Organic Syntheses

Preparation of Aryl Alkyl Ketenes

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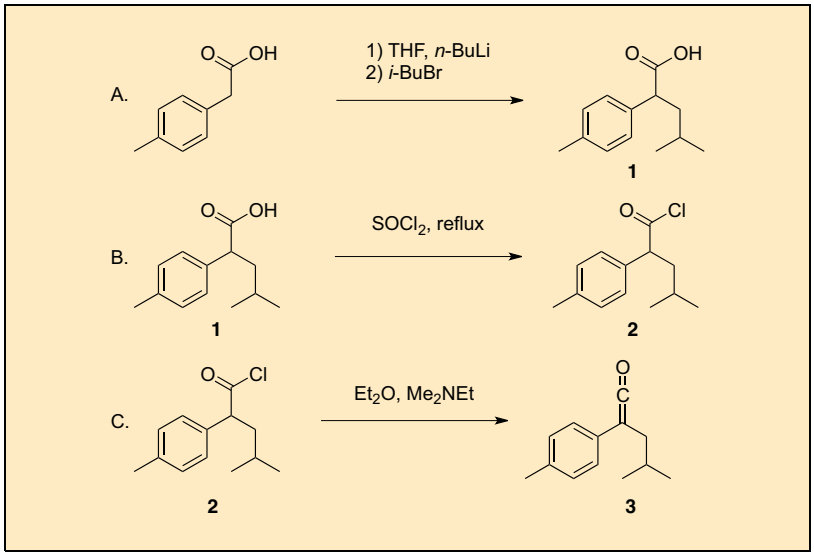

Procedure

A. *4-Methyl-2-(p-tolyl)pentanoic acid (**1**).* An oven-dried 1-L, one-necked round-bottomed flask fitted with a 4 x 2 cm egg-shaped stir bar is cooled under a stream of nitrogen. *p*-Tolylacetic acid (Note 1) (17.06 g, 114 mmol, 1 equiv) is added and the flask is sealed with a rubber septum. Tetrahydrofuran (THF) (Note 2) (~700 mL) is added by cannula and the flask is placed under a nitrogen atmosphere delivered through an 18-gauge

DOI: 10.15227/orgsyn.094.0001

needle. The solution is cooled to 0 °C and stirred vigorously (Note 3). *n*-Butyllithium (2.5 M in hexane, 100 mL, 250 mmol, 2.2 equiv) is added dropwise by cannula (Note 4) (Figure 1). The reaction is maintained at 0 °C for 90 min, at which point isobutyl bromide (16.0 mL, 148 mmol, 1.3 equiv) (Note 5) is added via a 30 mL syringe over a period of 15 min, causing the reaction to turn yellow. The reaction is allowed to warm to room temperature slowly (Note 6) and stirred overnight (ca. 18 h). The completion of the reaction is checked by TLC (Note 7). The reaction is quenched by the addition of water (150 mL), which causes the reaction to turn from a white-yellow suspension into a clear and biphasic system. The volatile components are removed by rotary evaporation (35 ºC, 4 mmHg). The solution is then acidified to pH 1 (Note 8) by addition of concentrated HCl (~15 mL) over a period of 5 min. The aqueous layer is extracted with diethyl ether (4 x 150 mL). The combined organic extracts are dried over $MgSO_4$, filtered, and concentrated by rotary evaporation (30 ºC, 4 mmHg). The residue is placed under high vacuum with stirring (0.2 mmHg) over 12 h to yield the product as a white solid (23.0 g, >99%) (Notes 9 and 10).

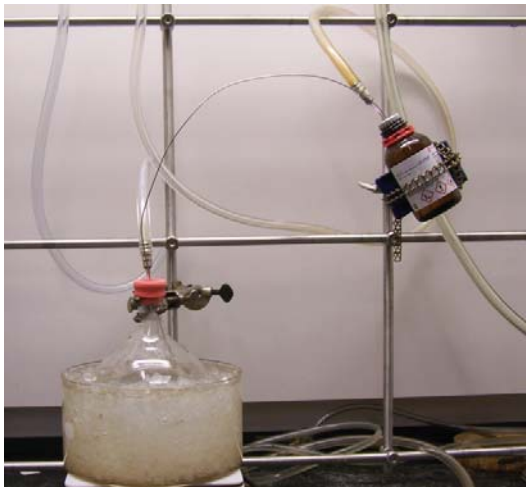

Figure 1. Addition of *n*-BuLi to *p*-Tolylacetic Acid

B. *4-Methyl-2-(p-tolyl)pentanoyl chloride (**2**)*. An oven-dried 50-mL round-bottomed flask with a 14/20 ground glass joint is fitted with a 1.6 x 0.7 cm egg-shaped magnetic stir bar and Liebig condenser capped with a nitrogen inlet, and the flask is allowed to cool under nitrogen. The condenser is

removed and the flask is charged with **1** (12.00 g, 58 mmol, 1 equiv) and thionyl chloride (6.3 mL, 87 mmol, 1.5 equiv) (Note 11). The condenser is replaced and the flask is placed in a pre-heated oil bath set at 90 °C for 1 h. The reaction turns brown and considerable gas evolution is observed during the first 30 minutes of this period. The reaction is cooled to room temperature, the condenser is removed, and K_2CO_3 (~4 g) (Note 12) is added in a single portion. The mixture is stirred until gas evolution ceases (~15 min), and placed on a rotary evaporator (40 ºC, 4 mmHg) for 1 h (Note 13). The flask is then fitted with a vacuum distillation head connected to a multiflask receiving bulb (Figure 2) (Note 14). A single fraction (0.2 mmHg, 130 °C) of **2** (10.28 g, 79%) was obtained (Note 15) as a colorless liquid (Note 16).

Figure 2. Distillation Apparatus used in Step B

C. *4-Methyl-2-(p-tolyl)pent-1-en-1-one (**3**)*. All glassware is oven dried. A 300-mL schlenk tube with a 2.5 cm wide valve and 24/40 joint is fitted with

a 3.2 x 1.6 cm egg-shaped stir bar and a rubber septum (Note 17). The flask is purged (0.4 mmHg) and backfilled with dry nitrogen through an 18 G needle three times as it is allowed to cool to room temperature. Compound **2** is then added via 20 mL syringe (10.8 g, 48 mmol, 1 equiv), followed by diethyl ether (150 mL) via 50 mL syringe. The solution is stirred (Note 18) and dimethylethylamine (20.7 mL, 192 mmol, 4 equiv) (Note 19) is added via multiple uses of a 20 mL syringe, and the reaction begins to turn yellow and a white precipitate begins to form in the yellow solution (Figure 3, left). The valve on the schlenk flask is closed and the reaction is stirred for 72 h. The reaction is then filtered as follows (Figure 3, right): a 1-necked (24/40) 500 mL round-bottomed flask with a sidearm with a ground-glass stopcock (stopcock A) is placed under a stream of argon through tube A, and fitted with a 100-mL schlenk filter with a sidearm with a ground-glass stopcock (stopcock B) and 14/20 female ground glass joint. A tube is connected to the

