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One-Pot Synthesis of Benzopinacolone Derivatives from Acetophenones

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Pinacolone and benzopinacolone derivatives are an important class of organic compounds due to their uses in polymer synthesis and more recently as biologically active compounds. The conventional synthesis of such molecules is generally done in two steps, the pinacol coupling followed by the pinacol/pinacolone rearrangement. Aiming to prepare benzopinacolone derivatives in a greener fashion, we present here a one-step synthesis from acetophenones in the presence of zinc and *tert*-butyl chloride. To develop the methodology, conditions to prepare 3,3-diphenyl-2-butanone from acetophenone were optimized. To assess the scope, different substituted acetophenones were tested, resulting in the corresponding benzopinacolones at moderate yields (20-50%) with high purity. Structural elucidations were performed by ^{1}H and ^{13}C NMR (nuclear magnetic resonance spectroscopy) and GC-MS (gas chromatography-mass spectrometry).

Keywords: pinacolones, benzopinacolones, acetophenones, one-pot synthesis

Introduction

The pinacol/pinacolone rearrangement, discovered in the mid-19th century, is an important transformation in organic synthesis. It is a reaction that involves the dehydration of vicinal diols, resulting in a carbocation intermediate that is stabilized by the shift of one of the substituents forming an oxonium ion.[1] Despite being a "classic" reaction, the pinacol/pinacolone rearrangement is still investigated[2] and used in total synthesis.[3,4] Pinacolone, for example, is a precursor of triazolylpinacolone in the synthesis of the fungicide triadimefon and in the synthesis of the herbicide metribuzin. Also, the acetyl group of the pinacolone can be used for several transformations, from addition to the carbonyl group to reductive amination.[5] On the other side, benzopinacolones have applications as radical initiators in the synthesis of polymers. Polyarylates containing benzopinacolone group showed excellent solubility in organic solvents and good thermal properties.[6]

The synthesis of pinacolone derivatives is commonly done in two steps. It requires a pinacol coupling from ketones, leading to the diol, followed by the pinacol/pinacolone rearrangement. Some attempts to directly obtain pinacolones from ketones have already been reported, but involve the use of specific reagents (antimony pentachloride)[7] or high-cost reagents (SmI_2, for example),[8] or very hygroscopic reagents ($AlCl_3$ with zinc).[9] Another report published by Salama *et al.*[10] uses a mixture of tetrachlorosilane with zinc. In this case, reaction times are relatively high, varying between 10 and 26 reaction hours. In this work, we present a milder and faster alternative for obtaining benzopinacolone derivatives from acetophenones using low-cost and easy-to-handle reagents.

Results and Discussion

Initially, based on the work of Paul *et al.*,[11] our group was focused on developing a new methodology for inserting the *tert*-butyl group into aromatics via the Friedel-Crafts reaction. When phenothiazine was mixed with zinc powder, activated carbon and *tert*-butyl chloride in ethyl acetate, 3,5-di-*t*-butylphenothiazine was obtained in 32% isolated yield (Scheme 1a). Given the success of alternative alkylation, the objective was to expand the methodology with several substituted arenes (Scheme 1b). However, the alkylation reaction was not observed in the majority of the compounds. However, an interesting result was observed with acetophenone. After column purification and analysis by nuclear magnetic resonance (NMR) and gas chromatography-mass spectrometry (GC-MS), 3,3-diphenylbutan-2-one (compound **1**) in 49% yield was obtained (Scheme 1c).

With this result in hand, the effect of each reagent on the conversion of acetophenone into compound **1** was tested. The results are summarized in Table 1. We observed that

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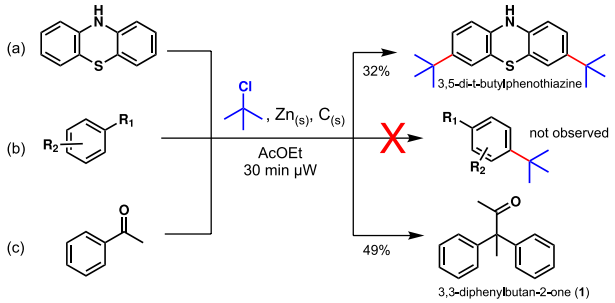


Scheme 1. Synthesis of 3,5-di-*t*-butylphenothiazine (route a), unsuccessful alkylation of arenes (route b) and synthesis of 3,3-diphenyl-2-butanone (route c).

