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REVIEW

α-Halo Ketones in C-, N-, O-, and S-Alkylation Reactions

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Abstract—The review summarizes and analyzes both theoretical aspects and practical applications of C-, N-, O-, and S-alkylation with α-halo ketones of aliphatic, alicyclic, aromatic, and heterocyclic compounds. Some reactions of α-halo ketones with difunctional nucleophiles are also discussed.

I. INTRODUCTION

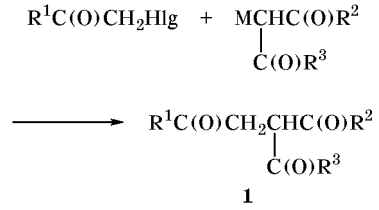
α-Halo ketones are very important organic reagents which have been utilized in the synthesis of a huge number of both aliphatic and heterocyclic compounds. In the previous review [1] we considered syntheses of nitrogen-containing heterocycles from α-halo ketones and demonstrated a wide synthetic potential of these reagents. On the other hand, preparation of aliphatic compounds via C-, N-, O-, and S-alkylation reactions involving α-halo ketones is very important from both theoretical and practical viewpoints. Accumulation of experimental data on reactions of α-halo ketones with nucleophiles is now in progress. Studies in this field extend general theoretical views on nucleophilic substitution reactions, their mechanisms, effects of the α-halo ketone and nucleophile structure, solvent effects, etc. Despite a large number of publications on this topic, it still remains difficult to predict the structure of products which could be formed by reactions of α-halo ketones with various nucleophiles. Furthermore, C-, N-, O-, and S-alkylations with α-halo ketones gave rise to numerous practically important products. For example, reactions of α-halo ketones with amines led to formation of α-amino ketones which constituted a quite promising class of compounds from the viewpoint of purposeful search for medical preparations exhibiting various kinds of pharmacological activity and (what is significant) having a minimal negative effect on the organism [2]. C-Alkylation reactions were used to synthesize ketocarboxylic acids which are difficult to obtain by other methods. Products of O- and S-alkylation are starting materials in the synthesis of substituted furans and thiophenes, respectively.

Taking into account the above stated, we thought it reasonable to consider in detail some aspects of C-, N-, O-, and S-alkylation with α-halo ketones, reactions with polyfunctional nucleophiles being discussed in a separate section.

II. C-ALKYLATION

Let us focus on C-alkylation of acetylacetone and other β-diketones with α-halo ketones, which follows Scheme 1.

Scheme 1.



1

R^1 = 2-$NO_2C_6H_4$, R^2 = R^3 = Me, M = Na [3]; R^1 = 4-ClC_6H_4, R^2 = R^3 = Ph, M = K [4]; R^1 = Ph, 4-PhC_6H_4, 1,2,3,4-tetrahydronaphthalen-6-yl, 4-cyclohexylphenyl, R^2 = 4-ClC_6H_4, R^3 = Me, M = Na [5]; R^1 = R^2 = R^3 = Me, M = Ni [6].

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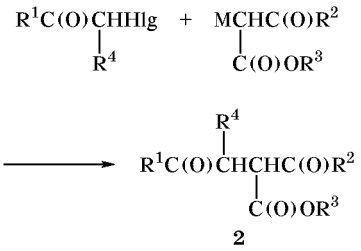
These reactions afforded triketones **1**. Characteristically, only anhydrous solvents were used, such as diethyl ether–ethanol [3], acetone [4], and 2-propanol [5]. However, the reaction is not always strictly selective. Boya *et al.* [6] reported that 1-chloro-2-propanone reacted with acetylacetone in the presence of Ni(II) to give the expected triketone in a poor yield together with a mixture of unidentified products.

Diketo esters **2** were obtained by reactions of α-halo ketones with ethyl acetoacetate and other keto esters (Scheme 2). The reactions were carried out in toluene [7], diethyl ether [8, 10], or acetone [12].

Scheme 2.

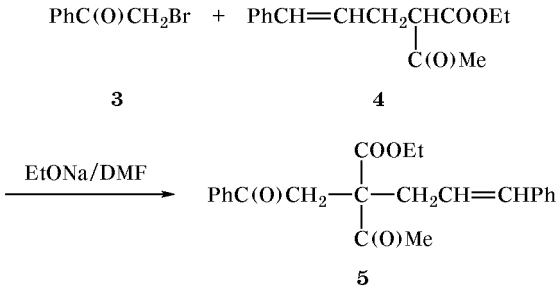


2

R^1 = Ph, R^2 = Me, R^3 = Et, R^4 = H, M = Na [7]; R^1 = 4-PhC_6H_4, R^2 = Me, R^3 = Et, R^4 = H, M = Na [8]; R^1 = Ar, R^2 = Me, R^3 = Et, R^4 = H, M = Na, K [9]; R^1 = 4-$MeOC_6H_4$, R^2 = R^3 = Et, R^4 = H, M = Na [10]; R^1 = 4-$O_2NC_6H_4$, R^2 = 4-(2-methylimidazo[4,5-*c*]pyridyl)phenyl, R^3 = Et, R^4 = H, M = Na [11]; R^1 = R^2 = Me, *t*-Bu, Ph, R^3 = Et, R^4 = H, Me, M = K [12].

The reaction of bromoacetophenone (**3**) with ethyl 2-cinnamylacetoacetate (**4**) in the presence of sodium ethoxide in DMF provides an example of C-alkylation leading to cyclic enones: The product is unsaturated diketo ester **5** [13] (Scheme 3).

Scheme 3.

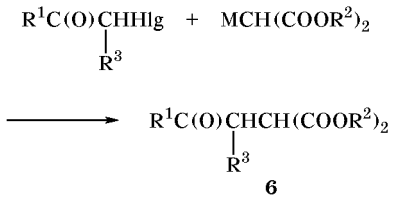


3 **4**

5

Most attention was given to reactions of α-halo ketones with dicarboxylic acid esters. As a result, keto diesters **6** were synthesized (Scheme 4). These reactions should be carried out under nitrogen [20] to prevent decomposition of the products. Subsequent treatment of keto diesters with an alkali solution gives practically important keto dicarboxylic acids [17, 23].

Scheme 4.

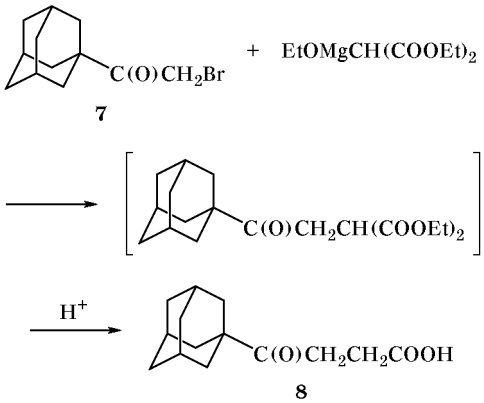


6

R^1 = R^3 = Me, R^2 = Et, M = Na [14]; R^1 = 4-PhC_6H_4, R^2 = Et, R^3 = H, M = Na [15]; R^1 = 2,3-$(MeO)_2C_6H_3$, R^2 = Et, R^3 = Me, M = Na [16]; R^1 = benzo[*b*]thiophen-2-yl, R^2 = Et, R^3 = H, M = Na [17]; R^1 = R^3 = Me, R^2 = Bu, M = Na [18]; R^1 = Ph, R^2 = Et, R^3 = Me, M = Na [19]; R^1 = Me, R^2 = Et, R^3 = H, M = Na [20]; R^1 = phthalimidomethyl, R^2 = Et, R^3 = H, M = Na [21]; R^1 = 4-(4-fluorophenyl)-5-(4-chlorophenyl)-3-pyrazolyl, R^2 = Me, R^3 = H, M = Na [22]; R^1 = 4-ClC_6H_4, R^2 = Et, R^3 = H, M = Na [23]; R^1 = Me, R^2 = Et, R^3 = H, M = Na [24]; R^1 = Me, R^2 = Et, R^3 = Ph, M = Na [25].

