



PCP: A review of synthetic methods for forensic clandestine investigation

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Abstract

A review of the synthetic routes to phencyclidine (PCP, 1-(1-phenylcyclohexyl)piperidine) available in the open literature is presented. The emphasis herein is directed toward the forensic investigation of clandestine PCP laboratories. Six published synthetic routes to PCP/analogues are discussed. Each method is rated for overall yield, degree of difficulty and potential hazard, in order to assist the forensic chemist in evaluation of a particular clandestine operation. One clandestine recipe is illustrated and discussed.

Key words: Phencyclidine; Synthetic methods; Review

1. Introduction

This review addresses the chemistry of phencyclidine (PCP) manufacture in clandestine laboratories and covers the period 1924–1991, with information compiled from the open literature and on-site clandestine PCP laboratory notes or recipes. The only previous review of this nature was that of Shulgin in 1976 [1] which was limited in scope for possible alternative routes.

Since diversity exists in literature methods and between clandestine laboratories, we felt that a composite literature review and discussion of the chemistry involved would be of assistance in correlating notes or procedures found in clandestine laboratory sites to authentic open literature references. Herein we have attempted a

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graduated scale of 1–10, with ten being the most difficult. Further, each route has been assigned an expected overall yield and potential hazard, estimated by literature sources and the practical laboratory experience of the authors.

An overview of synthetic approaches to phencyclidine is outlined in Fig. 1 with reference annotations [3–37]. In Table 1, precursors which are commercially available and exploitable in Routes I–VII are listed. Although only Routes I and II have been encountered in clandestine laboratory sites, Routes III–VI are viable literature routes and potential diversion routes from the DEA precursor ‘watch-list’.

In a practical, educational sense, an authentic clandestine recipe for the manufacture of PCP is included and discussed. This recipe, referred to as the PCP- ‘bucket method’, is a ‘real world’ case patterned after Route I-C-D and creatively removed from the controlled atmosphere of the clinical laboratory.

2. Route I

The synthetic approach to PCP, which starts from a ketone and a secondary amine, is illustrated in Fig. 2, with cyclohexanone (1) and piperidine. Route I con-

OVERVIEW OF SYNTHETIC ROUTES TO PCP

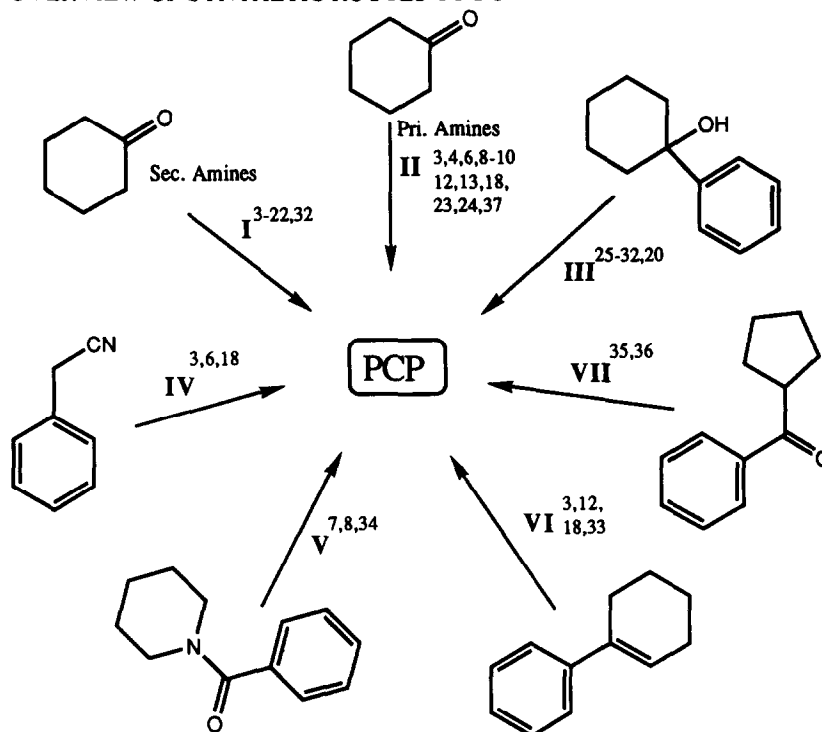


Fig. 1. Routes I–VII illustrate the different synthetic routes to PCP and analogs. Each route starts from precursors available from commercial sources: I, cyclohexanone and secondary amine; II, cyclohexanone and primary amine; III, 1-phenyl-1-cyclohexanol; IV, benzylcyanide; V, *N*-benzoylpiperidine; VI, 1-phenyl-1-cyclohexene; and VII, cyclopentylphenyl ketone.