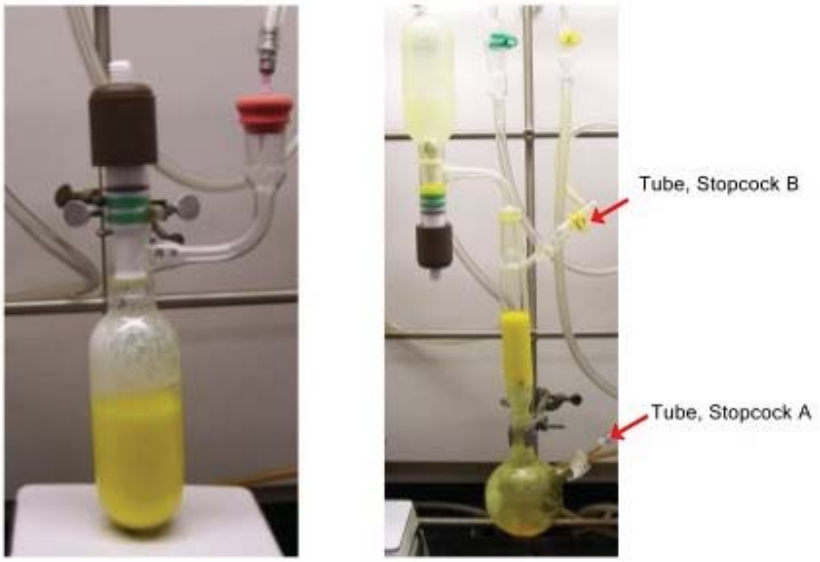

Figure 3. Reaction Assembly for Step B and Filtration Assembly

schlenk line and to the filter's sidearm at stopcock B. The septum is removed from the reaction vessel and the vessel placed on top of the filtration apparatus. Stopcock A is closed, and the filter apparatus is purged by applying a vacuum (0.5 mmHg) via stopcock B and backfilling with argon three times. With stopcock A closed, the tube attached to the lower

stopcock (tube A) is placed under vacuum. The reaction vessel's valve is then opened slowly. When ~3 cm of reaction mixture has collected above the frit, vacuum is gently applied to the flask by quickly opening and closing stopcock A. If the level of reaction mixture approaches stopcock B, the schlenk flask's valve is closed temporarily to prevent the reaction mixture from entering tube B. When all of the liquids have entered the collection flask, stopcock B is closed, and the solvent and excess amine are removed under high vacuum. The collection flask is placed in a warm water bath (~30 °C) to expedite the concentration, which takes ~30 minutes. Stopcock A is closed, and the apparatus backfilled with argon through stopcock B. The tube attached to stopcock A is backfilled with argon and removed from the apparatus, a rubber septum is placed over the end of the sidearm, and tube A is fitted with a luer-lock connector and a 1.5" 18 gauge needle. A 50-mL round-bottomed flask with a 14/20 ground glass joint is fitted with a rubber septum, which is pierced with the needle on tube A. A cannula is placed between the 50-mL flask and the septum on sidearm A (Figure 4). The flask, cannula, and end of the sidearm are purged (0.6 mmHg) and backfilled with argon three times. Stopcock A is then

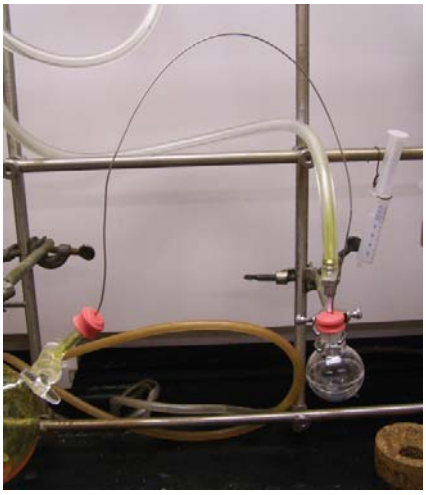

Figure 4. Cannula placed between Round-bottomed Flask and the Schlenk Flask

opened and the crude ketene is transferred to the round-bottomed flask. The flask is backfilled with argon and the cannula removed. The septum is

removed from the 50-mL flask and the flask is immediately attached to a vacuum distillation apparatus equipped with a multiflask collector (Figure 5) with tared receiving flasks. The distillation apparatus is then purged (0.5 mmHg) and backfilled with argon three times. The ketene is then distilled in one fraction (0.15 mmHg, 120 °C) (Note 20). Upon completion of the distillation, the apparatus is refilled with argon. The receiving flask is removed, and is quickly equipped with a septum. Compound **3** is obtained as a yellow liquid (6.30 g, 70%) (Notes 20, 21, and 22).

Figure 5. Distillation Apparatus used in Step C

Notes

1. Unless otherwise noted all chemicals were purchased from Sigma-Aldrich (reagent grade) and used without further purification. *p*-Tolylacetic acid (99%) was purchased from Acros.
2. THF (Fisher, HPLC grade, 99.9%) and ether (Fisher, ACS, 99,9%) used as reaction solvents were sparged with dry nitrogen, and subsequently passed over columns of activated alumina and Q5 catalyst.

3. The reaction is stirred at 900-1000 rpm. The monoanion of *p*-tolylacetic acid is highly insoluble and a thick white slurry forms over the first half of the addition and dissipates over the second half.
4. An entire 100 mL bottle of *n*-butyl lithium is added over a period of approximately 20 minutes. The submitters generally used fresh *n*-butyl lithium, but unopened samples that had been stored at -10 ºC for two months were just as effective. The checkers used fresh *n*-butyl lithium.
5. Reagent grade isobutyl bromide (99%) was purchased from Sigma-Aldrich and used as received.
6. It is important to leave the flask in the ice bath. If the ice bath is removed, butane is evolved vigorously.
   A 0.5 mL aliquot of the reaction is added to a mixture of 1 mL water, 1 mL EtOAc, and 5 drops concentrated hydrochloric acid. A TLC is taken of the organic layer, *p*-tolylacetic acid, and a co-spot of starting material and the reaction mixture. Aluminum backed Silica gel 60 F_{254} plates were purchased from EMD Chemicals Inc. The TLC plate was eluted with pure ethyl acetate, and the plate was visualized under 254 nm UV light. The R_f of the starting material was 0.79, and the R_f of the product was 0.91.
7. pH was determined by EMD Millipore colorpHast® pH Test Strips.
8. The reaction was performed at half-scale and provided 11.8 g (>99%) of a white solid.
9. Compound **1** displays the following physiochemical properties: R_f = 0.43 (30% ethyl acetate / 70% hexanes), mp 61-63 ºC, ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.91 (d, *J* = 6 Hz, 6H), 1.48 (m, 1H), 1.66 (m, 1H), 1.92 (m, 1H), 2.33 (s, 3H), 3.63 (t, *J* = 8 Hz, 1H), 7.14 (d, *J* = 8 Hz, 2H), 7.22 (d, *J* = 8 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 21.1, 22.2, 22.7, 25.8, 42.0, 49.1, 128.0, 129.4, 135.7, 137.2, 180.7; IR (KBr) 2957, 273, 2644, 1702, 1513, 1466, 1437, 1413, 1386, 1370, 1324, 1300, 1286, 1252, 1213, 1189, 1120, 1044, 943, 835, 790, 727, 693, 669, 636, 503 cm^{-1}; HRMS (ESI) $[M - H]^+$ calcd for $C_{13}H_{17}O_2$ 205.1234, found; 205.1238; Anal. Calcd. for $C_{13}H_{18}O2$: C, 75.69; H, 8.80. Found: C, 75.43; H, 8.86.
10. Thionyl chloride (ReagentPlus, 99.5%, low iron) was purchased from Sigma Aldrich and used as received
11. Anhydrous Potassium carbonate (Reagent grade, 100.6% assay) was purchased from JT Baker.
12. It is imperative to apply vacuum slowly to prevent bumping both on the rotovap and the vacuum distillation assembly.