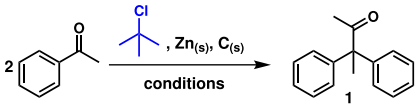
the reaction depends on *tert*-butyl chloride (experiment 2) and zinc powder (experiment 3). The use of other organic chlorides, such as dichloromethane and chloroform, did not lead to the expected product. We also observed that the activated carbon was not necessary. Furthermore, a simple reflux for 1 h is enough and therefore the microwave irradiation was omitted. We chose reflux for heating because of the open system, unlike the sealed tube required for microwave irradiation. Also, microwave irradiation does not allow large scale setup. Thus, it was possible to optimize the amounts of *t*-butyl chloride (6 equiv.) and zinc (3 equiv.) for 1 mmol of acetophenone. The maximum yield obtained was 66% (experiment 10).

With the optimized reaction conditions with acetophenone, we investigated the scope of the reaction with substituted acetophenones. The results are described in Table 2. The corresponding products were obtained in yields ranging from 20 to 72%. The product derived from 4-(*tert*-butyl)acetophenone, 3,3-bis(4-(*tert*-butyl)phenyl)butan-2-one (compound **2**) is new. We observed that a resonance donor group, such as methoxy (–OCH_3), contributed significantly to the reaction, obtaining the corresponding product (compound **6**) in 72% isolated yield. This result is possibly related to the greater stabilization of the carbocation intermediate formed during the rearrangement of the aromatic group (see below). For donor groups due to inductive effect, however, the contribution is absent. In the case of the *tert*-butyl group, the steric effect may be involved in the regular yield of the product, compared to the reaction with acetophenone. For substrates containing electronegative (–Br) or heteroaromatic groups, the stabilization of the carbocation intermediate is lower, which would justify the low yields obtained. It is worth mentioning that in the case of 2-acetyl-5-chlorothiophene, there was a dehalogenation of the expected product due to the presence of metallic zinc. There are reports of reductive dehalogenation of aromatics and heteroaromatics mediated by zinc.[12]

We observed that this methodology also worked for benzophenone, leading to β-benzopinacolone (compound **7**) in 34% isolated yield. Considering that it is a one-pot methodology starting from ketone and comparing it with the usual methodologies for obtaining benzopinacolone always starting from benzopinacol, we believe that it is an interesting result to be explored in more depth at an opportune moment.

Based on the work of Grant *et al.*[9] and Salama *et al.*,[10] the formation of benzopinacolone derivatives probably

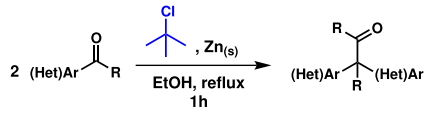
Table 1. Optimization for the synthesis of compound **1** from acetophenone

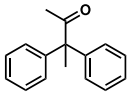
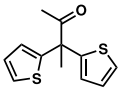
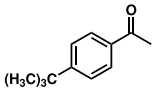
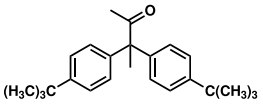
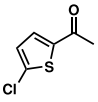
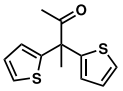
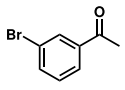
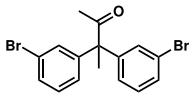
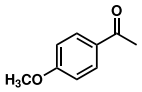
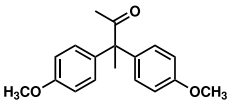
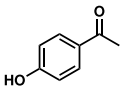
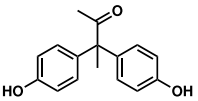
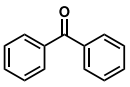
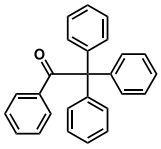