Table 1
List of precursors for the synthesis of PCP which are commercially available

Compound	Supplier	Route	Price (\$.1992)
Bromobenzene	Aldrich	I	
Phenyl magnesium bromide	Aldrich	I	
Phenyl lithium	Aldrich	I, II	
Cyclohexanone	Adrich	I, II	14.5/kg
Piperidine	Adrich	I, II	55.5/kg
Benzyl cyanide	Aldrich	IV	19.0/kg
1-Phenyl-1-cyclohexanol	Lancaster	III	85.0/50 g
1-Phenyl-1-cyclohexanecarbonitrile	Lancaster	I	78.0/50 g
1-Phenyl-1-cyclohexene	Lancaster	VI	62.3/25 g
Cyclopentylphenyl ketone	Aldrich	VII	49.8/100 g

Route I: Secondary Amine Precursors to PCP (the most frequent clandestine route)

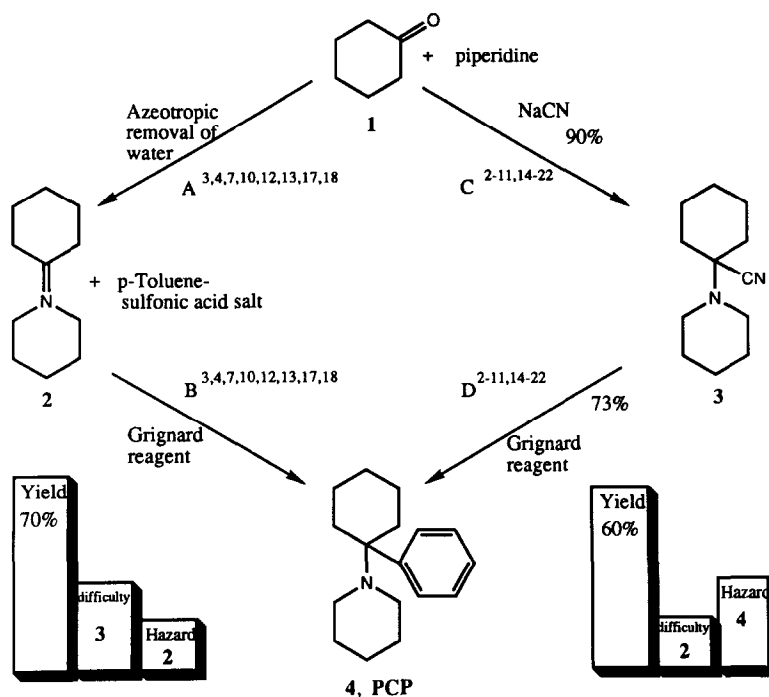


Fig. 2. Route I illustrates the two most commonly employed clandestine routes to PCP. Cyclohexanone and piperidine are combined to give intermediates 2 or 3, addition of phenyl magnesium bromide completes the synthesis to give 4, PCP.

sists of two alternative synthetic approaches, both of which are the most facile and clandestinely popular routes to PCP. Although the initial chemistry which described 1-(*N*-piperidino)cyclohexylcarbonitrile (PCC, **3**) was published by Kotz and Merkel in 1926 [2], the synthesis is normally conducted in a clandestine setting as per the procedures of Maddox et al. [3] and Kalir et al. [4]. The Schiff base (imine, **2**) is obtained from cyclohexanone-piperidine with the removal of water. This Schiff base adduct may be driven to completion with the azeotropic removal of water (Route I-A, **2**) [3] or trapped as the carbonitrile intermediate (Route I-C, **3**) [3,4]. Completion of these syntheses (B and D) may be achieved by reaction with phenyl magnesium bromide (Grignard reagent) followed by product work-up [3,4]. This Grignard reagent addition to an alpha-amino-carbonitrile (**3**) was initially published by Bruylants in 1924 [5].

The distinction, in Route I-C-D, between the procedures of Kalir et al. or Maddox et al. is that, in the procedure of Kalir et al. the carbonitrile intermediate (**3**) is prepared from a pH-adjusted mixture of ketone, amine and sodium cyanide [4]. Conversely, in the procedure of Maddox et al. the carbonitrile intermediate (**3**) is prepared from a mixture of ketone, amine, sodium cyanide and sodium bisulfite [3]. In the latter procedure, the sodium bisulfite coordinates with the cyclohexanone, thus increasing its aqueous solubility and, furthermore, promoting nucleophilic attack by the secondary amine [38].

Nucleophilic attack of the Grignard reagent upon PCC (**3**, Route I-D) does not occur at the nitrile carbon, as in the classical sense [39], but does occur at the electron deficient carbon alpha to the nitrile [40]. This results in nitrile displacement. The product, PCP (**4**) may be retrieved from the reaction with or without quenching the reaction mixture and converted to the HCl salt.