13. The submitters reported the distillation was performed through the use of a Kugelrohr apparatus.
14. When the reaction was performed on a slightly larger scale, the identical product was obtained (14.4 g, 86%).
15. Compound **2** should be used immediately as it is water reactive. It displays the following spectroscopic properties: ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.93 (dd, *J* = 3, 7 Hz, 6H), 1.51 (dt, *J* = 14.2, 6.6 Hz, 1H), 1.75 (m, 1H), 2.04 (m, 1H), 2.36 (s, 3 H), 4.03 (t, *J* = 8 Hz, 1 H), 7.19 (s, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 21.1, 22.0, 22.7, 25.6, 42.0, 61.2, 128.3, 129.8, 133.0, 138.1, 175.2; IR (film) 2951, 2871, 1789, 1514(m), 1468, 1387, 1369, 1255, 1170, 1127, 1038, 982, 875, 840, 820, 751, 729, 703, 561, 541, 446 cm^{-1}; HRMS (EI) [M+] calcd for $C_{13}H_{17}OCl$: 224.0968. Found: 224.0972. Anal. Calcd. for $C_{13}H_{17}ClO$: C, 69.48; H, 7.62. Found: C, 69.49; H, 7.59.
16. Sigma-Aldrich SKU Z124656 for 24/40 joints, Z124591 for 14/20 joints.
17. The reaction is stirred between 700-900 rpm to maintain the amine hydrochloride salt in suspension.
18. Dimethylethylamine (Sigma-Aldrich, 97%) was distilled from CaH_2 (90-95%, Alfa-Aesar) and stored in bottles over KOH in a dessicator with drierite. This compound is stable for at least 7 months stored in this fashion.
19. Compound **3** must be stored under an inert atmosphere. Ketenes are sensitive to water, heat, and light. The submitters report that aryl alkyl ketene are stable indefinitely in a nitrogen-filled glovebox at –40 °C. When determining the mass of the compound, the impact of the inert atmosphere must be considered.
20. A reaction performed on half scale provided the same product (3.20 g, 71%).
21. Compound **3** displays the following physiochemical properties: ^{1}H NMR (500 MHz, C_6D_6) δ: 0.79 (d, *J* = 7 Hz, 6 H), 1.61 (m, 1 H), 1.96 (d, *J* = 7 Hz, 2 H), 2.10 (s, 3 H), 6.89 (d, *J* = 8 Hz, 2 H), 6.95 (d, *J* = 8 Hz, 2 H); ^{13}C NMR (125 MHz, C_6D_6) δ: 21.0, 22.4, 27.4, 33.4, 37.8, 124.8, 129.7, 130.1, 134.0, 206.3; IR (film): 2957, 2925, 2869, 2096, 1819, 1747, 1608, 1513, 1466, 1385, 1367, 1243, 1124, 1020, 935, 809 cm^{-1}. HRMS (EI) [M+] calcd for $C_{13}H_{16}O$: 188.1201; Found: 188.1200. Anal. Calcd. for $C_{13}H_{16}O$: C, 82.94; H, 8.57. Found: C, 82.58; H, 8.40.

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The procedures in *Organic Syntheses* are intended for use only by persons with proper training in experimental organic chemistry. All hazardous materials should be handled using the standard procedures for work with chemicals described in references such as "Prudent Practices in the Laboratory" (The National Academies Press, Washington, D.C., 2011; the full text can be accessed free of charge at http://www.nap.edu/catalog.php?record_id=12654). All chemical waste should be disposed of in accordance with local regulations. For general guidelines for the management of chemical waste, see Chapter 8 of Prudent Practices.

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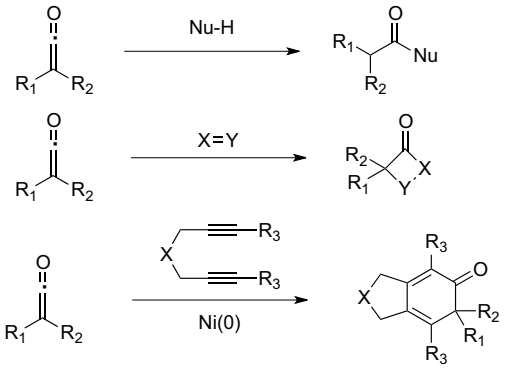
Discussion

Ketenes are useful synthetic building blocks due to their propensity to undergo [2 + 2] cycloaddition reactions with several different partners including alkenes[2], aldehydes or ketones[3], and imines[4] to form a cyclobutanones, β-lactones, and β-lactams. Nucleophiles can also add to the O=*C*=C carbon.[5] These reactions have been reviewed extensively.[6] Recently, chiral nucleophilic catalysts or chiral auxiliaries have been employed to

impart enantioselectivity on these cycloadditions[7] and addition[8] reactions. Furthermore, reports of transition metal catalyzed carbon-carbon bond forming reactions of ketenes are beginning to emerge, including a Ni catalyzed [2 + 2 + 2] cycloaddition reaction of diynes and ketenes, which forms cyclohexadienones[9], and a Rh catalyzed three component reaction of silyl acetylene and two ketenes, which forms 1,3-enynes bearing carboxylic esters.[10] These reactions are of particular interest as they resist decarbonylation of transition-metal ketene complexes, which forms unreactive metal carbonyl complexes.[11]



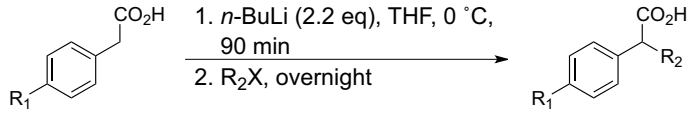
Scheme 1. Reactions of Ketenes

Several other methodologies exist to generate ketenes: cracking of ketene dimers,[12] pyrolysis of anhydrides,[13] Wolff rearrangement of α-diazo ketones,[14] and reduction of α-halo acid halides[15]. These methods require high temperatures, formation and handling of diazo compounds, low substrate scope, and/or extra steps. Trapping of ketenes *in situ*[16] is much more common than isolating reactive ketenes due to their tendency to dimerize, and most of these reactions produce by-products that make isolation difficult. Dehydrohalogenation[17] is therefore the most popular method of synthesizing and isolating ketenes. Some ketenes prepared in this communication have been previously reported,[7d-e,8a,10,18] albeit on smaller scale. These reported preparations lack the detail essential for an *Organic Syntheses* article, and are lower yielding, presumably due to the smaller scale.

This procedure was found to be general for the synthesis of a variety of aryl-alkyl ketenes bearing substituents in the para position and different primary and secondary alkyl chains. The first step was found to be very

general (Table 1) providing carboxylic acids in excellent yields with no further optimization required.