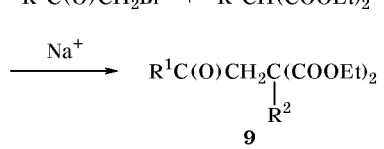
The reaction of 1-adamantyl bromomethyl ketone (**7**) with ethoxymagnesium diethyl malonate, followed by hydrolysis, afforded 4-(1-adamantyl)-3-oxopropionic acid (**8**) [26] (Scheme 5). Its sodium salt exhibited choleretic activity.

Scheme 5.



7 **8**

Scheme 6.



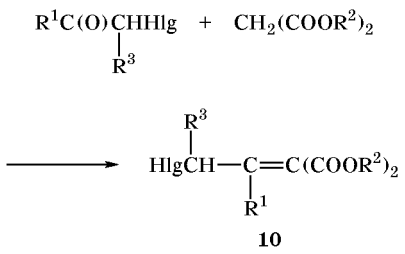
9

R^1 = 4-MeC_6H_4, R^2 = Me [27]; R^1 = 3-MeO-6-$O_2NC_6H_3$, R^2 = MeC(O)NH [28].

Keto diesters (**9**) were obtained by the action of α-halo ketones on diethyl methylmalonate [27] and diethyl acetylaminomalonate [28] (Scheme 6). The products are used in the synthesis of heterocyclic compounds.

All the above examples refer to nucleophilic substitution reactions. In addition, other pathways of the reaction of α-halo ketones with CH acids have been reported, e.g., as shown in Scheme 7.

Scheme 7.



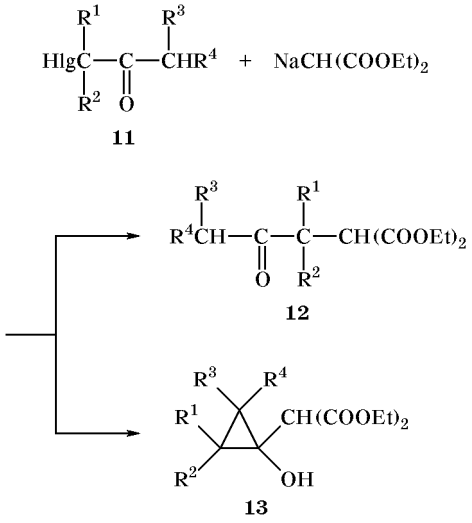
10

R^1 = Me, Ph, R^2 = Et, R^3 = H, Me [29]; R^1 = R^3 = Me, R^2 = Et [30]; R^1 = Me, Ph, R^2 = Me, R^3 = H, Me [31].

In this case the reaction follows nucleophilic addition pattern at the carbonyl group. The process is carried out in anhydrous THF [29] or CCl_4–THF mixture [31] in the presence of $TiCl_4$; the temperature is varied from –10°C [31] to ambient [29], and pyridine is used as catalyst. The products are unsaturated dicarboxylic acid diesters **10**.

Sakai *et al.* [30] studied in detail how the degree of branching of the carbon chain at the halogen atom affects the direction of reactions of α-halo ketones **11** with diethyl malonate sodium salt in THF (Scheme 8).

Scheme 8.



11

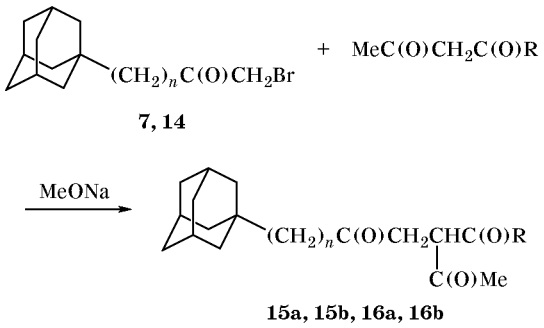
12

13

These reactions could lead to both S_N2 products, keto diesters **12**, and Favorskii rearrangement products, cyclopropyl alcohols **13**. It was found that the S_N2 process leading to compounds **12** occurs if there is at least one hydrogen atom on the carbon atom attached to halogen, i.e., if R^1 = H or R^2 = H. When that carbon atom is tertiary (e.g., R^1 = R^2 = Me), Favorskii rearrangment occurs to give cyclopropyl alcohols (**13**).

We have effected C-alkylation of acetylacetone and ethyl acetoacetate with 1-adamantyl bromomethyl ketone (**7**) and 3-(1-adamantyl)-1-bromo-2-propanone (**14**) [32] under various conditions (Scheme 9).

Scheme 9.



7, 14

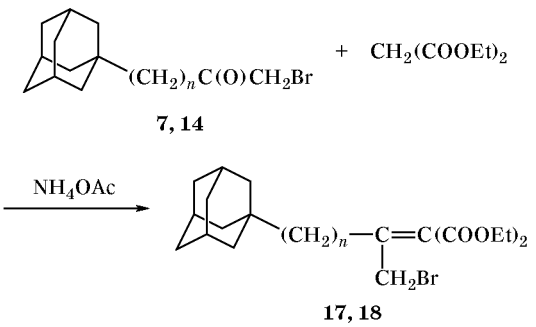
15a, 15b, 16a, 16b

15, *n* = 0; **16**, *n* = 1; R = Me (**a**), OEt (**b**).

The reactions were performed in a mixture of anhydrous diethyl ether with anhydrous methanol in the presence of sodium methoxide as a base or in anhydrous diethyl ether in the presence of metallic sodium. We thus isolated 3-[2-(1-adamantyl-2-oxoethyl]pentane-2,4-dione (**15a**), ethyl [2-(1-adamantyl-2-oxoethyl]-3-oxobutanoate (**15b**), 1-(1-adamantyl)-4-acetylhexane-2,5-dione (**16a**), and ethyl 5-(1-adamantyl)-2-acetyl-4-oxopentanoate (**16b**).

α-Halo ketones **7** and **14** react with diethyl malonate in the presence of catalytic amounts of acetic acid and ammonium acetate to give unsaturated

Scheme 10.



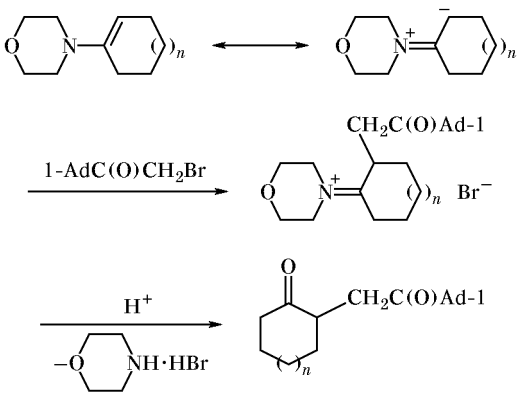
7, 14

17, 18

diesters of the adamantane series: diethyl [1-(1-adamantyl)-2-bromoethylidene]malonate (**17**) and [2-(1-adamantyl)-1-bromomethylethylidene]malonate (**18**) [32] (Scheme 10). Thus, while studying C-alkylation of CH acids with α-halo ketones of the adamantane series (compounds **7** and **14**), we have found that the main factors determining the reaction direction are the solvent and the catalyst. Their variation allows us to obtain both products of C-alkylation and unsaturated esters.

Reactions of α-halo ketones with enamines have been studied poorly. Cyclic γ-diketones can be synthesized by reaction of α-halo ketones with cyclic enamines. With a view to obtain new γ-diketones of the adamantane series, 1-adamantyl bromomethyl ketone (**7**) was brought into reactions with 1-morpholinocyclopentene and 1-morpholinocyclohexene in benzene. The subsequent hydrolysis with 10% hydrochloric acid afforded 2-[2-(1-adamantyl)-2-oxoethyl]-cyclopentanone and 2-[2-(1-adamantyl)-2-oxoethyl]-cyclohexanone, respectively [33] (Scheme 11).

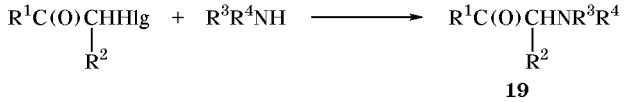
Scheme 11.