Clandestine laboratory samples have been encountered where the PCP is present as the HBr salt or a mixture of HBr and HCl salts. It is presumed that this is the result of direct acid quenching of the reaction mixture followed by aqueous/chloroform extraction. This effects the removal of the PCP from the acid layer into the chloroform as the ion-pair (PCP + HBr⁻). This fortuitous isolation of PCP·HBr is probably the serendipitous response of the clandestine chemist who, after acid quenching the Grignard reaction followed by basification in order to remove the tertiary amine product (PCP) is beset with the copious emulsions of magnesium hydroxide. The chemist responds by adjusting the pH (to the acid side), out of sheer frustration and continues extractions to find the crystalline product (PCP salt) upon evaporation of the solvent. This argument is offered since, it is doubtful that the phenomenon of ion-pairing is understood or HBr is purchased.

The overall yields on both Routes I A-B and C-D are high (60–70%) with synthetic degrees of difficulty (2–3) well within the reach of most clandestine chemists, notwithstanding the required generation of phenyl magnesium bromide (Grignard reagent). This latter consideration is probably facilitated by the sheer quantity of reagent (critical mass) typically employed on a clandestine scale. The use of potassium or sodium cyanide in Route I C-D increases the potential hazards involved in this approach and the forensic chemist should treat the laboratory site and the intermediate (**3**) with the proper care and respect. The transportation and handling of PCC (**3**) has resulted in individuals reporting incidences of nausea, faintness,

dizziness, vomiting and hospitalization. This is probably due to the potential for thermal elimination of hydrogen cyanide from PCC, yielding *N*-1-(1-cyclohexenyl)-piperidine (**2**) which may further hydrate back to the precursors: cyclohexanone and piperidine.

3. Route II

Secondary phencyclidine analogs (Fig. 3, Route II, **6**) have been prepared in clandestine situations following the procedure of Maddox et al. [3]. Here the Schiff base (**5**), resulting from cyclohexanone (**1**) and a primary amine, is treated with phenyl lithium. These analogs, which were once of some clandestine popularity during the 1970s, have been encountered infrequently in the last 10 years.

In practical synthetic applications, the primary amine should have a boiling point above the azeotropic removal of water-benzene or water-toluene, in order to drive the reaction forward to the product, **5**. This would limit this synthetic approach to primary amines above pentylamine. Interestingly, clandestine analogs of methyl, ethyl, and propylamine have been encountered. Here, the azeotropic removal of water is replaced by the in situ use of anhydrous sodium sulfate or potassium hydroxide. Thus, clandestine laboratories have been discovered in which reactions involved cyclohexanone, ethylamine, and anhydrous sodium sulfate in diethyl ether or toluene being stirred. Instructions are outlined [3,4] describing the decanting of the liquid from the hydrated inorganic salt with the addition of phenyl lithium. This would then be followed by work-up of the product — phenylcyclohexylethylamine (PCE). A variation on this theme, utilizing a primary amine and cyclohexanone which traps the imine (Schiff base) as the carbonitrile intermediate (like Route I-C) has been published by Kalir et al. [24].

The yield achieved for most PCE type analogs (**6**) is 60% with a low degree of difficulty. Possibly the only drawback is the use of lithium which is extremely moisture sensitive, reacting violently with water. Thus, lithium is normally stored and transported in oil. Washing with hexanes or benzene prior to use is typical and an inert working atmosphere (nitrogen or argon) is preferable.

The analog **6**, Route II-A has been used in medicinal chemistry to elaborate a variety of synthetic possibilities. In Route II-B, the Eschweiler–Clark method [41] of secondary amine methylation has been used to yield **7** [3,6,8,10,37]. If the primary amine in Route II-A was benzylamine, the product (**6**-benzyl analog) may be catalytically hydrogenated in order to remove the benzyl group (splitting out toluene) [42]. This is illustrated in Route II-D [3] leading to the primary amine (**9**). Continuation of **9** via a double internal amine alkylation produces PCP, illustrated in Route II-E [3,4,18,25–32].

Tertiary amines of varying description have been produced from **6** with the use of Route II-C [3,8,10,30,37]. Here, an acid chloride (or anhydride) is reacted with the secondary host (**6**). The resulting amide is reduced with lithium aluminium hydride to give alkyl analogs, **8**.

Route II-G [3] highlights the chemistry of utilizing an acetal-protected alcohol to produce the *N*-ethylhydroxyl analog, **10**. This has been used commercially and such analogs have been encountered from clandestine sources. Furthermore, such chemis-