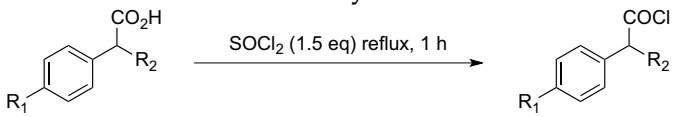
Table 1. Alkylation of Aryl Acetic Acids



R_1	R_2	X	yield (%)
H	*n*-Bu	Br	99
F	*i*-Bu	Br	93
H	*i*-Bu	Br	97
Me	*i*-Bu	Br	98
OMe	*i*-Bu	Br	94
F	*i*-Pr	I	99
H	*i*-Pr	I	97
Me	*i*-Pr	I	95
OMe	*i*-Pr	I	98
H	*s*-Bu	I	96

Furthermore, the conversion of the carboxylic acids to acid chloride was just as general, providing acid chlorides in good yields (Table 2).

Table 2. Conversion of Carboxylic Acids to Acid Chlorides

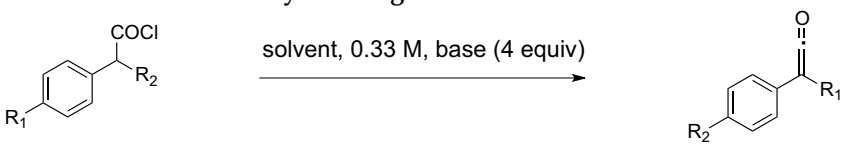


R_1	R_2	bp (mTorr/˚C)	yield (%)
H	*n*-Bu	200/150	74
F	*i*-Bu	120/120	76
H	*i*-Bu	400/150	78
Me	*i*-Bu	200/130	83
OMe	*i*-Bu	200/220	86
F	*i*-Pr	110/100	83
H	*i*-Pr	150/120	82
Me	*i*-Pr	110/140	77
OMe	*i*-Pr	300/150	84
H	*s*-Bu	170/160	80

Dehydrohalogenation of acyl chlorides was also found to be general after some tuning for each compound. Forming ketenes with secondary alkyl groups required heating at 60 ºC, which necessitated a solvent/base

change from Et_2O/Me_2NEt to THF/Et_3N. Substrates with electron donating groups required longer reaction times than ketenes with electron withdrawing groups, due to enhanced acidity of substrates with electron withdrawing groups (Table 3).

Table 3. Dehydrohalogenation of Acid Chlorides



R_1	R_2	temperature	solvent	base	time (h)	bp (mTorr/°C)	yield (%)
H	*n*-Bu	rt	Et_2O	$MeNEt_2$	36	150/100	74
F	*i*-Bu	rt	Et_2O	$MeNEt_2$	36	110/100	68
H	*i*-Bu	rt	Et_2O	$MeNEt_2$	36	120/100	72
Me	*i*-Bu	rt	Et_2O	$MeNEt_2$	72	150/120	74
OMe	*i*-Bu	rt	Et_2O	$MeNEt_2$	72	140/160	61
F	*i*-Pr	60°	THF	Et_3N	24	140/60	74
H	*i*-Pr	60°	THF	Et_3N	48	150/100	77
Me	*i*-Pr	60°	THF	Et_3N	72	240/100	71
OMe	*i*-Pr	60°	THF	Et_3N	96	150/180	78
H	*s*-Bu	60°	THF	Et_3N	48	160/100	73

References

1. Department of Chemistry, University of Utah, Salt Lake City, UT, 84112. louie@chem.utah.edu; we gratefully acknowledge the NIH (GM076125), the NSF (1213774), and the DOE for financial support.
2. a) Binsch, G.; Feiler, L. A.; Huisgen, R. *Tetrahedron Lett*. **1968**, *43*, 4497–4501. b) Frey, H. M.; Isaacs, N. S. *J. Chem. Soc. B.* **1970**, 830–832.
3. a) Brady, W. T.; Saidi, K. *J. Org. Chem*. **1979**, *44*, 733–737. b) Pons, J.-M.; Kocienski, P. *Tetrahedron Lett*. **1989**, *30*, 1833–1836.
4. a) Moore, H. W.; Hughes, G.; Srinivasachar, K.; Fernandez, M.; Nguyen, Nghi, V.; Schoon, D.; Tranne, A. *J. Org. Chem.* **1985**, *50*, 4231–4238. b) Duran, F.; Ghosez, L. *Tetrahedron Lett.* **1970**, 245–248.
5. a) Micovic, V. M.; Rogic, M. M.; Mihailovic, M. L. *Tetrahedron*, **1957**, *1*, 340–342. b) Lombardo, L. *Tetrahedron Lett.* **1985**, *26*, 381–384. c) Andaraos, J.; Kresge, A. J. *J. Am. Chem. Soc.* **1992**, *114*, 5643–5646. d) Dunbar, R. E.; White, G. C. *J. Org. Chem*. **1958**, *23*, 915–916. e) Kita, Y.; Matsuda, S.; Kitagaki, S.; Tsuzuki, Y.; Akai, S. *Synlett* **1991**, 401–402.