III. N-ALKYLATION

Reactions of α-halo ketones with amines are the most widely used N-alkylation processes. Numerous examples of such syntheses have been reported. Here, we consider only the data published since 1980. All these reactions can be represented by a single general scheme (Scheme 12). However, apart from α-amino ketones **19**, reactions of α-halo ketones with amines can result in formation of carboxamides **20** as shown in Scheme 13. Obviously, these processes follow different mechanisms. Kinetic studies of the reactions of aromatic α-halo ketones with amines, leading to α-amino ketones **19**, showed [63–71] that (1) the reactions follow the S_N2 substitution pattern; (2) dissociation of the N–H bond is a fast step; and (3) such compounds as, e.g., acetic acid accelerate the reaction.

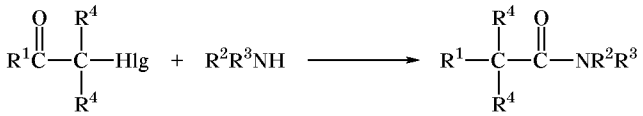
Scheme 12.



19

R^1 = 3,4-$(MeO)_2C_6H_3$, R^2 = Me, NR^3R^4 = 4-(1*H*-benzotriazol-1-yl)piperidino [34]; R^1 = 5,6-benzocoumarin-3-yl, R^2 = H, R^3 = H, R^4 = Ar [35]; R^1 = Ph, R^2 = H, R^3 = Me, R^4 = Ar [36]; R^1 = R^3 = Me, R^2 = H, R^4 = 4-FC_6H_4 [37]; R^1 = 4-$EtOC_6H_4$, 4-$PrOC_6H_4$, 4-$BuOC_6H_4$, 4-$C_5H_{11}OC_6H_4$, 4-ClC_6H_4, 4-BrC_6H_4, 4-C_6H_4, R^2 = H, Ph, R^3 = R^4 = Et, NR^3R^4 = piperidino, morpholino [38]; R^1 = Ar, R^2 = R^3 = H, R^4 = Ar [39]; R^1 = Ar, R^2 = H, Me, NR^3R^4 = 4-(diphenylmethyl)-1-piperazinyl [40]; R^1 = Ar, R^2 = H, R^3 = Me, R^4 = 2-IC_6H_4 [41]; R^1 = 3,4-$(MeO)_2C_6H_3$, R^2 = R^3 = H, R^4 = $PhCH_2$ [42]; R^1 = Ph, R^2 = R^3 = H, R^4 = Ar, cyclohexyl [43]; R^1 = 3,4-$(PhCH_2O)_2C_6H_3$, R^2 = H, R^3 = *i*-Pr, R^4 = $PhCH_2$ [44]; R^1 = 5-methyl-2-thienyl, R^2 = H, R^3 = Me, R^4 = $PhCH_2$ [45]; R^1 = 4-PhC_6H_4, R^2 = Me, R^3 = R^4 = Et [46]; R^1 = 3-indolyl, R^2 = H, NR^3R^4 = piperidino [47]; R^1 = *t*-Bu, R^2 = R^3 = H, R^4 = Me [48]; R^1 = 1-(2-$O_2NC_6H_4CH_2$)-2-pyrrolyl, R^2 = H, R^3 = Me, R^4 = $PhCH_2$ [49]; R^1 = 3,4-$(MeO)_2C_6H_3$, R^2 = Me, NR^3R^4 = 4-(1-formyl-1,3,5-cyclohexatrienyl)-1-piperazinyl [50]; R^1 = 3,4-$(HO)_2C_6H_3$, R^2 = R^3 = H, R^4 = *i*-Pr [51]; R^1 = Ar, R^2 = H, NR^3R^4 = 4-(3-oxobutyl)phenyl-1-piperazinyl [52]; R^1 = Ar, R^2 = R^3 = Et, R^4 = *i*-Pr [53]; R^1 = *i*-Bu, R^2 = R^3 = H, R^4 = *t*-Bu [54]; R^1 = Ph, R^2 = H, R^3 = $PhCH_2$, R^4 = $PhCH_2CH_2$ [55]; R^1 = benzofuran-2-yl, R^2 = H, NR^3R^4 = 4-phenyl-1-piperazinyl, piperidino [56]; R^1 = Ph, R^2 = R^3 = H, R^4 = 2-(3-indolyl)ethyl, 2-(4-imidazolyl)ethyl [57]; R^1 = 3-NO_2-4-$(PhCH_2O)C_6H_3$, R^2 = H, R^3 = *i*-Pr, R^4 = $PhCH_2$ [58].

Scheme 13.



20

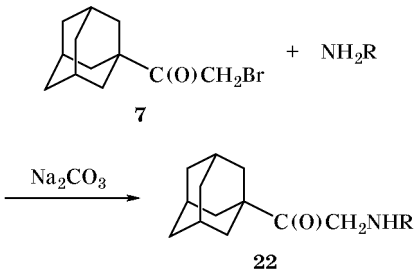
R^1 = Ph_2CH, R^2 = R^3 = Et, R^4 = H [59]; R^1 = *N*-acetyl-9,10-dihydroacridin-10-yl, R^2 = R^3 = Et, R^4 = H [60]; R^1 = $PhCH_2$, NR^2R^3 = piperidino, R^4 = H [61]; R^1 = 1,2-dimethyl-3-indolyl, R^2 = H, R^3 = Me, Et, R^4 = Me [62].

Amides **20** are formed as a result of the Favorskii rearrangement. There is no unambiguous interpretation of its mechanism. This problem has been considered in detail in some reviews [72–75]. Most authors prefer the cyclopropane mechanism.

Using as examples two α-halo ketones of the adamantane series, 1-adamantyl bromomethyl ketone

(**7**) and 1-adamantylmethyl chloromethyl ketone (**21**), we examined the effect of the ketone structure on the reaction direction [76, 77]. The reactions of ketone **7** with amines gave a series of 2-(1-adamantyl1)-1-R-aminoethan-2-ones **22** (Scheme 14). An equimolar mixture of the reactants was heated in ethanol for 0.5–36 h in the presence of sodium carbonate. The yields of amino ketones **22** were 78–96%.

Scheme 14.

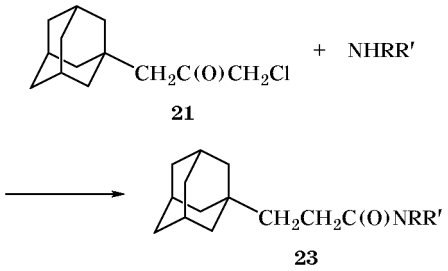


R = Me, 1-adamantyl, 4-MeC_6H_4.

α-Amino ketones **22** were also synthesized by reaction of ketone **7** with amines in diethyl ether, followed by treatment with 10% aqueous Na_2CO_3.

By reactions of 1-adamantylmethyl chloromethyl ketone (**21**) with various amines in diethyl ether in the absence of a base at room temperature we obtained *N*-mono- and *N*,*N*-disubstituted 3-(1-adamantyl)-propanamides **23** [77] (Scheme 15). Just the presence of a methylene bridge between the adamantane fragment and carbonyl group in α-halo ketone **21** (i.e., the presence of a hydrogen atom in the α′-position) favors the Favorskii rearrangement to occur in ether at room temperature in the absence of a base.

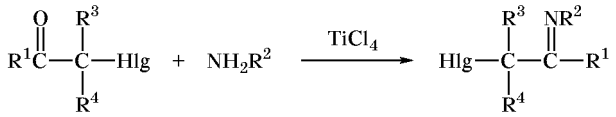
Scheme 15.



R = R′ = Et; R = H, R′ = 1-adamantyl; R = H, R′ = 4-MeC_6H_4, NRR′ = piperidino.

Apart from α-amino ketones **19** and amides **20**, reactions of α-halo ketones with amines could give α-halo ketone imines **24** [78–80] (Scheme 16).