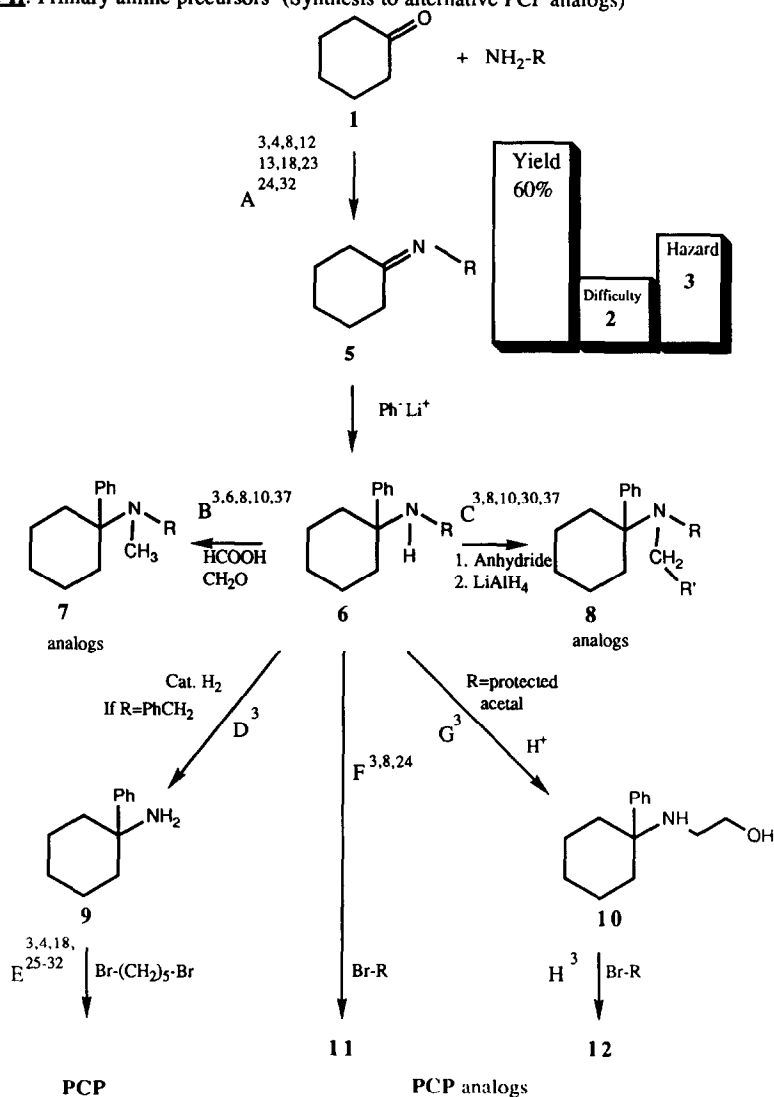
Route II: Primary amine precursors (Synthesis to alternative PCP analogs)

Fig. 3. Route II illustrates the second most popular clandestine approach to a PCP analog. Cyclohexanone is combined with a primary amine to give 5. This is followed by reaction with phenyl lithium to yield 6. Other elaboration from 6 are also possible, B, C, D, E, F, and G.

try has been found in the clandestine methamphetamine venue with the compound *N*-ethylhydroxy methamphetamine [43].

4. Route III

Route III illustrates the synthesis of PCP beginning with the commercially available precursor 1-phenyl-1-cyclohexanol (13, see Fig. 4). Conversion of this alcohol,

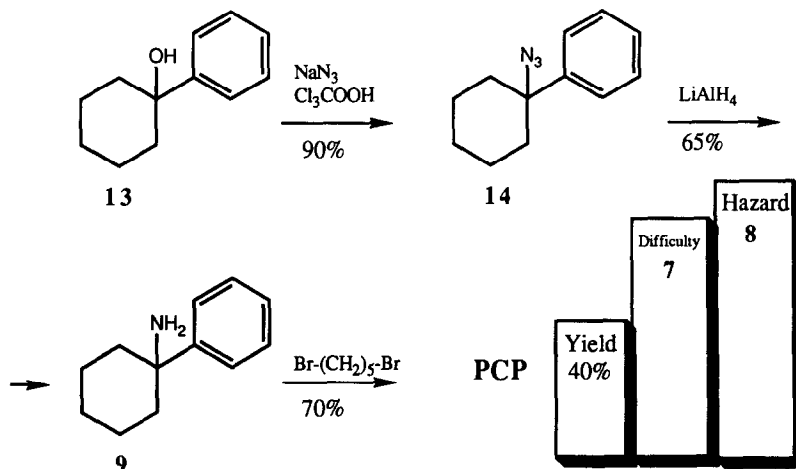
Route III: Alternative Synthesis of PCP^{20,25-32}

Fig. 4. Route III illustrates the most popular pharmaceutical approach to PCP analogs. The precursor, 1-phenyl-1-cyclohexanol (**13**) is reacted with sodium azide to **14**. Reduction of **14** produces **9**, which is double alkylated to PCP analogs.

13, to the azide, **14**, has been conducted with sodium azide [25–32] or diisopropyl azodicarboxylate [44]. The reduction of the azide, **14**, to the primary amine, **9**, has been conducted with lithium aluminum hydride [25–32] or catalytically with Raney nickel [44,45] or palladium on carbon [46]. Transformation of the primary amine to the target PCP analog was effected as previously described with the use of a double halo-alkyl/amination reaction [3,4,18,25–32].