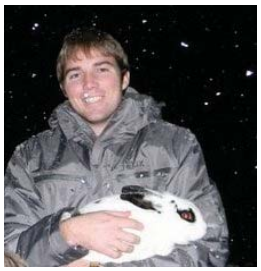
6. a) Tidwell, T. T. *In: Ketenes*, Wiley-Interscience; New York, 1995. b) Allen, A. D.; Tidwell, T. T.; *Chem. Rev.* **2013**, *113*, 7287–7342. c) Tidwell, T. T. *Angew. Chem. Int. Ed.* **2005**, *44*, 6812–6814. d) Science of Synthesis (Houben-Weyl); Danheiser, R. L., Ed.; Georg Thieme Verlag: Stuttgart, 2006; Vol. 23. e) Fu, N. and Tidwell, T. T. *Organic Reactions* **2015**, *87*, 257.
7. a) Zemribe, R.; Romo, D. *Tetrahedron Lett.* **1995**, *36*, 4159–4162. b) Dymock, B. W.; Kocienski, P. J.; Pons, J. *Chem. Commun.* **1996**, 1053–1054. c) Douglas, J.; Taylor, J. E.; Churchill, G.; Slawin, A. M. Z.; Smith, A. *J. Org. Chem.* **2013**, *78*, 3925–3938. d) Hodus, B. L.; Fu, G. C. *J. Am. Chem. Soc.* **2002**, *124*, 1578–1579.
8. a) Dai, X. D.; Nakai, T.; Romero, J. A. C.; Fu, G. C. *Angew. Chem. Int. Ed.* **2007**, *46*, 4367–4369. b) Hodus, B. L.; Fu, C. G. *J. Am. Chem. Soc.* **2002**, *124*, 10006–10007.
9. Kumar, P.; Troast, D. M.; Cella, R.; Louie, J. *J. Am. Chem. Soc.* **2011**, *133*, 7719–7721.
10. Ogata, K.; Ohashi, I.; Fukuzawa, S. *Org. Lett.* **2012**, *14*, 4214–4217.
11. a) Sugai, R.; Miyashita, A.; Nohira, H. *Chem. Lett.* **1988**, 1403–1406. b) Groatjahn, D. B.; Bikzhanova, G. A.; Collins, L. S. B.; Concolino, T.; Lam, K.; Rheingold, A. L. *J. Am. Chem. Soc.* **2000**, *122*, 5222–5223. c) Staudaher, N. D.; Arif, A. M.; Louie, J. L. *J. Am. Chem. Soc.* **2016**, *138*, 14083–14091.
12. a) Andreades, S.; Carlson, H. D. *Org. Synth.* **1965**, *45*, 50. b) Turro, N. J.; Leermakers, P. A.; Wilson, H. R.; Neckers, D. C.; Byers, G. W.; Vesley, G. F. *J. Am. Chem. Soc.* **1965**, *87*, 2613–2619.
13. a) Fisher, G. J.; MacLean, A. F.; Schnizer, A. W. *J. Org. Chem.* **1953**, *18*, 1055–1057. b) Danheiser, R. L.; Savariar, S.; Cha, D. D. *Org. Synth.* **1989**, *68*, 32–40. c) Depres, J.; Greene, A. E. *Org. Synth.* **1989**, *68*, 41–48.
14. a) Meier, H.; Zeller, K. *Angew. Chem. Int. Ed.* **1975**, *14*, 32–43. b) Bachmann, W. E.; Struve, W. S. *Organic Reactions* **1942**, *1*, 38–62. c) Smith, L. I.; Hoehn, H. H. *Org. Synth.* **1940**, *20*, 47.
15. a) Krepinski, L. R.; Hassner, A. *J. Org. Chem.* **1978**, *43*, 2879–2881. b) Smith, C. W.; Norton, D. G. *Org. Synth.* **1953**, *33*, 29.
16. a) Danheiser, R. L.; Okamoto, I.; Lawlor, M. D.; Lee, T. W. *Org. Synth.* **2003**, *80*, 160. b) Rasik, C. M.; Salyers, E. M.; Brown, M. K. *Org. Synth.* **2016**, *93*, 401–412.
17. Taylor, E. C.; McKillop, A.; Hawks, G. H. *Org. Synth.* **1972**, *52*, 36.
18. a) Rasik, C. M.; Brown, M. K. *J. Am. Chem. Soc.* **2013**, *135*, 1673–1676. b) Rasik, C. M.; Hong, Y. J.; Tantillo, D. J.; Brown, K. M. *Org. Lett.* **2014**, *16*, 5168–5171.

Appendix
Chemical Abstracts Nomenclature (Registry Number)

Phenylacetic acid; (103-82-2)
Butyllithium; (109-72-8)
Isobutyl Bromide; (78-77-3)
Thionyl Chloride; (7719-09-7)
Dimethylethylamine; (598-56-1)

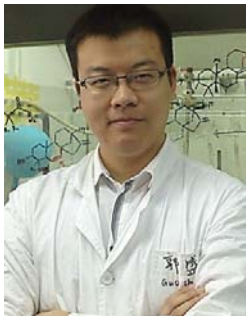
Nick Staudaher was born in Worcester, MA in 1989. He attended the University of Vermont where he worked in the labs of Thomas Hughes and Matthias Brewer, and earned his B.S. in Chemistry in 2011. He is currently working on his Ph.D. in the Louie group at the University of Utah. His research is focused on the reactivity of Nickel π-complexes, particularly Nickel ketene-complexes. When not in the laboratory, he enjoys rock climbing, skiing, and road biking.

Joe Lovelace was born in Phoenix, AZ in 1994 but grew up in Boise, ID. He is currently in his fourth year as a Biochemistry Major and Premedical Student at Middlebury College in Vermont. He worked as an intern for Nick and the Louie group over the summer of 2015. In his free time Joe spends his days whitewater kayaking, rock climbing, hunting, and fishing.

