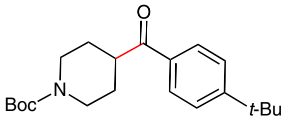
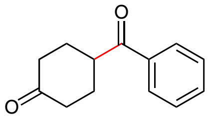
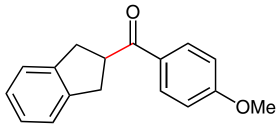
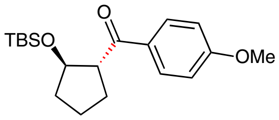
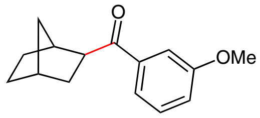
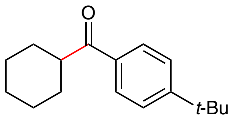
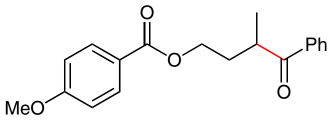
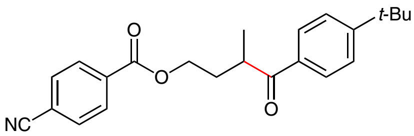
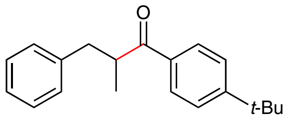
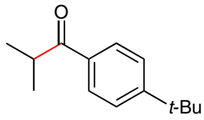
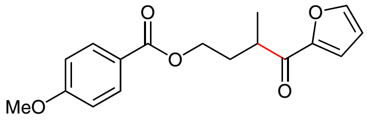
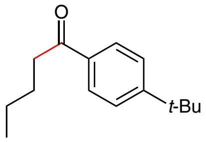
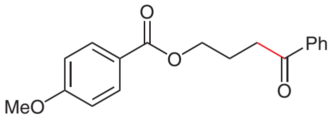
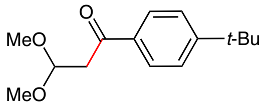
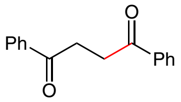
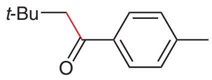
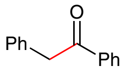
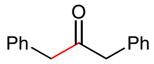
Entry[a]	Product	Small-scale yield[b] (%)	Large-scale yield[c] (%)
6	 **3**	72	75
7	 **4**	75	70
8	 **5a**	72	69
9	 **6**	76[d]	90[d]
10	 **7**	83[d]	72[d]
11	 **8**	65	80
12	 **9**	84	85
13	 **10**	82	90
14	 **11**	70	90
15	 **12**	76	80

Table 1 Scope and Limitations of Ketone Preparation by Procedure 1 (continued)

Entry[a]	Product	Small-scale yield[b] (%)	Large-scale yield[c] (%)
16	 **13**	45	35
17	 **14**	70	70
18	 **15**	75	70
19	 **16**	79	53
20	 **17**	70	60
21	 **18**	–[e]	30
22[f]	 **19a**	76	40
23[f]	 **19b**	90	76

[a] Unless otherwise noted, alkyl iodides were used as the halide coupling partners.

[b] Isolated yield from 0.15 mmol of alkyl halide.

[c] Isolated yield from 4.5 mmol of alkyl halide.

[d] dr >20:1.

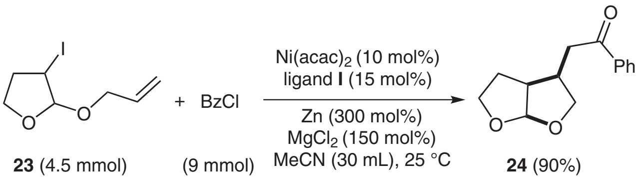
[e] Not available.

[f] Standard conditions except that BnBr was used with bis(cyclooctadienyl)nickel(II) and 4,4′-di-*tert*-butyl-2,2′-bipyridine.

To evaluate the compatibility of the reaction with various substituents on the aroyl chloride, we converted a series of arylcarboxylic acids (2.5 equivalents) into the corresponding acyl chlorides. After completely removing excess thionyl chloride, we subjected the resulting acid chloride to reductive coupling reactions in situ (Scheme 1, Procedure 2; Table 2). Modified Procedure 2 gave comparable results to those obtained from Procedure 1 with commercially available acyl chlorides (Table 2, entries 1, 7, 11, and 13). Note that the present gram-scale reactions do not generally show a loss of coupling efficiency compared with the previously reported small-scale reactions (entries 1–10 and 14). Aroyl chlorides bearing *ortho* substituents or electron-withdrawing substituents generally gave moderate yields (entries 2, 5, and 6). Alkyl iodides containing phthalimidyl moieties separated from the iodide group by three carbon atoms were also moderately effective reactants under the coupling conditions (entries 12 and 14).