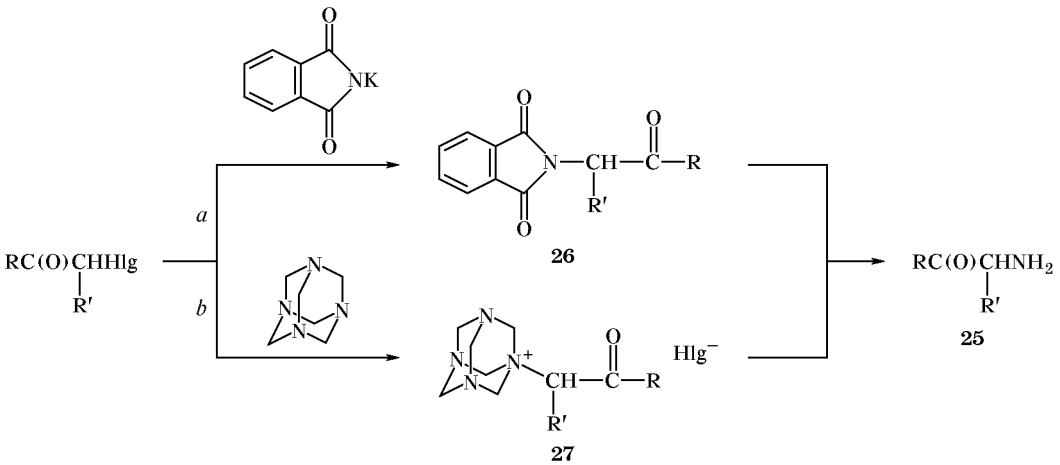
Scheme 16.



R^1 = Me, R^2 = *t*-Bu, R^3 = Me, Et, Pr, *i*-Pr, R^4 = H [78]; R^1 = Me, R^2 = *i*-Pr, *t*-Bu, cyclohexyl, R^3 = H, Me, R^4 = Me [79]; R^1 = Ph, 4-MeC_6H_4, R^2 = *i*-Pr, R^3 = R^4 = Me [80].

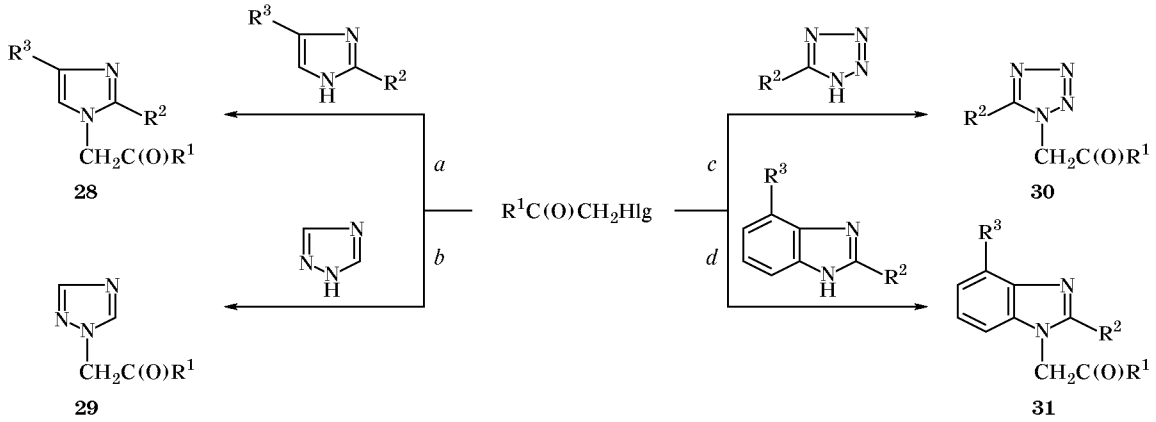
This reaction cannot be classed with N-alkylation: It follows the acid-catalyzed addition pattern at the

Scheme 17.



a: R = *t*-Bu, R′ = H [81]; R = Et, R′ = H [82]; R = R′ = Me [83]; R = Ph, R′ = Me [84]; R = 2,6-$Me_2C_6H_3$, R′ = Me [85]; R = Me, R′ = H [86]; R = 4-$ClC_6H_4CH_2C(Me)_2CH_2$, R′ = Me [87]; R = 1-adamantyl, R′ = H [88]; R = 1-adamantymethyl, R′ = H [89]; *b*: R = 4-PhC_6H_4, R′ = H [90]; R = Ph, 4-BrC_6H_4, 4-ClC_6H_4, R′ = H [91]; R = 4-HOC_6H_4, R′ = H [92].

Scheme 18.



a: R^1 = 2-HO-5-ClC_6H_3, R^2 = R^3 = H [93]; R^1 = Me, Ph, R^2 = Me, R^3 = NO_2 [94]; R^1 = Ph, 4-ClC_6H_4, 4-$MeOC_6H_4$, 4-FC_6H_4, R^2 = R^3 = H [95]; R^1 = 5-chloro-2-thienyl, R^2 = R^3 = H [96]; R^1 = Ph, 4-FC_6H_4, 4-ClC_6H_4, 4-BrC_6H_4, R^2 = H, Me, R^3 = NO_2 [97]; *b*, R^1 = 4-ClC_6H_4 [98]; R^1 = Ph [99]; *c*: R^1 = Ph, R^2 = H, Me [100]; R^1 = Me, R^2 = H [101]; *d*: R^1 = Ph, R^2 = Me, Cl, EtO, R^3 = Me [102].

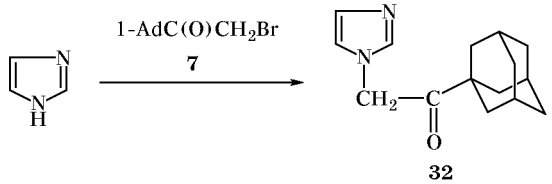
carbonyl group. Titanium tetrachloride is used as catalyst. From α-halo ketone imines as starting compounds, De Kimpe and co-workers [78–80] synthesized such heterocycles as aziridines, imidazolidin-2-ones, and imidazolidine-2-thiones.

Primary α-amino ketones **25** are available via reaction of α-halo ketones with phthalimide potassium salt or urotropin. Phthalimido ketones **26** (Gabriel reaction) or urotropinium hydrohalides **27** are formed as intermediates. Their hydrolysis leads to α-amino ketones **25** (Scheme 17).

N-Alkylation processes also include reactions of α-halo ketones with azoles. In the present review we do not consider N-alkylation with α-halo ketones of heterocyclic compounds, finally leading to fused heterocyclic systems. Such reactions were reviewed previously [1]. Reactions of NH-azoles, namely imidazole, 1,2,4-triazole, tetrazole, and benzimidazole, with α-halo ketones result in formation of the corresponding azolyl ketones **28**–**31** (Scheme 18). A keen interest in this reaction is explained by continuous search for biologically active substances among azolyl ketones.

A series of papers have been published on the N-alkylation of azoles with halo ketones of the adamantane series. For example, the formation of 1-(1-adamantyl)-2-(1-imidazolyl)ethanone (**32**) by reaction of imidazole with 1-adamantyl bromomethyl ketone (**7**) has been reported [103] (Scheme 19).

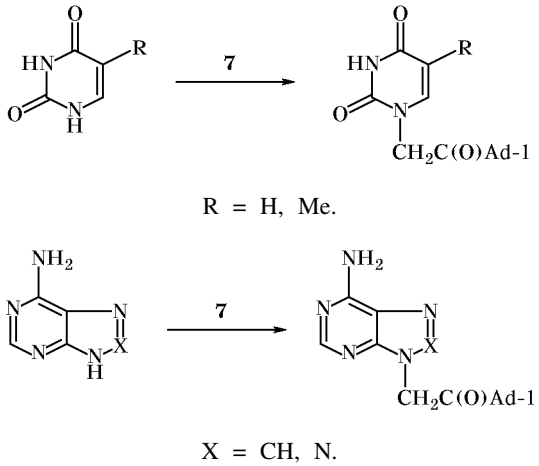
Scheme 19.



Regioselective alkylation of uracil and thymine at N^1, of adenine and 8-azaadenine at N^9, and of theophyllin at N^7 was effected with the use of 1-adamantyl bromomethyl ketone (**7**) under conditions of phase-transfer catalysis (Scheme 20). Under analogous conditions, the corresponding N^1,N^3-dialkyl derivatives were obtained from 5,5-diethyl- and 5-ethyl-5-phenylbarbituric acids [104].