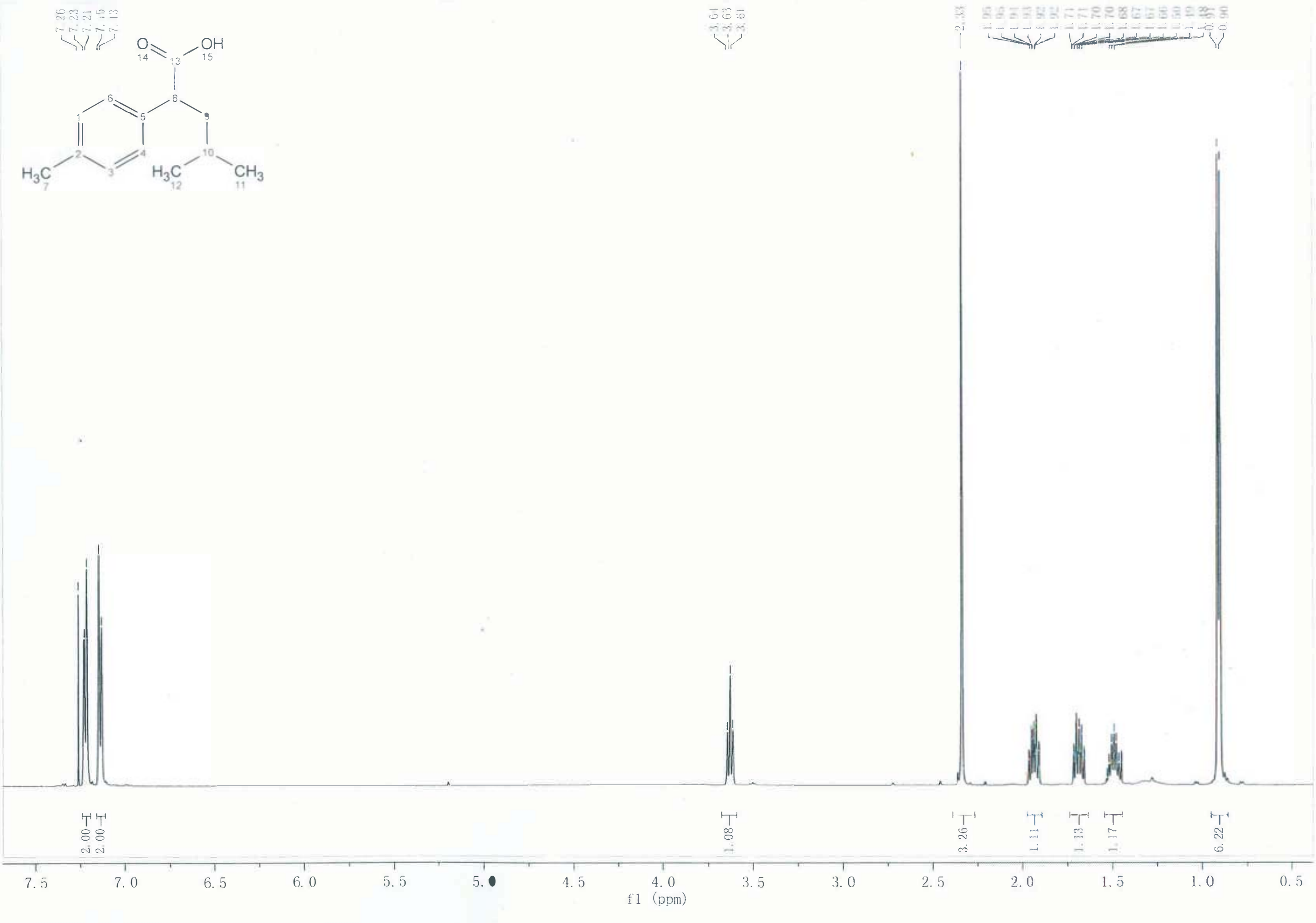


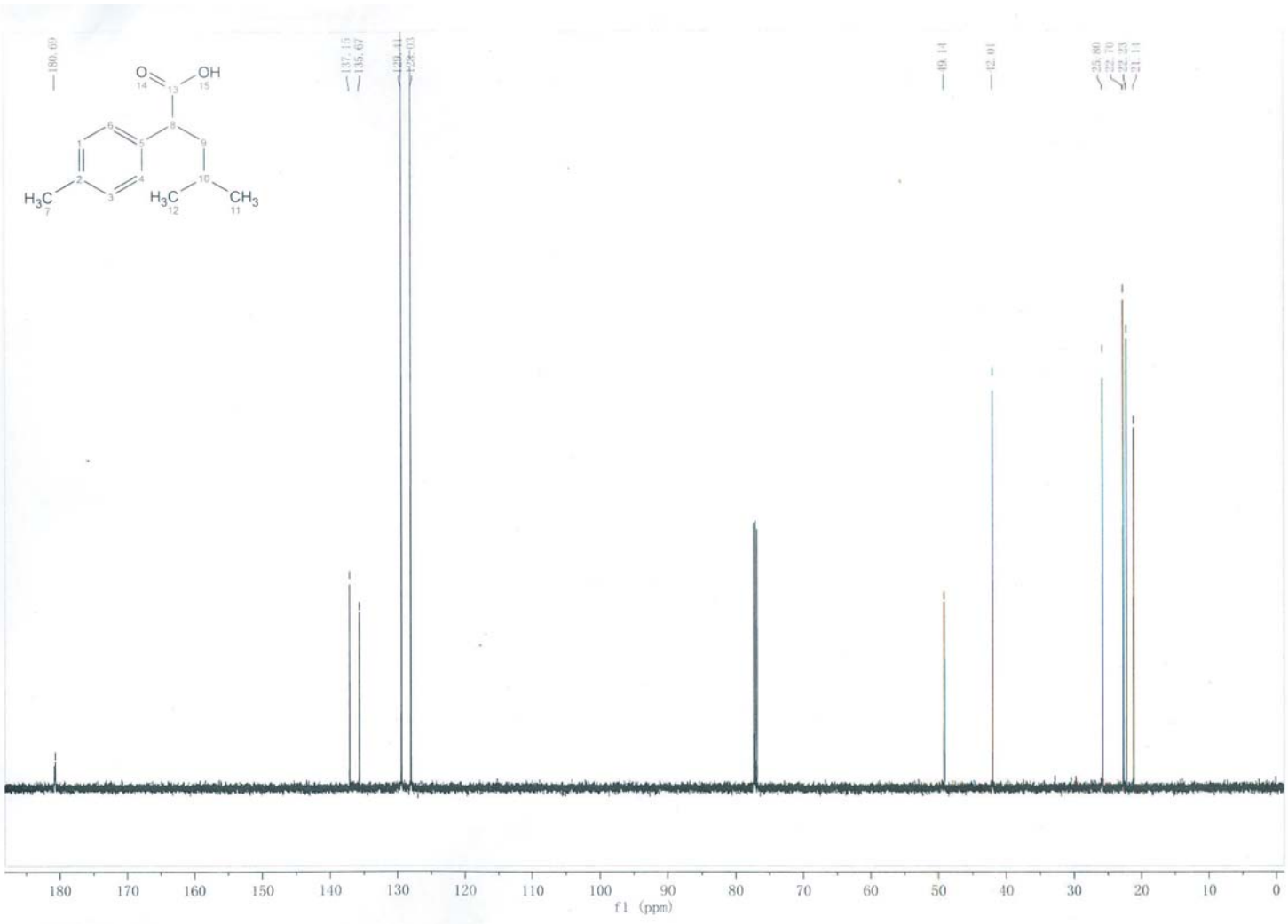
Michael P. Johnson was born and raised in Manti, UT. He received an Associate of Science from Snow College. He left Snow for two years to serve as an LDS missionary in France. After receiving his associate's degree, he returned to France to teach English. He is also a member of the Air Force Reserves and recently returned from a brief deployment to Afghanistan. He enjoys spending time with his wife, visiting the wonderful mountains of Utah, and making blueberry muffins.

Janis Louie was born in San Francisco, CA. She earned her Bachelors of Science at the University of California, Los Angeles and her Ph.D. at Yale University under the tutelage of Professor John F. Hartwig. She then worked as a NIH postdoctoral fellow at the California Institute of Technology under the guidance of Professor Robert H. Grubbs before starting her professorship at the University of Utah in 2001. Her research centers on the development of new base metal catalysts. In her free time, she enjoys fitness training, real estate, and spending time with her family.



Sheng Guo was born in Hubei, China. He received his B.S. degree in chemistry from Wuhan University in 2011. He earned his Ph.D. in Shanghai Institute of Organic Chemistry (SIOC) in 2016 under the supervision of Prof. Dawei Ma, working on total synthesis of complex natural products.