In spite of its ready availability and the ease of conducting this three-step synthesis to PCP, this route has not attracted clandestine attention. Perhaps this is due to the general unfamiliarity, even among professional chemists, with azide chemistry and the troublesome work-up procedures of the lithium aluminum hydride reaction mixture. Furthermore, sodium azide is highly toxic and contact with mineral acids will create toxic hydrazoic acid. The potential fire hazards of lithium aluminum hydride are also not to be minimized. We rate the potential hazard of such a clandestine operation as very high, (8). The overall yield of this route is placed at 40% with a degree of difficulty more than twice that of Routes I and II.

5. Route IV

Route IV illustrates yet another approach to PCP analogs which has been published in the open literature (Fig. 5) [3]. However, again, no known clandestine operation has utilized this route to date. The low cost and ease of subverting the precursor watch list are perhaps outweighed by the degree of difficulty of this multi-step approach. From beginning to end this method would involve: first, working with sodium amide under anhydrous conditions to effect C-alkylation (**15–16**) [3]; second,

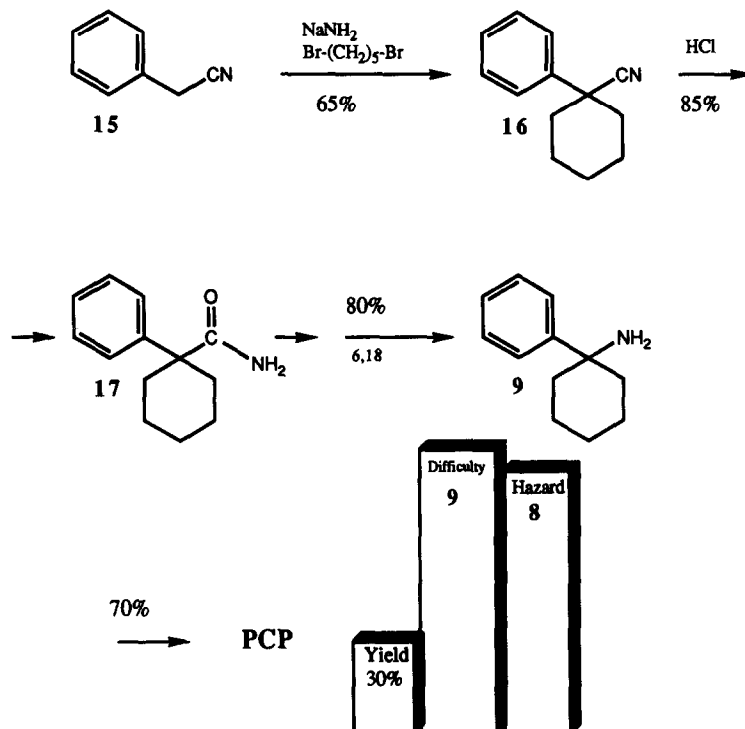
Route IV: Alternative Synthesis of PCP³

Fig. 5. Route IV illustrates a synthetic approach to PCP starting from benzyl cyanide (15). Carbon alkylation of 15 yields 16 which is followed by hydrolysis to 17. Beckmann rearrangement and hydrolysis produces 9. Nitrogen alkylation of 9 yields PCP.

acid hydrolysis of the carbonitrile (16–17) [3]; third, Beckmann rearrangement followed by acid hydrolysis of the *N*-formyl product leading to the primary amine analog (9) [3,6,18]; and, finally, double *N*-alkylation to PCP [3,4,18,25–32].

This route is rated with a high degree of difficulty for a clandestine operation primarily due to the use of sodium amide which is an extremely moisture-sensitive flammable solid. If the NaNH_2 is generated on site, ammonia gas and subzero temperatures are required (-30°C). Improvements in this initial step (15–16) have been achieved with the use of sodium hydride in anhydrous dimethyl sulfoxide [47]. However, it is doubtful that clandestine chemists can utilize a composite literature approach to a synthetic problem. Acid hydrolysis of 16–17 is sometimes sluggish and time consuming, especially for some aromatically substituted analogs. An alternative base hydrolysis has been published to facilitate this problem [48]. Beckmann rearrangement and hydrolysis (17–9) which has a respectable yield of 80%, would require the use of bromine and all of the associated ventilation problems for a clandestine operation. Overall, we score this route very high on the degree of difficulty (9) for a clandestine operation with high hazards (8) and low overall yield (30%).