Exp.	*t*-BuCl	Zn dust	Activated charcoal / mg	Solvent	Heating	time / min	Yield of compound **1** / %
1	8 equiv.	4,5 equiv.	50	AcOEt	microwave[a]	30	50
2	–	4,5 equiv.	50	AcOEt	microwave[b]	30	–
3	8 equiv.	–	50	AcOEt	microwave[b]	30	–
4	8 equiv.	4,5 equiv.	–	AcOEt	microwave[b]	30	27
5	8 equiv.	4,5 equiv.	–	CH_3CN	microwave[b]	30	63
6	8 equiv.	4,5 equiv.	–	$CHCl_3$	microwave[b]	30	43
7	8 equiv.	4,5 equiv.	–	THF	microwave[b]	30	traces
8	8 equiv.	4,5 equiv.	–	EtOH	microwave[b]	30	66
9	3 equiv.	3 equiv.	–	EtOH	reflux	60	traces
10	6 equiv.	3 equiv.	–	EtOH	reflux	60	66
11	4 equiv.	3 equiv.	–	EtOH	reflux	60	traces
12	6 equiv.	2 equiv.	–	EtOH	reflux	60	51

Experimental conditions: acetophenone (1 mmol). [a]150 W, 80 °C. [b]100 W, 80 °C.

Table 2. Scope of the one-pot methodology using substituted acetophenones and heterocyclic ketones



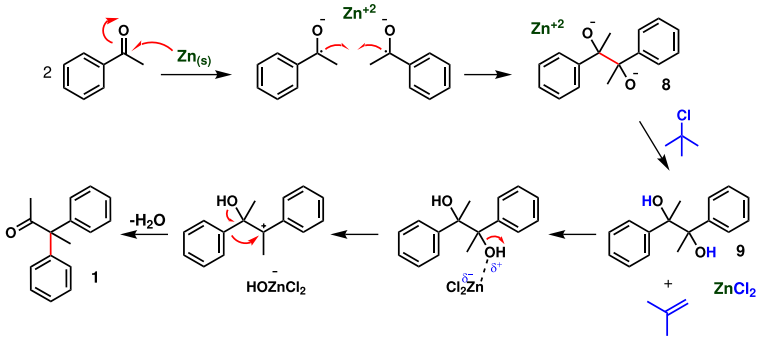
Starting material	Product	Isolated yield / %	Starting material	Product	Isolated yield / %
 Acetophenone	 3,3-diphenyl-2-butanone (**1**)	66	 2-Acetylthiophene	 3,3-di-2-thienyl-2-butanone (**5**)	32
 4'-*t*-butylacetophenone	 3,3-bis(4-(*tert*-butyl)phenyl)-2-butanone (**2**)	47	 2-Acetyl-5-chlorothiophene	 3,3-di-2-thienyl-2-butanone (**5**)	20
 3'-Bromoacetophenone	 3,3-bis(3-bromophenyl)-2-butanone (**3**)	26	 4-Methoxyacetophenone	 3,3-bis(4-methoxyphenyl)-2-butanone (**6**)	72
 4'-Hydroxyacetophenone	 3,3-bis(4-hydroxyphenyl)-2-butanone (**4**)	< 10	 Benzophenone	 1,2,2,2-tetraphenylethanone (**7**)	34

Experimental conditions: ketone (1 mmol), *t*-BuCl (6 mmol), $Zn_{(s)}$ (3 mmol), ethanol (5 mL).

occurs through a SER (single electron reduction) mechanism mediated by metallic zinc (Scheme 2), leading to the dianion intermediate (compound **8**). The dependence of *tert*-butyl chloride for the reaction is possibly because it serves as a source of protons for the formation of diol (compound **9**) via dehydrohalogenation. Thin-layer chromatography (TLC) analysis of the reaction medium after reflux indicated a more polar product, possibly pinacol (compound **9**). Attempts to isolate the diol failed as the compound was no longer visible after removal of the ethanol under reduced pressure and a more polar compound than acetophenone was formed. We believe that the evaporation of ethanol facilitated the removal of water from the rearrangement, leading to the product (compound **1**).