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22.23
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OH
14
13
15
1
2
3
4
5
6
7
8
9
10
11
12
H3C
H3C
CH3
180
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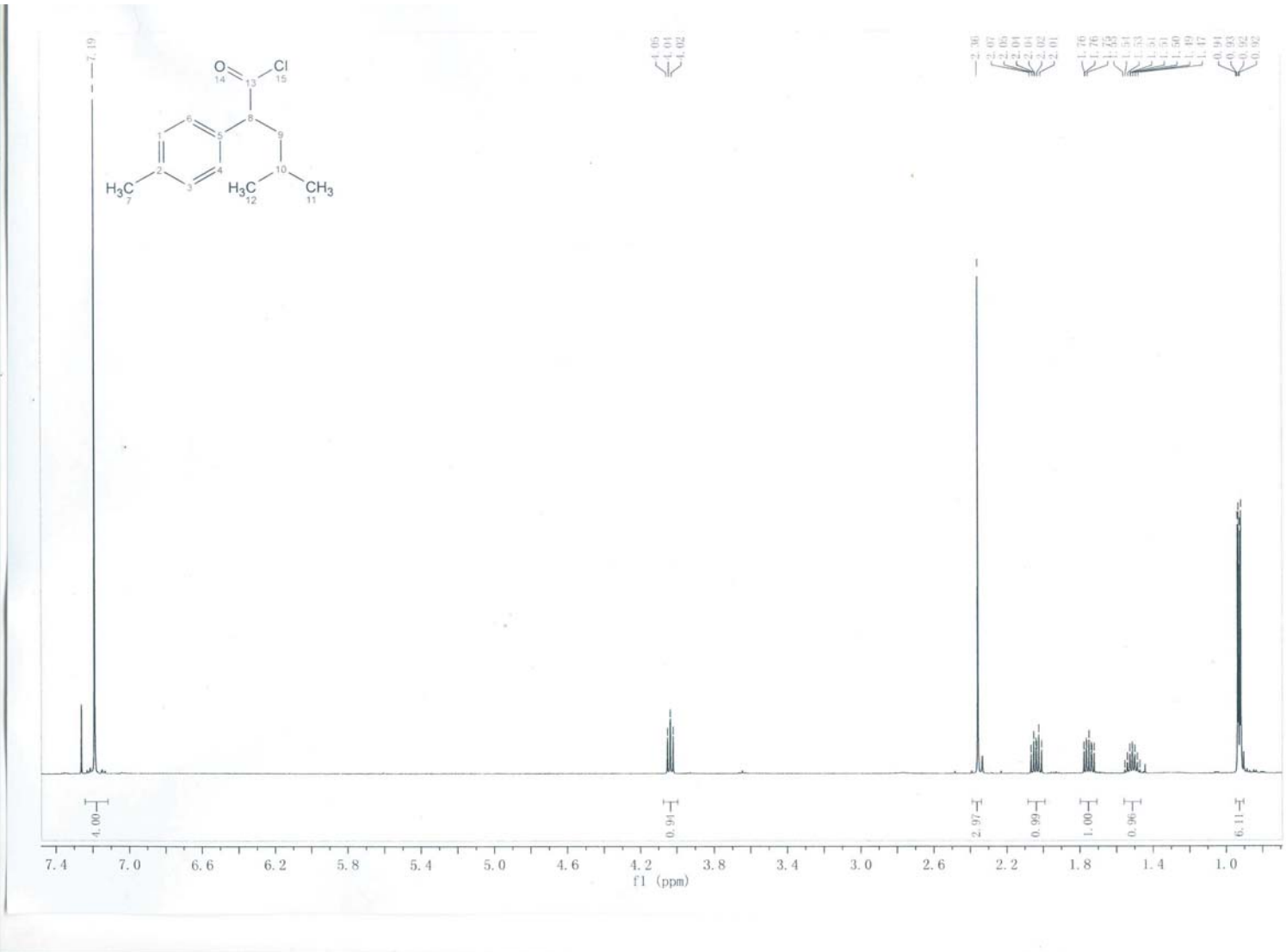
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1.53
1.51
1.51
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0.93
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0.92
O
14
Cl
15
13
8
1
6
5
9
2
4
10
3
H3C
7
H3C
12
CH3
11
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6.2
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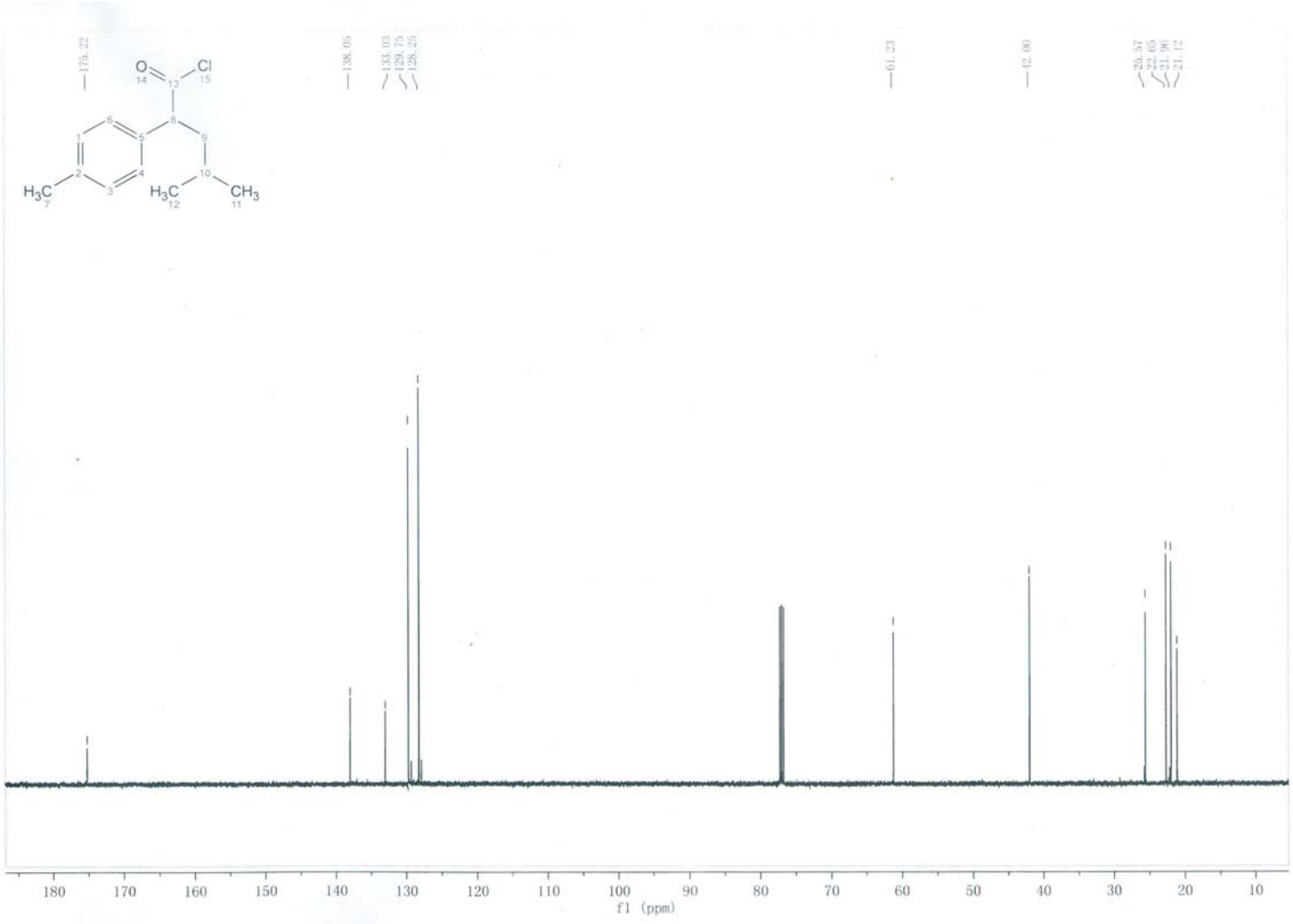
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14
Cl
15
13
1
2
3
4
5
6
8
9
10
H_3C
7
H_3C
12
CH_3
11
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100