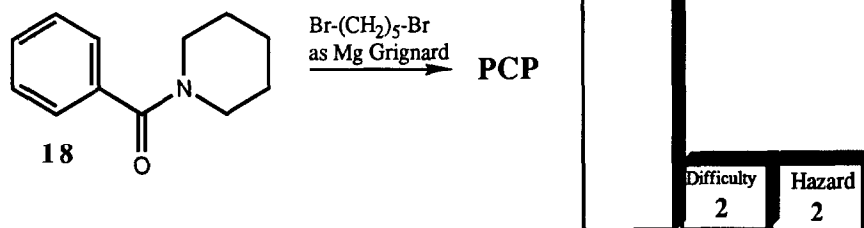
Route V: Alternative Synthesis of PCP^{7,8,34}

Fig. 6. Route V illustrates a one step synthesis of PCP from *N*-benzoylpiperidine (**18**) and an appropriate Grignard reagent.

6. Route V

A practical route in terms of clandestine operations is outlined as Route V (see Fig. 6). It starts from a precursor not currently under DEA 'watch list' scrutiny. This material, *N*-benzoylpiperidine (**18**), is also readily prepared from piperidine (precursor 'watch listed') and benzoyl chloride. In this PCP synthesis, **18** is combined with the organo-metallic derivative of 1,5-dibromopentane, existing as the lithium or magnesium coordinate. Product work-up yields PCP [7,8,34].

The degree of difficulty of this route is considered low; on our scale a 2–3. The primary difficulty would be associated with the initiation of the Grignard reagent and the requirements of anhydrous reaction conditions. Overall yield is expected to be high, approximately 70–80%.

7. Route VI

Closely allied to Route III is Route VI (see Fig. 7). Here the synthesis starts from the inexpensive and commercially available precursor 1-phenyl-1-cyclohexene (**19**) [3]. The same chemistry as outlined here has been used starting with the alcohol, 1-phenylcyclohexanol (**13**) [18,33]. The initial Ritter reaction [49] exploits the ambient nucleophilic nature of cyanide ion, effecting *N*-alkylation over C-alkylation in order to yield the formamide, **20**. The reaction is facile with expected moderate yields 50–60%. Hydrolysis of the formamide is also extremely simple and directly analogous to the chemistry involved in the Leuckart synthesis to amphetamine or methamphetamine [50,51]. This type of chemical transformation (from **19**–**20**–**9**), referred to as the synthesis of *t*-carbinamines, has also been exploited in the synthesis of methadone by Christol [52]. Completion of this PCP synthesis from 1-amino-1-phenylcyclohexane, **9**, with 1,5-dibromopentane is easy to conduct and yields are normally 65–75% with lengthy reaction times (1–6 days) [3,4,18,25–32].

The overall synthetic yield is approximately 30%; however, the degree of difficulty is quite low. The only associated hazards would be adding sulfuric acid to a mixture

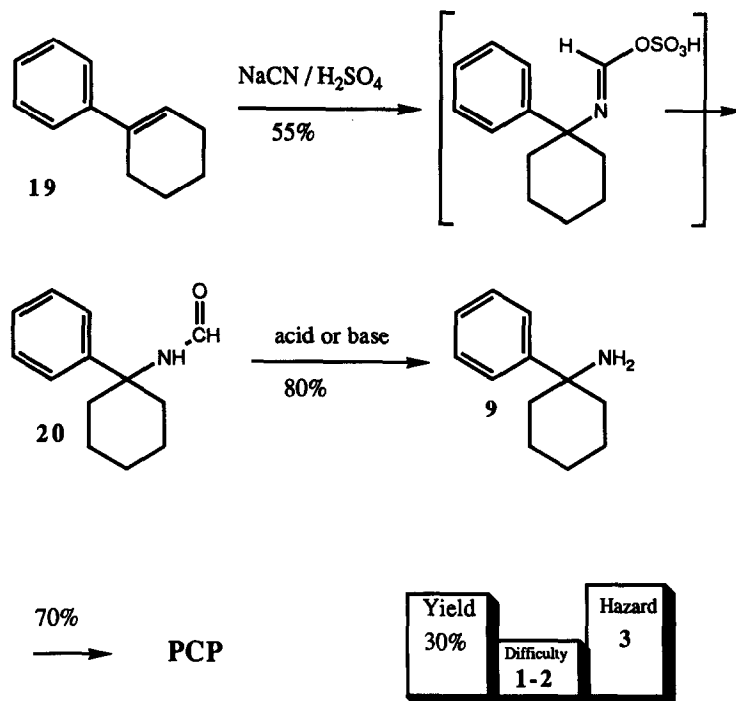
Route VI: Alternative Synthesis of PCP^{3,18,33}

Fig. 7. Route VI illustrates the synthesis of PCP which starts with a Ritter reaction (19–20). Hydrolysis of 20 produces 9 which is subjected to double internal amine alkylation to give PCP.

of the precursor (19 or 13) and sodium cyanide dissolved in acetic acid. This route would also obviate the use of a Grignard reagent with its associated difficulties and potential for initial spontaneous violent eruption.