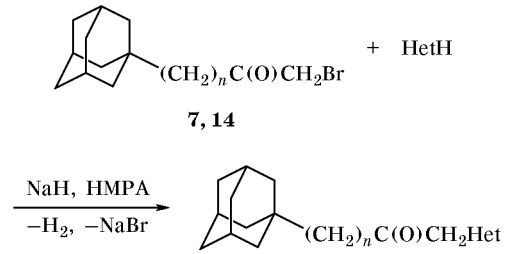
We examined the reactions of 1-adamantyl bromomethyl ketone (**7**) and 1-adamantylmethyl bromomethyl ketone (**14**) with azoles [105]. As N-nucleophiles we selected 1,2,4-triazole, benzimidazole,

Scheme 20.



benzotriazole, 3-amino-1,2,4-triazole, and 5-aminotetrazole. Reactions of ketones **7** and **14** with the above azoles in such systems as acetone–K_2CO_3, aqueous acetone–$NaHCO_3$, tetrahydrofuran–triethylamine, DMF–K_2CO_3, and ethanol–$NaHCO_3$ resulted in formation of multicomponent mixtures which were difficult to separate. We succeeded in effecting regioselective syntheses and obtaining 1-alkylated azoles **33** in up to 85% yield by using hexamethylphosphoramide (HMPA) as dipolar aprotic solvent and sodium hydride as base (Scheme 21).

Scheme 21.



n = 0, Het = 1,2,4-triazol-1-yl, 1-benzotriazolyl, 1-benzimidazolyl, 5-amino-1-tetrazolyl, 3-amino-1,2,4-triazol-1-yl; *n* = 1, Het = 1,2,4-triazol-1-yl, 1-benzotriazolyl, 1-benzimidazolyl, 5-amino-1-tetrazolyl.

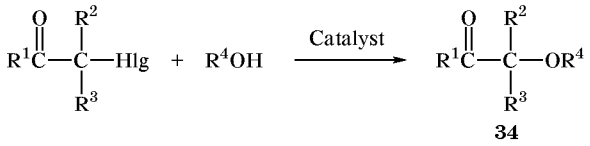
According to the ^1H NMR data, exocyclic amino group in the substrate remained almost intact. Sodium hydride, being a very strong base, reacts with azoles irreversibly. On the other hand, HMPA is a hard basic solvent which is capable of effectively solvating sodium cations, whereas azolide ions appear weakly solvated due to shielding of positive charge on the tetrahedral phosphorus atom. As a result, the nucleophilic reactivity of azolide ions significantly increases, and the alkylation occurs under mild conditions with high yields of the target 1-alkylazoles.

There are numerous published data on the synthesis of azolium ylides. Reactions of α-halo ketones with pyridine and its derivatives and the use of the resulting pyridinium ylides in organic synthesis were reviewed in detail in [106]. An analogous pattern is also typical of reactions of α-halo ketones with 1-alkylimidazoles [107–109], isoquinoline [110], etc.

IV. O-ALKYLATION

Most attention in the literature was given to O-alkylation with α-halo ketones of alcohols and carboxylic acids. α-Halo ketones react with both aromatic and aliphatic alcohols. Neutral molecules are considerably less reactive than the corresponding anions; therefore, reactions with alcohols are carried out in the presence of bases. In the first stage, alcohol reacts with a base to generate alkoxide ion which reacts with α-halo ketone in the second stage. The most widely used bases are potassium carbonate [111, 112, 114, 116–121], sodium methoxide [115], and also Amberlite IRA-40 (Cl^-) modified with some phenols (general formula of the support $[4\text{-}C_6H_4CH_2\overset{+}{N}Me_3][^-OC_6H_4R]$) [113]. The reaction yields ethers **34** (Scheme 22). The products were utilized by some authors [111, 114, 116, 118] in the synthesis of furans and benzofurans.

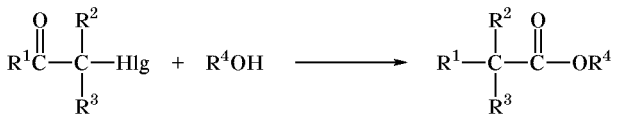
Scheme 22.



R^1 = Me, R^2 = $CH_2CH_2CHMe_2$, R^3 = H, R^4 = 3-$MeOCH_2$-4,6-$Cl_2C_6H_2$ [111]; R^1 = Ph, 4-ClC_6H_4, 4-BrC_6H_4, R^2 = R^3 = H, R^4 = 2-$HOCH_2C_6H_4$, 2-$HOCH_2$-4-ClC_6H_4, 2-$OHCH_2$-4-BrC_6H_4 [112]; R^1 = 4-BrC_6H_4, R^2 = R^3 = H, R^4 = 4-HOC_6H_4, 2-$NO_2C_6H_4$, 4-$NO_2C_6H_4$, 2-ClC_6H_4, 4-ClC_6H_4, 2-naphthyl [113]; R^1 = 3-$(MeO)C_6H_4$, R^2 = R^3 = H, R^4 = Ph [114]; R^1 = 4-HOC_6H_4, R^2 = R^3 = H, R^4 = Me [115]; R^1 = R^2 = Me, R^3 = H, R^4 = 3-$NO_2C_6H_4$, 4-$NO_2C_6H_4$ [116]; R^1 = 2,3-$Cl_2C_6H_3$, 4-ClC_6H_4, 4-BrC_6H_4, R^2 = R^3 = H, R^4 = 4-ClC_6H_4, 4-BrC_6H_4, 2-ClC_6H_4, 2,4-$Cl_2C_6H_3$ [117]; R^1 = R^2 = Me, R^3 = H, R^4 = 2,5-$Et_2C_6H_3$ [118]; R^1 = Ph, 4-FC_6H_4, 4-ClC_6H_4, 4-BrC_6H_4, 4-$MeOC_6H_4$, R^2 = R^3 = H, R^4 = 2-oxo-1,2-dihydroquinoxalin-7-yl [119]; R^1 = 4-MeO-C_6H_4, R^2 = 4-$MeOC_6H_4$, R^3 = H, R^4 = Ph [120]; R^1 = Me, R^2 = R^3 = Ph, R^4 = Me, Et, *i*-Bu, $PhCH_2$ [121].

As in the C- and N-alkylation, O-alkylation of alcohols with α-halo ketones leads to products not only of nucleophilic replacement of the halogen atom by R^4O group (ethers **34**) but also of the Favorskii rearrangement, esters **35** (Scheme 23).

Scheme 23.

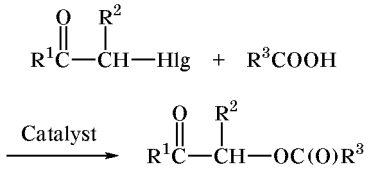


R^1 = Me, Et, R^2 = R^4 = Ph, R^3 = H [122]; R^1 = Et, *i*-Pr, R^2 = R^3 = H, R^4 = Me [123]; R^1 = $PhCH_2$, R^2 = R^4 = Me, R^3 = H, [124]; R^1 = $PhCH_2$, R^2 = R^3 = R^4 = Me [125]; R^1 = Et, *i*-Pr, Pr, Bu, $PhCH_2$, R^2 = Me, Et, R^3 = H, Me, R^4 = Me [126]; R^1 = Ar, R^2 = H, Me, Et, R^3 = H, R^4 = Me [127].

The reaction requires the presence of a base: PhONa [122], MeONa [123–126], $BF_3 \cdot 2CH_2OH$ [127]. However, in all cases mixtures of ethers **34** and esters **35** are formed. In addition, hydroxy ketone can be obtained [128]. The product ratio depends on the initial halo ketone. For example, the reaction of 1-chloro-1-phenyl-2-butanone with sodium methoxide in methanol yields ether **34** (R^1 = $MeCH_2$, R^2 = Ph, R^3 = H) and ester **35** at a ratio of 30 : 70 [129]. In an analogous reaction of 2-bromo-2,4-dimethyl-3-pentanone, a mixture of ether **34** (R^1 = *i*-Pr, $R^2 = R^3$ = Me), ester **35**, and ketone *i*-$PrC(O)C(Me)_2OH$ at a ratio of 84 : 1 : 15 was obtained [130].