Conclusions

We present a new methodology for obtaining pinacolone derivatives from acetophenones involving two reactions (pinacol-pinacolone reduction and rearrangement) in a one-pot process. The products were obtained in moderate yields through operationally simple protocols and mild



Scheme 2. Mechanistic proposal for the one-pot synthesis of compound **1** starting from acetophenone.

reaction conditions in relation to those in the literature. In particular, it was possible to obtain 3,3-bis(4-(*tert*-butyl) phenyl)-2-butanone, a new molecule with good isolated yield (47%).

Experimental

General information

Solvents and zinc dust were purchased from Synth (reagent grade, Diadema, Brazil) and used without further purification. Ketones were purchased from Sigma-Aldrich (St. Louis, USA). Analytical thin-layer chromatography (TLC) was performed with aluminum backed silica plates coated with a 0.25 mm thickness of silica gel 60 F254 (Merck, Darmstadt, Germany), exposure to vanillin or potassium permanganate solution and heating. Column chromatography separations were followed using 35-70 mm (240-400 mesh) silica gel purchased from Sigma-Aldrich (St. Louis, USA). Gas chromatography with flame ionization detection (GC-FID) analyses were recorded on a 450-GC (Varian, Palo Alto, USA) with a DB-5 (25 m × 0.25 mm) column (Agilent J&W, Santa Clara, USA) using H_2 as the carrier gas. Mixing and heating of Falcon and glass tubes were made in a Thermomixer® (Eppendorf, Hamburg, Germany). The low resolution mass spectra (LRMS) were obtained using gas chromatography-mass spectrometry (GC-MS) analysis was made in one ion trap, Varian 4000 (Palo Alto, USA) from Universidade Federal do ABC. The ^{1}H and ^{13}C NMR were made on Varian (500 MHz) (Palo Alto, USA) from Universidade Federal do ABC. The solvents used were deuterated chloroform ($CDCl_3$) and deuterated dimethyl sulfoxide (DMSO-d_6). The melting point analyses were made on Büchi B-540 or EZ-Melt SRS-Stanford Research Systems from Universidade Federal do ABC. The Microwave synthesis system were made on CEM Focused, model Discover, from Universidade Federal do ABC.

General procedure

A mixture containing ketone (1 mmol), zinc dust (200 mg, 3 mmol) and *t*-butyl chloride (600 µL, 5.5 mmol) in ethanol (10 mL) was stirred at vigorous reflux for 1 h. After, the resulting mixture was filtered and the solvent removed under reduced pressure. The residue was purified by flash chromatography, on silica gel, using ethyl acetate/hexane (9:1 or 4:1) as the eluent.

3,3-Diphenyl-2-butanone (CAS 2575-20-4) (compound **1**)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 (m, 4H), 7.30 (m, 2H), 7.23 (m, 4H), 2.13 (s, 3H), 1.90 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 209.1, 143.5, 128.3, 126.9, 62.2, 27.6, 26.4; LRMS (EI) *m/z* 225 ([M + H]$^+$,1), 181 (100), 166 (38), 153 (6), 103 (30). The spectra of the compound are in accordance with those previously reported.[1]

3,3-Bis(4-(*tert*-butyl)phenyl)-2-butanone (compound **2**)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35 (d, 4H, Ph-H), 7.14 (d, 4H, Ph-H), 2.12 (s, 3H), 1.85 (s, 3H), 1.34 (s, 18H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 209.6, 149.5, 140.5, 127.9, 125.1, 61.5, 34.3, 31.2; LRMS (EI) *m/z* 293 ([M-43]$^+$, 100), 248 (41), 233 (60), 205 (46), 179 (56), 129 (80), 115 (70).

3,3-Bis(3-bromophenyl)-2-butanone (CAS 108773-87-1) (compound **3**)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45 (m, 2H), 7.32 (m, 2H), 7.22 (t, 2H), 7.08 (m, 2H), 2.13 (s, 3H), 1.87 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 207.6, 145.1, 131.1, 130.4, 129.9, 127.0, 122.7, 61.8, 27.4, 26.1; LRMS (EI) *m/z* 339 ([M-43]$^+$, 64), 179 (100).