We also studied a ring closure–reductive ketone formation reaction using iodo derivative **23** as the reactant (Scheme 2), and we obtained ketone **24** in 90% yield, which is 20% more than that previously obtained from the same reaction performed on a small scale.

Finally, we examined the coupling reaction of four grams of 2-iodopropane with 4-*tert*-butylbenzoyl chloride by following Procedure 2 (Scheme 3). Ketone **12** was obtained in 75% yield, showing that our reductive ketone-formation method might be suitable for large-scale application.



Scheme 2 Reductive ring closure/ketone formation

Table 2 A Modified Procedure Using Crude Acid Chlorides

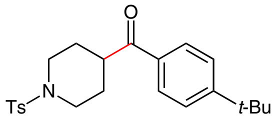
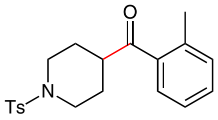
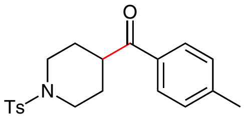
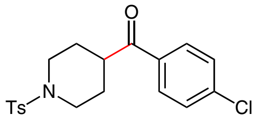
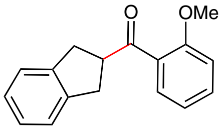
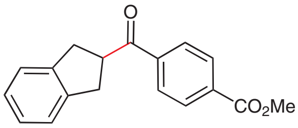
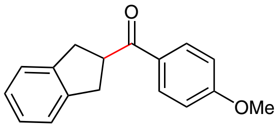
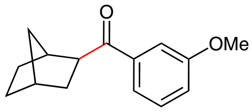
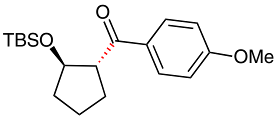
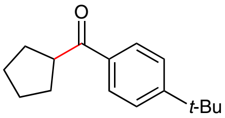
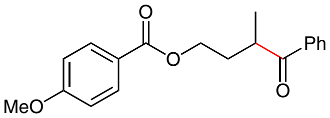
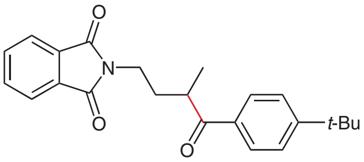
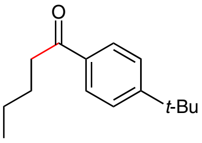
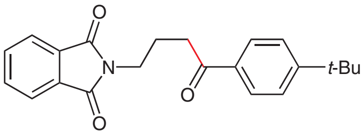
Entry[a]	Product	Small-scale yield[b] (%)	Large-scale yield[c] (%)
1	 **2b**	90	90
2	 **2f**	66	60
3	 **2g**	82	90
4	 **2h**	81	74
5	 **5b**	54	52
6	 **5c**	42	45
7	 **5a**	72	70
8	 **7**	83[d]	79[d]

Table 2 A Modified Procedure Using Crude Acid Chlorides (continued)

Entry[a]	Product	Small-scale yield[b] (%)	Large-scale yield[c] (%)
9	 **6**	76[d]	70[d]
10	 **20**	65	80
11	 **9**	–[e]	80
12	 **21**	–[e]	40
13	 **14**	–[e]	70
14	 **22**	40	40

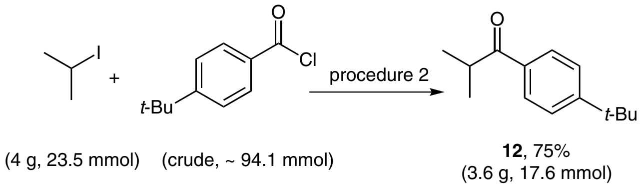
[a] Alkyl iodides were used unless otherwise mentioned.

[b] Isolated yield from 0.15 mmol of alkyl halide.

[c] Isolated yield from 4.5 mmol of alkyl halide.

[d] dr >20:1.

[e] Not available.



Scheme 3 Coupling of 2-iodopropane with 4-*tert*-butylbenzoyl chloride using Procedure 2 on a multigram scale

In conclusion, we examined the nickel-catalyzed reductive coupling of alkyl iodides with aroyl chlorides to give alkyl aryl ketones under mild reaction conditions on a gram scale. The reactions under the scaled-up conditions showed comparable coupling effectiveness to the same reactions performed on a small scale. The excellent functional group compatibility with a broad substrate scope, together with the convenient procedures and the good to excellent coupling efficiencies suggest that the method might have practical applications in the preparation of alkyl aryl ketones.