Numerous articles deal with reactions of α-halo ketones with carboxylic acids. In the present review we give only the data published since 1980. The products of these reactions are esters **36** (Scheme 24). Insofar as carboxylic acids are weak nucleophiles, the reactions are carried out in the presence of bases such as triethylamine [140] and K_2CO_3 [141] or with sodium or potassium salts of carboxylic acids [131–139]. The reactions can also be effected in the presence of phase-transfer catalysts, e.g., dibenzo-18-crown-6 [132], 18-crown-6 [138], and poly(ethylene glycol) [141].

Scheme 24.

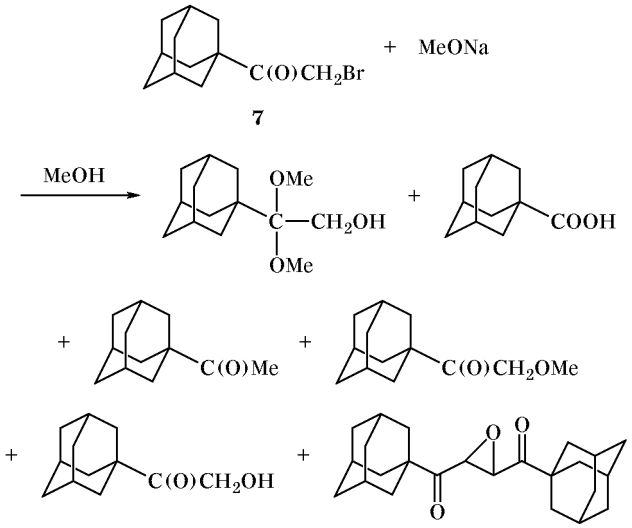


36

R^1 = 4-FC_6H_4, R^2 = H, R^3 = Me [131]; $R^1 = R^3$ = Ph, R^2 = H, 4-$NO_2C_6H_4$, 2-ClC_6H_4, 4-$MeOC_6H_4$, 2-MeC_6H_4, 3-MeC_6H_4 [132]; R^1 = Ph, R^2 = H, R^3 = H, Me, Et, Pr, Ph [133]; R^1 = 4-BrC_6H_4, 4-PhC_6H_4, R^2 = H, R^3 = 4-Ph-$C_6H_4CH_2CMe_2$ [134]; $R^1 = R^2$ = 4-$MeOC_6H_4$, R^3 = Me [135]; R^1 = 2,3,4,6-$(MeO)_4C_6H$, R^2 = H, R^3 = 4-$MeOC_6H_4$, 4-$NO_2C_6H_4$ [136]; R^1 = Ph, $R^2 = R^3$ = H [137]; R^1 = Ar, R^2 = H, Me, Et, R^3 = Ar [138]; R^1 = 4-$MeC(O)OC_6H_4$, 3-MeO-4-$MeC(O)OC_6H_3$, R^2 = H, R^3 = Me [139]; R^1 = 4-BrC_6H_4, 4-ClC_6H_4, 3-ClC_6H_4, 4-$NO_2C_6H_4$, 3-$NO_2C_6H_4$, 4-PhC_6H_4, R^2 = H, R^3 = Ph [140]; R^1 = Ph, R^2 = H, R^3 = Ph, 4-BrC_6H_4, 4-$MeOC_6H_4$, 4-$NH_2C_6H_4$, 2-naphthyl, 3-furyl [141].

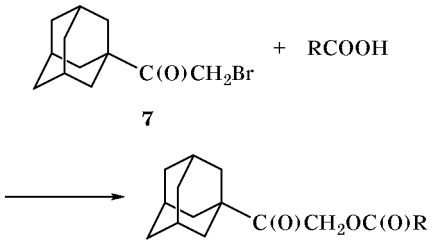
Only one example of O-alkylation with 1-adamantyl bromomethyl ketone (**7**) is known [142]. Its reaction with sodium (or potassium) methoxide (ethoxide, isopropoxide, or *tert*-butoxide) afforded, according to the GLC data, a mixture of 1-adamantyl hydroxymethyl ketone and the corresponding dimethyl acetal, 1-adamantyl methoxymethyl ketone, 2-(1-adamantyl)-2-methoxyoxirane, 1-adamantyl methyl ketone, 1-adamantanecarboxylic acid, etc. No reasonable explanation was given so far for the observed pattern, though it is obvious that the process includes reactions at the carbonyl group, nucleophilic substitution of halogen, and reactions involving C–H bond in the methylene unit (Scheme 25).

Scheme 25.



By reactions of α-bromo ketone **7** with such O-nucleophiles as carboxylic acids (formic, acetic, 2-furancarboxylic, 1-adamantanecarboxylic, 1-adamantylacetic) we synthesized 2-(1-adamantyl)-2-oxoethyl carboxylates **37** [32] (Scheme 26).

Scheme 26.



37

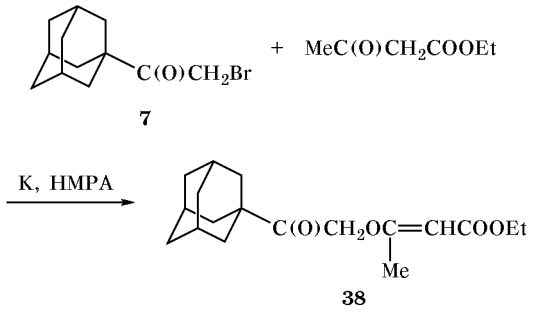
R = H, Me, 2-furyl, 1-adamantyl, 1-adamantylmethyl.

The reactions were carried out in acetone in the presence of triethylamine. Both triethylamine and the acid were taken in large excess. The yields of esters **37** were 35–98%.

CH acids are capable of reacting at both carbon and oxygen atoms. O-Alkylation of ethyl acetoacetate

with 1-adamantyl bromomethyl ketone (**7**) to obtain ~50% of ethyl 3-(1-adamantylcarbonylmethoxy)-2-butenoate (**38**) was effected in HMPA in the presence of metallic potassium [32] (Scheme 27).

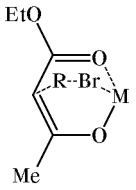
Scheme 27.



A fairly high yield of the O-alkylation product may be interpreted on the basis of the following considerations. Metallic potassium and ethyl acetoacetate give rise to a chelate-like structure where the potassium cation is coordinated to oxygen atoms of the enolate anion. Taking into account that potassium cation is softer than sodium cation, the oxygen–potassium bond in that complex has a greater ionic character than oxygen–sodium bond. Therefore, dissociation of the oxygen–potassium bond in solvents with a high dielectric constant should be essentially enhanced.

Hexamethylphosphoramide as dipolar aprotic solvent is superior to other related solvents. It is a hard basic solvent, and positive charge on the phosphorus atom in its molecule is essentially shielded. Therefore, HMPA is capable of effectively solvating potassium cations while enolate ions remain almost unsolvated and hence strongly nucleophilic. In addition, the high dielectric permittivity of HMPA favors dissociation of the oxygen–potassium bond. The above stated applies to a greater or lesser extent to other dipolar aprotic solvents, but HMPA is clearly most advantageous in the O-alkylation of ambident nucleophiles.

As noted above, the reactant structure is also an important factor determining the ratio of the C- and O-alkylation products. 1-Adamantyl bromomethyl ketone (**7**) is a soft alkylating agent, and high yields of the C-alkylation products derived therefrom indicate the absence of considerable steric hindrances upon formation of transition state.



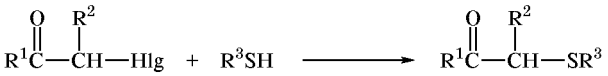
R = 1-AdC(O)CH_2, M = K, Na.

We can conclude that the structure of 1-adamantyl bromomethyl ketone (**7**) does not distinctly favor formation of O-alkylation products. Nevertheless, the first two factors (cation nature and solvent) obviously predominate, and the O-alkylation product is formed in a fairly high yield.

V. S-ALKYLATION

S-Alkylation with α-halo ketones has been well documented. Here, we present the data published since 1980. The reaction follows Scheme 28.