8. Route VII

Route VII is the final alternative synthesis to a PCP analog considered in this review (see Fig. 8). This scheme, outlined in Route VII, yields a ketamine analog [35,36]. Ketamine, itself, is an *ortho*-chloro complement of compound 24. Both of these variations, as well as the *N*-ethyl analog, have been clandestinely manufactured. The synthesis may be initiated from benzaldehyde or, as illustrated, from the commercially available cyclopentyl phenyl ketone (20). Bromination by way of *N*-bromosuccinimide (77%) or bromine in carbon tetrachloride at reduced temperatures (66%) affords the α -bromo ketone (21). Treatment of 21 with methylamine in benzene for prolonged periods (4–5 days) at room temperature produces the amino ketone 22 in respectable yields (84%). Transformation of the hydrochloride salt of the amino ketone 22 in decalin, directly to the ketamine analog, 24, is effected by thermal rearrangement at 180°C in 30 min. This result which is near

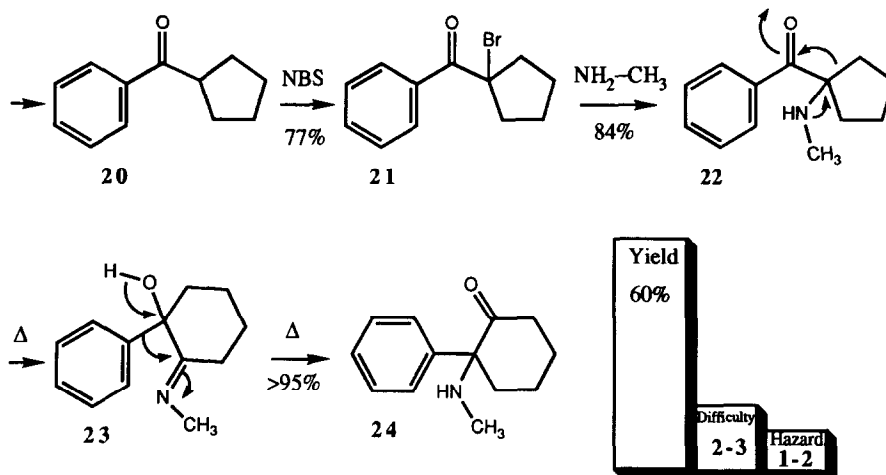
Route VII: Alternative Synthesis of PCP (Ketamine analog)^{35,36}

Fig. 8. Route VII illustrates the synthesis of ketamine analogs (24). The reaction is initiated from cyclopentylphenyl ketone (20) to α-bromo ketone 21, with the use of *N*-bromosuccinimide, followed by amination to 22. Thermo rearrangement produced the PCP analog 24.

quantitative and irreversible may be envisioned as an initial 1,2 alkyl sigmatropic shift of the amino ketone 22 to give the ring expanded intermediate 23. A second rearrangement of imine 23 by way of a 1,2-aryl sigmatropic shift furnishes the PCP-ketamine analog, 24.

The published yields for this synthetic approach are high, indicating that these analogs may be achieved in approximately 60% overall yield. Potential hazards are considered low and synthetic difficulties, relatively speaking, are minimal. The possible difficulty and/or hazard which may be encountered, would be, if the clandestine operation was conducting the thermal rearrangement on the 'base' of amine ketone 22. In this case, a steel bomb or other pressurized vessel would be required (incidences of clandestine laboratory use of 'pressure-cookers' have been encountered).

9. Discussion of the 'Bucket Method'

After reviewing the above legitimate literature routes for the manufacture of PCP we thought it helpful if we discussed a 'real world' example of a clandestine preparation of PCP. This is illustrated in Fig. 9 by what has come to be called the 'Bucket Method'. This clandestine recipe was seized in the execution of a search warrant at a clandestine laboratory site by a DEA forensic chemist. The recipe follows most closely the published procedure by Maddox et al. [3] and now serves as excellent tutorial discussion.

The 'Bucket Method', as it is called, for the manufacture of PCP is reproduced in Fig. 9. This is a creative recipe for the synthesis of PCP and ranks with other innovations which the author(s) have seen, like the use of a microwave oven to effect

Clandestine recipe used for the synthesis of PCP

"The Bucket Method"




