# Synthesis of Halo Compounds for Studies of Potential Benzyne Cyclizations

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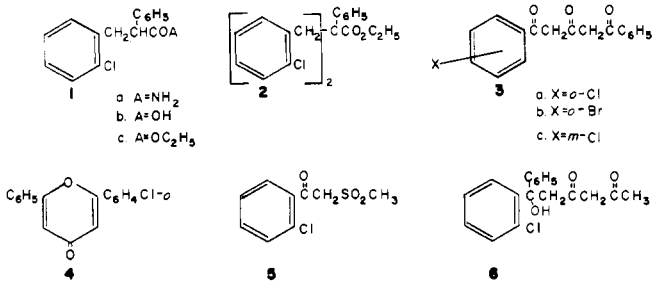
**Five types of compounds having an ortho or meta halogen and at least two readily ionizable hydrogens were synthesized as potential intermediates for benzyne cyclizations through multiple anions. These compounds included α-substituted phenylacetamide and phenylacetic acid, 1,3,5-triketones, a ketosulfone, and a hydroxy-β-diketone. Ethyl 3(o-chlorophenyl)-2-phenylpropionate was also prepared for studies of a potential monoanion cyclization. The limited success of these cyclization studies is presented.**

In connection with our work on benzyne cyclizations (*2*), the following synthetic methods, previously developed in our laboratories, have been extended to include a variety of new halo compounds.




Halo compounds 1a–c were prepared in 50–74% yield by the C-alkylation with *o*-chlorobenzyl chloride in liquid ammonia of disodiophenylacetamide (*5*), sodiophenylacetate (*3*), and ethyl sodiophenylacetate (*3*), respectively. In the case of the latter alkylation to prepare ester 1c, a dialkylation product 2 (3–8% yield) was also easily isolated and characterized. Halo 1,3,5-triketones 3a–c were prepared in 33–72% yield by the aroylation of benzoylacetone with methyl *o*-chlorobenzoate with sodium hydride in refluxing 1,2-dimethoxyethane (monoglyme). The procedure involved the convenient addition of a mixture of ester and benzoylacetone to the basic reagent, and it appears to be a generally applicable method. These 1,3,5-triketones can be readily converted to the substituted 4H-pyran-4-one (*7*) by dissolving the ketone in concentrated sulfuric acid at 0°; this was readily shown by the conversion of halotriketone 3a to pyrone 4 in 70% yield. Chlorosulfone, 5, was prepared in 61% yield by the monobenzoylation of dimethyl sulfone with methyl *o*-chlorobenzoate by means of sodium hydride in monoglyme (*6*). Chloro-β-diketone alcohol, 6, was prepared in 43% yield by the condensation of dipotassioacetylacetone with *o*-chlorobenzophenone in liquid ammonia (*6*).

Each compound was characterized by analysis (except 1b) and absorption spectra. Results are shown in Table I.

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Table I. Halo Compounds

| Compd no. | Name of compound | Mp or bp, °C | Yield, % | Reactants | Ref. to procedure[a,b] |
|---|---|---|---|---|---|
| 1a | 3(*o*-Chlorophenyl)-2-phenylpropionamide | 181–184[c] | 74 | *o*-Chlorobenzyl chloride 2-Phenylacetamide | (*5*) |
| 1b | 3(*o*-Chlorophenyl)-2-phenylpropionic acid | 120[d,e] | 50 | *o*-Chlorobenzyl chloride Phenylacetic acid | (*3*) |
| 1c | Ethyl 3(*o*-chlorophenyl)-2-phenylpropionate | 160–162/0.4 mm | 65 | *o*-Chlorobenzyl chloride Ethyl phenylacetate | (*3*) |
| 2 | Ethyl 2(*o*-chlorobenzyl)-3-(*o*-chlorophenyl)-2-phenylpropionate | 73–74[c] 210–215/0.4 mm | 3–8 | *o*-Chlorobenzyl chloride Ethyl phenylacetate | (*3*) |
| 3a | 1(*o*-Chlorophenyl)-5-phenyl-1,3,5-pentanetrione | 76–78.5[f] | 51 | Methyl *o*-chlorobenzoate Benzoylacetone | (*7*) |
| 3b | 1(*o*-Bromophenyl)-5-phenyl-1,3,5-pentanetrione | 79–81[f] | 33 | Methyl *o*-bromobenzoate Benzoylacetone | (*7*) |
| 3c | 1(*m*-Chlorophenyl)-5-phenyl-1,3,5-pentanetrione | 94–95[f] | 72 | Methyl *m*-chlorobenzoate Benzoylacetone | (*7*) |
| 4 | 2(*o*-Chlorophenyl)-6-phenyl-4*H*-pyran-4-one | 111–112[c] | 70 | 3a Sulfuric acid | (*8*) |
| 5 | 1(*o*-Chlorobenzyl)dimethyl sulfone | 78–80[c] | 61 | Dimethyl sulfone Methyl *o*-chlorobenzoate | (*6*) |
| 6 | 6(*o*-Chlorophenyl)-6-phenyl-2,4-hexanedione-6-ol | 92–94[c] | 43 | Acetylacetone *o*-Chlorobenzophenone | (*4*) |