Scheme 28.



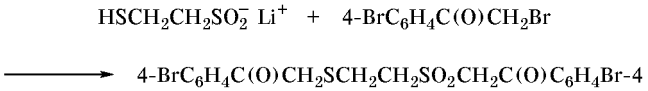
39

R^1 = 4-BrC_6H_4, R^2 = H, R^3 = Ph [143]; R^1 = Ph, R^2 = H, R^3 = Me_3CCH_2 [144]; R^1 = Me, CF_3, R^2 = H, R^3 = Ph, 4-ClC_6H_4 [145]; R^1 = Me, Et, Ph, R^2 = H, Me, R^3 = $PhCH_2$ [146]; R^1 = Ph, 4-BrC_6H_4, 5-methyl-2-furyl, R^2 = H, R^3 = [1,2]dioxino[4,5-*c*]pyridin-5-ylmethyl [147]; R^1 = 2-HOC_6H_4, 5-Cl-2-HOC_6H_3, R^2 = H, R^3 = Me, Et, Pr, Bu [148]; R^1 = Me, R^2 = H, Me, R^3 = 2,3-Cl_2-4-$MeOC_6H_2$ [149]; R^1 = Me, R^2 = H, R^3 = 8-quinolyl [150]; R^1 = R^2 = Ph, 4-ClC_6H_4, 4-MeC_6H_4, 4-$MeOC_6H_4$, R^3 = 4-MeC_6H_4, 3-ClC_6H_4, 3-$NO_2C_6H_4$ [151]; R^1 = R^3 = Ph, R^2 = Me [152]; R^1 = Me, R^2 = H, R^3 = 1-naphthyl [153]; R^1 = Ph, 4-$MeOC_6H_4$, R^2 = H, R^3 = $PhCH_2CH_2$ [154].

The nucleophilicity of thiols is enhanced by adding basic catalysts: triethylamine [143, 146, 149, 153], KOH [144, 145, 147], NaOH [148, 152], or EtONa [154]. Alternatively, the reaction is performed with the corresponding sodium thiolates instead of thiols [150, 151].

An interesting reaction occurring at two centers is the reaction of bromomethyl 4-bromophenyl ketone with lithium 2-sulfanylethanesulfinate, which leads to formation of 4-bromobenzoylmethyl 2-(4-bromobenzoylmethylsulfanyl)ethanesulfinate (**40**) [155] (Scheme 29).

Scheme 29.



40

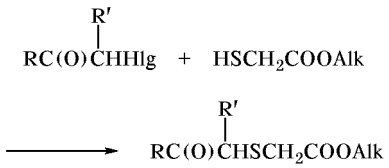
Analysis of published data allowed us to reveal some relations between the reagent structure and the reaction direction. For example, reactions of α-halo ketones with sulfur-containing compounds follow only the nucleophilic substitution pattern. Azoles, phthalimide potassium salt, urotropin, and carboxylic acids react in a similar way. Alcohols give rise to mixtures of nucleophilic substitution and Favorskii rearrangement products. Amines and CH acids occupy an intermediate place in this series: in most cases, nucleophilic substitution products are obtained, while in some cases rearrangement products can be formed.

VI. REACTIONS OF α-HALO KETONES WITH DIFUNCTIONAL NUCLEOPHILES

Even the most comprehensive review [72] dealing with reactions of α-halo ketones with nucleophilic reagents contains no data on reactions with compounds possessing several nucleophilic centers. However, such reactions attract interest not only from the viewpoint of practice but mainly from the theoretical viewpoint, for the results could substantiate and extend existing views on the nucleophilic reactivity.

If a substrate possesses several reaction centers, a reaction can be performed selectively at one of these by preliminarily protecting the other. An example of such synthesis is reaction of α-halo ketones with HS-containing carboxylic acids. The carboxy group in the latter is protected by esterification (Scheme 30).

Scheme 30.



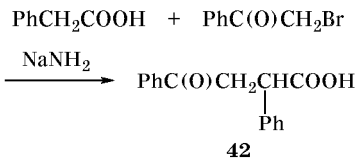
41

R = Me, R′ = H, Alk = Me [156]; R = Me, R′ = *i*-Pr, Alk = Me [157]; R = 2-Cl-5-$O_2NC_6H_3$, R′ = H, Alk = Et [158].

As in the S-alkylation of thiols, either sodium thiolates [156] or alkaline catalysts (MeONa) are used [157, 158]. However, examples of such protection of one of the reaction centers are few in number.

The rate and mechanism of nucleophilic substitution are strongly affected by nucleophilicity and basicity of the reagent and its concentration, nucleophilicity of the departing group, and substrate and solvent natures [159–161]. The nucleophilicity of a species (anion or neutral molecule) means its ability to form a covalent bond (with participation of a lone *p*-electron pair on one of its atoms) with a substrate having an electron-deficient carbon atom. Several nucleophilicity scales are known, but none of these can be regarded as universal, for they were determined relative to different substrates and in different media. Therefore, the presence of two reaction centers in a single molecule is especially interesting. In this case, the nucleophilicity of each center with respect to the other can be estimated, other conditions being equal. An illustratiion is the reaction of bromomethyl phenyl ketone with phenylacetic acid in the presence of sodium amide, which does not involve the carboxy group (the oxygen atom is less nucleophilic) but occurs at the carbon atom to give α-phenyl-β-benzoylpropionic acid (**42**) [162] (Scheme 31).

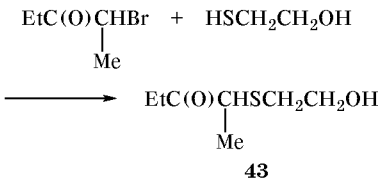
Scheme 31.



42

The reaction of equimolar amounts of 2-bromo-3-pentanone with 2-sulfanylethanol in anhydrous methanol in the presence of sodium at 10–15°C gave not O- but S-alkylation product **43** [163] (Scheme 32).

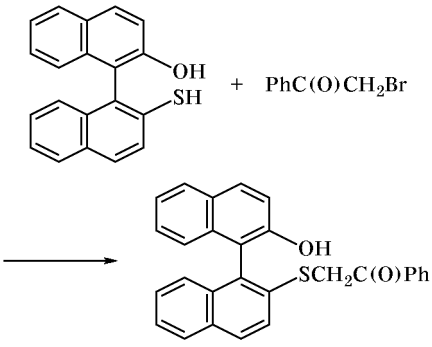
Scheme 32.



43

Likewise, the alkylation of 2-sulfanyl-2′-hydroxy-1,1′-binaphthalene with phenacyl bromide afforded sulfide **44** [164] (Scheme 33).

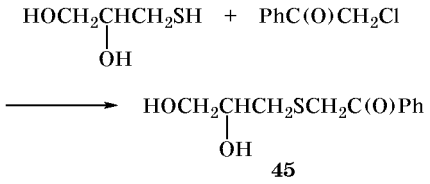
Scheme 33.



44

Phenacyl chloride reacts with 3-sulfanyl-1,2-propanediol in tetrahydrofuran at 0°C under nitrogen to give 2,3-dihydroxypropyl phenacyl sulfide (**45**) [165] (Scheme 34).

Scheme 34.

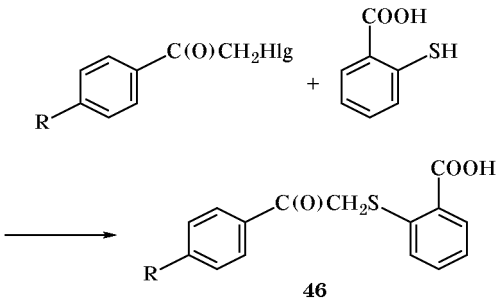


45

From the reactions shown in Schemes 32–34 it follows that the reactivity of sulfur-containing nucleophiles in protic solvents is higher than the reactivity of oxygen-containing analogs [159–161]: $^-SR > ^-OR$ and $^-SH > ^-OH$.