<p>Bucket A</p>  <p>198 - Sodium Metabisulphate = 200 - Cyclohexanone</p>	<p>Our Notes:</p> <p>Ingredient for making the carbonitrile : combine A and B</p>
<p>Bucket B</p>  <p>190 - Cyanide = 230 - Piperidine</p>	
<p><u>GERNARD REACTION</u></p>	
<p>Bucket C</p>  <p>74 Magnesium Metal turnings 475 Bromobenzene 3.5 inches Ether 2 Iodine Crystals</p>	<p>Grignard is misspelled.</p>
<p>(Add ether after baggie blows, plus 25 g Bromobenzene) Add Gernard Reaction into 3.5 inches of coleman with 150 P's crystal. Stir; pour off cyanide. Add more Coleman and stir till hard at touch --- pour off liquid. Splash on Muratic and stir.</p>	<p>Composite of Grignard Bucket contained insid plastic bag.</p>
<p><u>2ND STEP</u></p>	<p>Exothermic reaction rips open plastic bag.</p>
<p>Crystals will form; save! Add more muratic, and repeat as above. Stir a lot.</p>	<p>"P" = Carbonitrile</p>
<p>1/3 cup Lye , plus 3/4 and 4/4 pints of water. Splashes on crystals; cover. On ether, 2 layers will form. Use top layer liquid and cover sludge with more ether and try for more liquid.</p>	<p>"Splash on Muratic" into Coleman - Muratic Acid mixture.</p>
	<p>PCPHCl forms out of Coleman - Muratic acid mixture.</p>
	<p>Extraction of PCPHCl to obtain PCP base in Ether.</p>

Fig. 9. The 'Bucket Method' is a recipe used for the clandestine synthesis of PCP.

ring coupling in a methaqualone synthesis, the use of a pressure-cooker to effect chlorination of ephedrine in a methamphetamine synthesis, the use of a modified fire-extinguisher as a hydrogenator in an amphetamine laboratory, or the use of pipe bombs to effect the synthesis of phenyl-2-propanone.

This synthesis was conducted in plastic garbage buckets lined with disposable trash bags. As may be gleaned from brief overview, the quantities of material involved were large, approximately 2 molar. Our notes regarding the inferences to the procedure are annotated on the right-hand side of Fig 9. Obviously, Bucket A was added to Bucket B (or vice versa), this mixture was stirred with a stick and allowed to stand for one day. The product (PCC) formed as a crystalline (or semi-crystalline)

cake on top of the aqueous layer. Removal of the cake and allowing for air drying resulted in the materials used later in the procedure where it is referred to as '150 P's'. Next the Grignard reagent was prepared in Bucket C (note Grignard is misspelled in the recipe). The exothermic reaction of this large quantity of a Grignard reagent preparation resulted in the trash bag ripping open — 'baggie blows'. The PCC, which is soluble in hexanes or 2,2,4-trimethylpentane, is added into the Grignard reagent — Bucket C. After reaction of the PCC and the phenyl magnesium bromide is complete the product (PCP) is decanted — 'Add more Coleman and stir till hard to touch — pour off liquid'. This effects removal of the PCP from the reaction mixture. Next follows the production of the hydrochloride salt with 'Splash on Muratic and Stir'. The slurry or crystals of PCP/HCl are saved — 'Crystals will form; save!' The last paragraph describes the extraction of PCP with base — 'Lye', into the 'top layer'.

Evaluation of such clandestine laboratories is one of the primary responsibilities of the forensic chemist, not only for on site safety and appropriate evidence collection, but also for court reconstruction. In this respect, one of the questions that is often posed is 'How much knowledge of chemistry (in the opinion of the forensic chemist) did the clandestine chemist possess?' The 'Bucket Method' is a good illustration of the apparent dilemma which may be faced in this regard. Obviously, the method is an abbreviation of Route IC-D. This abbreviation in itself may represent an attempt to camouflage the process but it is hard to draw chemical expertise from such circuitry. To confound the forensic chemist's evaluation of the 'Cooker's knowledge' is the fact that he or she has misspelled Grignard in the text. However certain other facts point to his/her chemical cognizance. These are the use of Coleman fuel in place of ethyl ether, muratic acid in place of hydrochloric acid and Lye in place of sodium hydroxide. Although these may be common substitutes in the clandestine laboratory community one other point clearly (in the opinion of the authors) indicates the 'Cooker's knowledge'. This is the fact that the product is removed from the Grignard — carbonitrile reaction mixture in a direct manner. This is to say, the 'Cook knows' enough chemistry to realize that the reaction need not be quenched (as in most Grignard reactions) before the product can be removed. This puts his/her knowledge beyond the average undergraduate chemist who would read the papers by Maddox et al. or Kalir et al. and follow the instruction verbatim. Both articles describe the quenching (HBr hydrolysis [3] or NH₄Cl hydrolysis [4]) of the reaction mixture before product work-up.

10. Conclusion

The synthesis of phencyclidine has been reviewed with emphasis upon possible clandestine manufacture routes. These alternative Routes I–VII have been discussed in terms of chemistry, safety, yield, synthetic difficulty and a 'real-world example' (the Bucket Method). The popularity, speaking in terms of clandestine manufacture, remains with the use of Route I-C-D, following procedures of Maddox et al. [3] and Kalir et al. [4]. Other routes which are highlighted herein have undoubtedly contributed to the more than thirty different analogs of PCP which have appeared in the clandestine market [53].

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