3,3-Bis(4-hydroxyphenyl)-2-butanone (CAS 84224-55-5) (compound **4**)

^{1}H NMR (500 MHz, $CDCl_3$ + DMSO-d_6) δ 7.61 (d, 4H), 7.41 (d, 4H), 2.70 (s, 3H), 2.40 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$ + DMSO-d_6) δ 208.2, 154.7, 132.9, 127.8, 113.8, 59.2, 26.0, 25.2; LRMS (EI) *m/z* 213 ([M-43]$^+$, 64), 165 (24), 119 (70), 91 (52), 43 (100).

3,3-Di-2-thienyl-2-butanone (CAS 13196-17-3) (compound **5**)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29 (dd, 2H), 7.00 (dd, 2H), 6.95 (dd, 2H), 2.21 (s, 3H), 2.02 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 205.9, 147.3, 126.6, 126.0, 125.0, 56.9, 28.6, 26.3; LRMS (EI) *m/z* 193 ([M-43]$^+$, 82), 160 (15), 109 (100), 65 (25). The spectra of the compound are in accordance with those previously reported.[2]

3,3-Bis(4-methoxyphenyl)-2-butanone (CAS 22927-05-5) (compound **6**)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.12 (d, 4H), 6.88 (d, 4H), 3.82 (s, 6H), 2.10 (s, 3H), 1.83 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 209.5, 158.3, 135.7, 129.3, 113.6, 60.8, 55.1, 27.3, 26.5; LRMS (EI) *m/z* 241 ([M-43]$^+$, 100), 211 (5), 183 (4), 165 (4), 133 (18).The spectra of the compound are in accordance with those previously reported.[2]

1,2,2,2-Tetraphenylethanone (CAS 466-37-5) (compound **7**)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.68 (m, 2H), 7.25 (m, 18H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.8, 143.1, 137.4, 131.6, 131.0, 130.8, 127.7, 126.6, 71.0. The spectra of rhe compound are in accordance with those previously reported.[3]

Supplementary Information

Supplementary information (spectral data, NMR spectra and mass spectra) is available free of charge at http://jbcs.sbq.org.br as PDF file.

Acknowledgments

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References

1. Billamboz, M.; Banaszak, E.; Rigo, B.; *ChemistrySelect* **2018**, *3*, 10236. [Crossref]
2. Mishler II, R. E.; Biradar, A. V.; Duncan, C. T.; Schiff, E. A.; Asefa, T.; *Chem. Commun.* **2009**, *41*, 6201. [Crossref]
3. Shi, H.; Du, C.; Zhang, X.; Xie, F.; Wang, X.; Cui, S.; Peng, X.; Cheng, M.; Lin, B.; Liu, Y.; *J. Org. Chem.* **2018**, *83*, 1312. [Crossref]
4. Kassehin, U. C.; Adjibode, S. A.; Bautista, O.; Gbaguidi, F. A.; Quetin-Leclercq, J.; McCurdy, C. R.; Frédérick, R.; Poupaert, J. H.; *J. Med. Chem. Sci.* **2019**, *2*, 17. [Crossref]
5. Pinacolona, https://www.fishersci.es/shop/products/pinacolone-97-thermo-scientific/11474023, accessed in July 2024.
6. Watanabe, S.; Murayama, H.; Murata, M.; Masuda, Y.; Tanabe, M.; Imai, Y.; *J. Polym. Sci., Part A: Polym. Chem.* **1998**, *36*, 2229. [Crossref]
7. Ciminale, F.; Lopez, L.; Nacci, A.; D'Accolti, L.; Vitale, F.; *Eur. J. Org. Chem.* **2005**, *8*, 1597. [Crossref]
8. Li, J.; Li, S.; Jia, X.; *Synlett* **2008**, *10*, 1529. [Crossref]
9. Grant, A. A.; Allukian, M.; Fry, A. J.; *Tetrahedron Lett.* **2002**, *43*, 4391. [Crossref]
10. Salama, T. A.; Elmorsy, S. S.; Khalil, A. G. M.; *Tetrahedron Lett.* **2007**, *48*, 4395. [Crossref]
11. Paul, S.; Nanda, P.; Gupta, R.; Loupy, A.; *Synthesis* **2003**, *18*, 2877. [Crossref]
12. Binder, D.; Pyerin, M.; Steindl, R.; Weisgram, M.; *Monatsh. Chem.* **1998**, *129*, 887. [Crossref]

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