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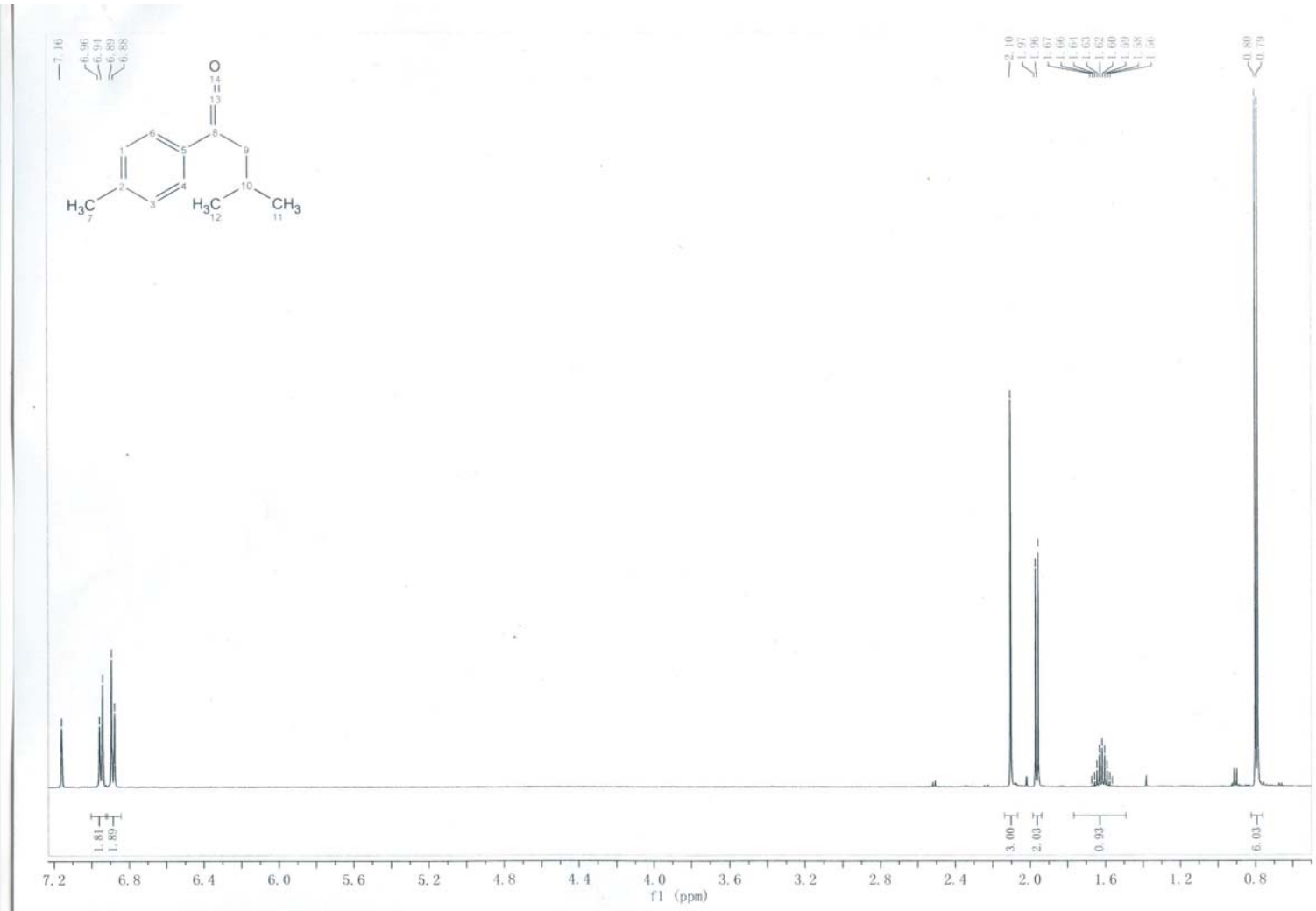
f1 (ppm)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1.59
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0.79
O
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13
8
6
5
1
9
2
4
10
3
H_3C
7
H_3C
12
CH_3
11
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3.00
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7.2
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6.4
6.0
5.6
5.2
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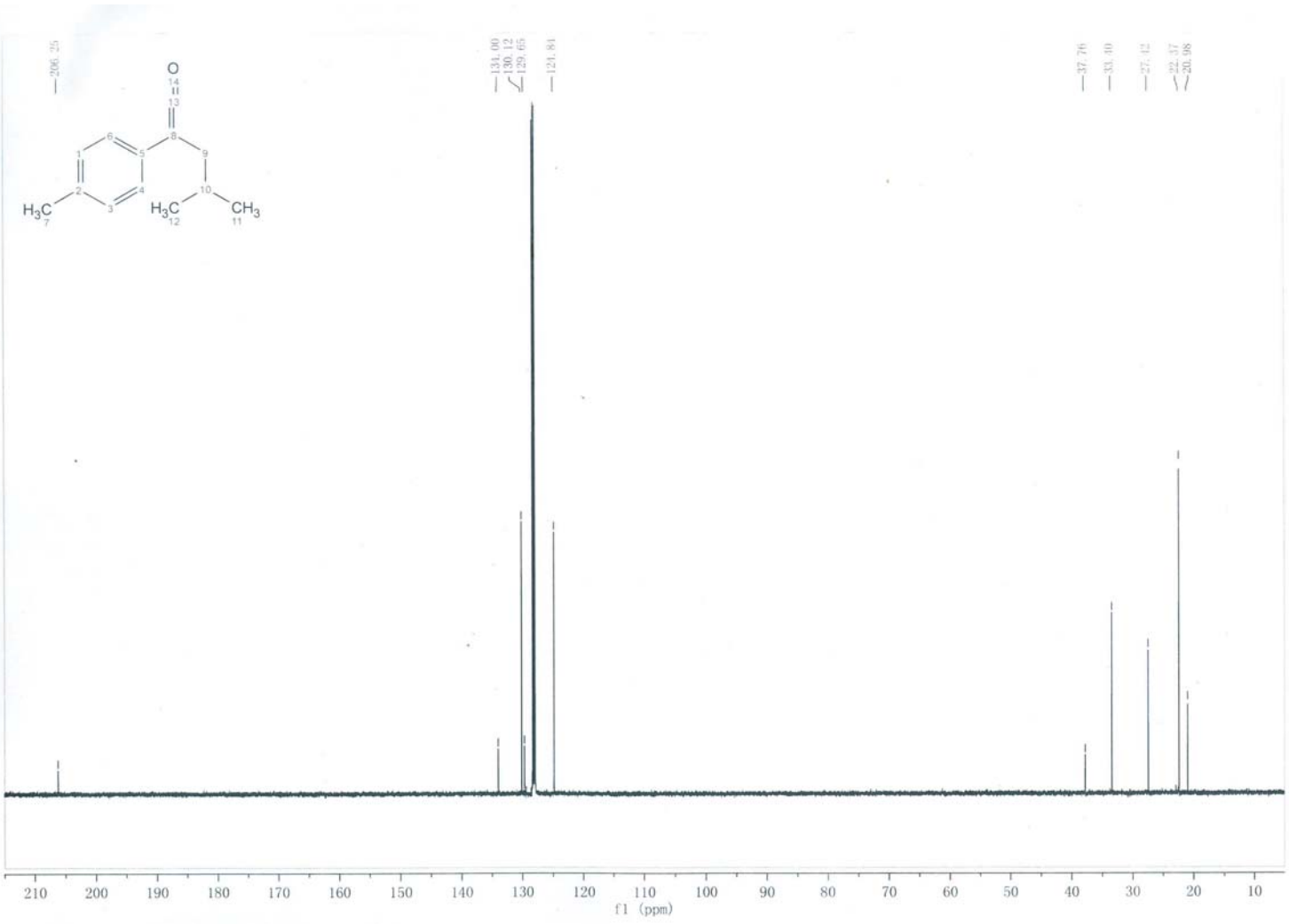
f1 (ppm)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5
1
9
2
4
10
3
H3C
7
H3C
12
CH3
11
210
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180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)