Different nucleophilicity series have been reported [159–161, 166, 167]. According to published data, the nucleophilic reactivity of carboxylate ion is much lower than that of thiolate ion. In fact, aryl halomethyl ketones react with 2-sulfanylbenzoic acid (reactant ratio 1:1) in 70% ethanol in the presence of potassium carbonate at the thiol rather than carboxy group [168] (Scheme 37).

Scheme 35.

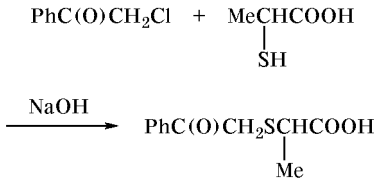


46

R = H, OMe, NO_2, Cl.

Phenacyl chloride reacts in a similar way with 2-sulfanylpropionic acid in aqueous acetone in the presence of NaOH [169] (Scheme 36).

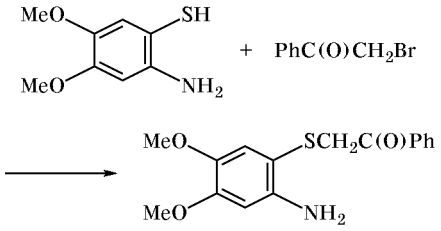
Scheme 36.



47

The reaction of 2-amino-4,5-dimethoxybenzenethiol with phenacyl bromide in methanol–DMF (3:1) gave only the S-alkylation product, sulfide **48** [170]

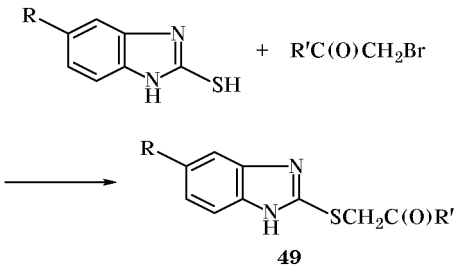
Scheme 37.



48

Though N-alkylation of azoles with α-halo ketones occurs fairly readily, 5-substituted benzimidazole-2-thiols reacted with α-bromo ketones at –3 to 0°C in alcohol in the presence of sodium ethoxide to afford 2-phenacyl(acetonyl)sulfanylbenzimidazole derivatives **49** [171] (Scheme 38).

Scheme 38.

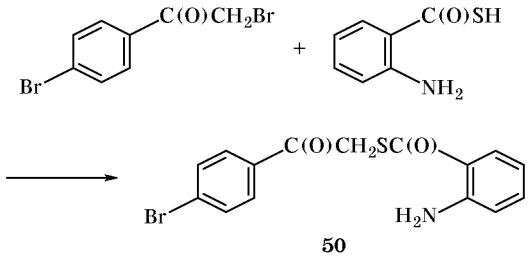


49

R = H, Me, Cl, Br, NO_2, R′ = Me, Ph.

It is believed [167] that substituent at the SH group does not affect the reaction direction. *S-p*-Bromophenacyl *o*-aminobenzothioate (**50**) was obtained by reaction of *o*-aminobenzothioic acid with *p*-bromophenacyl bromide [172] (Scheme 39).

Scheme 39.

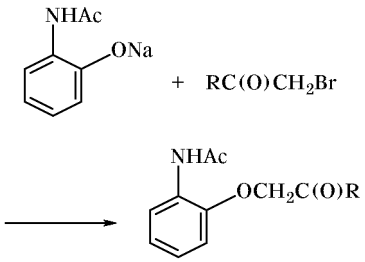


50

In the above reactions, the RS^- ion is a stronger nucleophile than RO^-. However, the latter is more

reactive than amino group, as follows from the results of the reaction of sodium *o*-acetylaminophenoxide with α-bromo ketones [173] (Scheme 40).

Scheme 40.

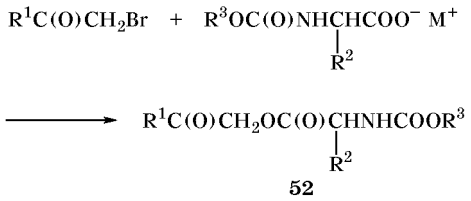


51

R = Me, *t*-Bu.

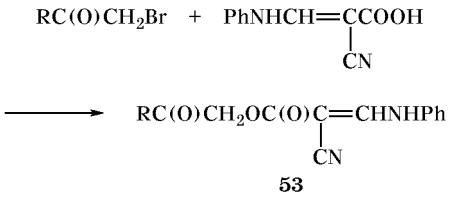
Nucleophilicity of an atom depends on the nature of groups directly attached thereto. Electron-donor groups increase the nucleophilic power while electron-withdrawing groups reduce it [159–161]. In keeping with all nucleophilicity series reported in [159–161, 166, 167], $RCOO^-$ ion is a weaker nucleophile than amino group. The presence of an electron-acceptor substituent (COOR, Ph) in the amino group reduces its basicity, and the reaction occurs at the carboxy group, leading to esters **52** and **53** (Scheme 41).

Scheme 41.



52

52, R^1 = Ph, R^2 = Alk, R^3 = $PhCH_2$ [175]; R^1 = Ph, 4-FC_6H_4, 2,5-$(MeO)_2C_6H_3$, α-naphthyl, 4-biphenylyl, R^2 = *i*-Pr, $PhCH_2$, R^3 = $PhCH_2$, *t*-Bu [175].

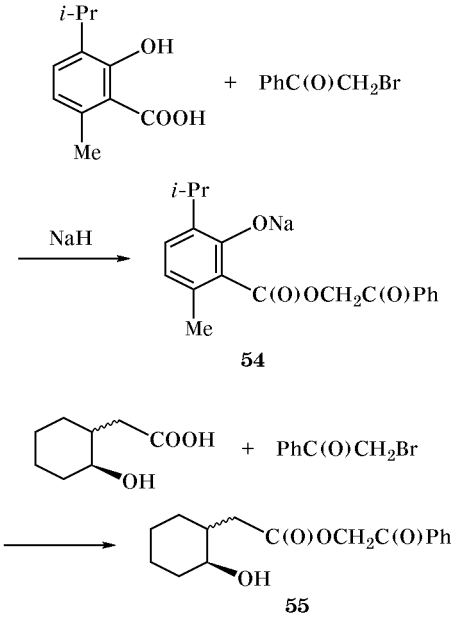


53

54, R^1 = Ph [176].

Nucleophilic power of a reagent is also influenced by the solvent [177]. Polar solvents reduce the nucleophilicity of a strongly solvated ion (usually, of an anion derived from a strongly electronegative atom) to a greater extent than of a weakly solvated ion. This means that the nucleophilicity series can change, depending on the solvent [178]. Protic solvents stabilize anionic species via hydrogen bonding. Formation of hydrogen bonds is more important for stabilization of small anions. Aprotic solvents are not capable of solvating anions. Therefore, anions in aprotic solvents are solvated to a lesser extent than in protic ones. As a result, a small anion has a greater energy than a large anion and is a stronger nucleophile. For example, in protic solvents alkoxide ions RO^- (R = Et, Ph, etc.) are usually more nucleophilic than carboxylate ions $RCOO^-$. The pattern changes to the reverse in going to aprotic solvents. This is confirmed by the following data. Phenacyl bromide reacts with 2-hydroxy-3-isopropyl-6-methylbenzoic acid in anhydrous DMF in the presence of KF, and the subsequent treatment with sodium hydride yields ester **54** [179]. Analogous reaction with 2-hydroxycyclohexanecarboxylic acid leads to formation of ester **55** [180] (Scheme 42).

Scheme 42.



The existence of a large number of potential nucleophiles and various α-halo ketones provides the possibility for wide application of S_N2 reactions in organic synthesis. In fact, almost any functional group possessing a heteroatom with a lone electron pair can act as nucleophile under certain conditions. In the present review we have shown that the number of α-halo ketones is also unlimited. However, the data given in the last section of the review suggest that

the main advantage of S_N2-like reactions is the possibility for selective introduction of $RC(O)CH_2$ groups into a desired site of a molecule.

Thus the available published data illustrate a wide utility of C-, N-, O-, and S-alkylation with α-halo ketones in organic synthesis. Reactions of these compounds with difunctional nucleophiles supplement and extend the existing theoretical views on S_N2 substitution reactions.

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