[a] Infrared spectra supported assigned structure, and they were taken on a Perkin-Elmer 137 Infracord. [b] All analyses were performed by Jannsen Pharmaceutica, Beerse, Belgium, and M-H-W Laboratories, Garden City, Mich. Elemental analyses for C, H (all new compounds), N (compound 1a), halogen compounds (all but compounds 1c and 2), and S (compound 5) were submitted for review and are in agreement with theoretical values. [c] Recrystallized from 95% ethanol. [d] Lit mp 122°, see ref. *1*. [e] Recrystallized from methanol–water. [f] Recrystallized from methanol.

The treatment of 1a–c, 3a–c, 5, and 6 with an excess of potassium amide in liquid ammonia failed to give more than a trace amount of cyclic product arising from a benzyne intermediate. Usually polymeric material or starting material was isolated; however, trace amounts of products were obtained from the cyclization of chloroamide 1a (mp 124–129°, $C_{15}H_{13}NO$) and chloroester 1c mp 146–147°, $C_{32}H_{27}O_3$).


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# Acetals and Ketals


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**Thirteen open-chain simple cyclic and spirocyclic acetals and ketals were studied. The synthesis of all the cyclic compounds was accomplished by an alcoholysis reaction. The infrared and proton magnetic resonance spectra were measured and correlated.**


A number of cyclic acetals and ketals were synthesized and their proton magnetic resonance (PMR) and infrared spectra were compared with some purchased open-chain acetals and ketals. The cyclic compounds included one spirocyclic case.

All the compounds synthesized were prepared by an alcoholysis reaction. This proved to be a simple and expedient method for obtaining the cyclic compounds and it made no difference whether an ethoxy or methoxy acetal or ketal were alcoholyzed.

The synthesis of spirocyclic orthocarbonates by the alcoholysis of methyl or ethyl orthocarbonate was not possible because all attempts to prepare methyl and ethyl orthocarbonates (*4*, *6*) by the reaction of chloropicrin and alkoxides and with several variants proved futile and resulted in a violent explosion when an attempt was made to distill the product. The Ponzio (*5*) synthesis using carbon tetrabromide was not attempted since only "a very small quantity" was reported to form.

Attempts to substitute boron trifluoride etherate, aluminum chloride, or benzenesulfonic acid for hydrochloric acid as a catalyst resulted in poorer yields. The compounds studied were 1–13 (Figure 1).

The primary use of the infrared determinations was to establish the absence of any carbonyl or hydroxyl absorption in the acetal or ketal studied. The correlations reported earlier (*2*) for the C—O—C—O—C bands in acetals and ketals were in the range of 1000–1200 $cm^{-1}$ and are reported for compounds 1–13. The presence of a minimum of two bands between 1150 and 1080 characteristic of the C—O—C antisymmetric stretch in cyclic compounds free of substantial ring strain and open chain compounds suggested by Tchamler (*7*) appeared in all of the compounds. The predicted band between 1050 and 1110 $cm^{-1}$ occurred in all compounds. The compounds in which the C—O—C—O—C group was in a ring (1–7) showed at least a single band in this region which may or may not be a duplicate of the band between 1080 and 1150 $cm^{-1}$. In all of the open-chain compounds (11–13) except 10, three bands were present in a rather precise location ($\pm 2$ $cm^{-1}$): 1058, 1078,

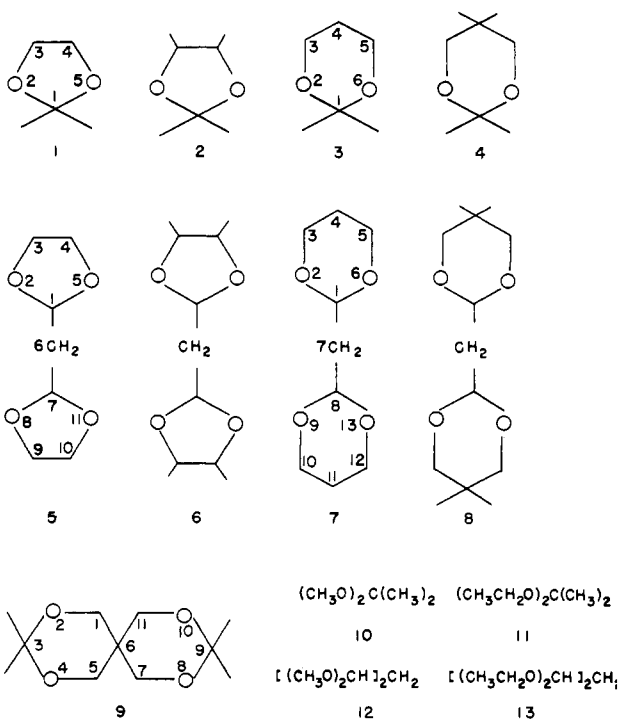


Figure 1. Acetal and ketal structures

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