All reagents were of reagent grade quality and used as received, unless otherwise indicated. All reactions were carried out under N_2 unless otherwise indicated. Ni(acac)$_2$ (J&K, China), Ni(COD)$_2$ (Aldrich), zinc powder (Aldrich), anhyd $MgCl_2$ (Alfa Aesar) were purchased and used as received. MeCN (ACS, ≥99.5%) was purchased from Aladdin Co. (China). Ligand **I** was synthesized according to the literature procedure.[7] 2-Iodopropane (Aldrich), 1-

iodobutane (Aladdin), iodocyclohexane (Alfa Aesar), iodocyclopentane (Alfa Aesar), and 1-iodo-2,2-dimethylpropane (Acros) were used as received. Column chromatography was performed on silica gel (300–400 mesh; Qingdao-Haiyang Co. China). All NMR spectra were recorded on Bruker Avance 500-MHz spectrometer at STP unless otherwise indicated. IR spectra were recorded by using a Thermo Nicolet Avatar 370 FTIR spectrometer (Thermo Nicolet). Mass spectra were obtained by using a Shimadzu GCMS-QP2010 SE instrument.

Reaction of Alkyl Halides with Commercial Aroyl Chlorides; Procedure 1

A flame-dried Schlenk tube was charged with the alkyl iodide (4.50 mmol, 100 mol%), 4,7-diphenyl-1,10-phenanthroline (ligand **I**; 0.222 g, 0.675 mmol, 15 mol%), $MgCl_2$ (0.642 g, 6.75 mmol, 150 mol%), $Ni(acac)_2$ (0.117 g, 0.45 mmol, 10 mol%), and Zn powder (0.882 g, 13.5 mmol, 300 mol%). The tube was capped with a rubber septum then evacuated and backfilled three times with N_2. The aroyl chloride (9.0 mmol, 200 mol%) and MeCN (30 mL) were then added from a syringe, and the mixture was stirred for 12 h under a N_2 at 25 °C. The resulting mixture was filtered through a pad of Celite that was then washed with CH_2Cl_2 (3 × 30 mL). The organic phases were combined and concentrated to give a residue that was purified by flash column chromatography.

Reaction of Alkyl Halides with Crude Aroyl Chlorides; Procedure 2

A mixture of the arylcarboxylic acid (11.25 mmol, 100 mol%) and $SOCl_2$ (4.2 mL, 500 mol%) was refluxed for 4 h. Excess $SOCl_2$ was removed under reduced pressure to give a crude aroyl chloride that was used for reductive coupling without further purification. The coupling reaction was conducted by an identical procedure to that adopted in Procedure 1, except that 11.3 mmol (250 mol%) of the crude aroyl chloride was used instead of the commercial material.

Reaction of Benzyl Bromide with Aroyl Chlorides

A flame-dried Schlenk tube was charged with BnBr (4.50 mmol, 100 mol%), 4,4′-di-*tert*-butyl-2,2′-bipyridine (0.181 g, 0.675 mmol, 15 mol%), $MgCl_2$ (0.642 g, 6.75 mmol, 150 mol%), and Zn powder (0.882 g, 13.5 mmol, 300 mol%). The tube was placed in a dry glove box and $Ni(COD)_2$ (0.124 g, 0.45 mmol, 10 mol%) was added. The tube was then capped with a rubber septum and removed from the glove box. The aroyl chloride (9.0 mmol, 200 mol%) and MeCN (30 mL) were added from a syringe and the mixture was stirred for 12 h under N_2 at 25 °C. The resulting mixture was filtered through a pad of Celite that was then washed with CH_2Cl_2 (3 × 30 mL). The organic phases were combined and concentrated to give a residue that was purified by flash column chromatography.

3,3-Dimethyl-1-(4-tolyl)butan-1-one (18)

This was prepared from *t*-$BuCH_2I$ (0.596 mL, 4.50 mmol, 100 mol%) and 4-MeC_6H_4COCl (9.0 mmol, 1.19 mL, 200 mol%) according to Procedure 2, and purified by column chromatography (silica gel, 3% EtOAc–hexanes) to give a colorless oil; yield: 0.257 g (1.35 mmol, 30%).

IR (KBr): 3088, 3034, 2955, 2868, 1687, 1671, 1607, 1572, 1465, 1363, 1252, 1234, 1179, 1010, 800, 776, 578 cm^{-1}.

^1H NMR (500 MHz, CDCl3): δ = 7.86 (d, *J* = 8.3 Hz, 2 H), 7.26 (d, *J* = 8.14 Hz, 2 H), 2.85 (s, 2 H), 2.43 (s, 3 H), 1.07 (s, 9 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 200.2, 143.4, 136.1, 129.1, 128.4, 49.9, 31.4, 30.1, 21.6.

MS (EI, 70 eV): *m/z* (%) = 190 (5) [M^+], 175 (7), 134 (55), 119 (100), 91 (25), 89 (2), 65 (10).

Acknowledgment

We thank Dr. Hongmei Deng (Shanghai University) for help regarding the use of the NMR facility. Financial support was provided by the Chinese NSF (Nos. 2097209 and 21172140), the Program for Professor of Special Appointment at Shanghai Institutions of Higher Learning, Shanghai Education Committee, and Shanghai Leading Academic Discipline Project (No. S30107).

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