SYNTHESIS OF STERICALLY HINDERED HETEROAROMATIC KETONES UNDER PHASE-TRANSFER AND METAL-COMPLEX CATALYSIS CONDITIONS.* (REVIEW)

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We have correlated data on methods for obtaining sterically hindered ketones, derivatives of furan, thiophene, pyrrole, and pyridine. We examine routes to arylation of chroman-4-ones and synthesis of sterically hindered unsaturated and silicon-containing heteroaromatic ketones.

Keywords: heteroaromatic ketones, sterically hindered ketones, alkylation, arylation, phase-transfer catalysis, metal-complex catalysis.

Sterically hindered ketones are of interest as synthons for asymmetric synthesis, and also as intermediates in fine organic synthesis and synthesis of biologically active compounds. In this paper, we examine new methods using phase-transfer and metal-complex catalysis to obtain sterically hindered heteroaromatic ketones of the type Het–$COCH_2R$, Het–$COCHR_2$, or Het–$COCR_3$ (Het = hetaryl; R = alkyl, aryl, hydroxy, alkoxy) and related structures (such as arylated chroman-4-ones). In this review, we present the major approaches to synthesis of these compounds and indicate the reactivity of the substrates and the selectivity of the processes.

1. STERICALLY HINDERED KETONES OF THE FURAN AND THIOPHENE SERIES

1.1. Synthesis of Furan and Thiophene Saturated Ketones

Classical methods for synthesis of sterically hindered furan and thiophene ketones (Het–$COCH_2R$, Het–$COCHR_2$, or Het–$COCR_3$, where Het = 2- and 3-furyl or thienyl; R = alkyl, aryl) are mainly based on acylation of furan and thiophene by carboxylic acid chlorides or anhydrides by the Friedel–Crafts reaction [1,2]. But this method is not commonly used because there are a very limited number of branched acylating agents.

Phase-transfer catalysis significantly expands the options for synthesis of the compounds under consideration. Alkylation of 2-acetylfuran, 2- and 3-acetylthiophenes **1** by alkyl and benzyl halides have been conducted in a two-phase catalytic system liquid/solid/benzene or toluene in the presence of catalytic amounts of 18-crown-6. Thus alkylation of ketones **1** by methyl iodide at room temperature leads to the corresponding

* Dedicated to Professor Ya. L. Gol'dfarb memory on the occasion of his 100th birthday.

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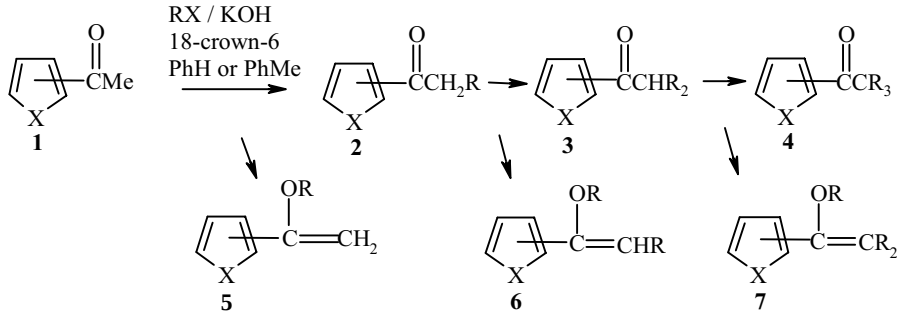
0009-3122/01/3701-0005$25.00

C-dialkylation products **3** in 52-75% yield [3, 4]. According to mass spectroscopy data, ketone formation occurs through the monomethylation products **2**, disappearing from solution by the end of the reactions. Compounds **3** at room temperature do not undergo any subsequent transformations. But 2-furyl and 3-thienyl isopropyl ketones of type **3** at elevated temperature can be alkylated to the corresponding *tert*-butyl ketones **4**, isolated in 50% and 11% yields respectively.



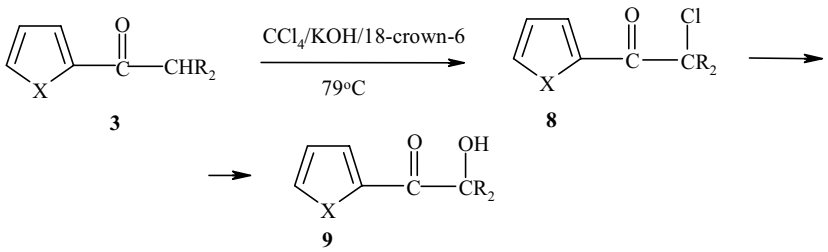
X = O, S; RX = MeI, EtI, *n*-PrI, BuI, $PhCH_2Br$

When ketones are reacted with electrophiles that are softer than MeI, such as EtI, *n*-PrI, and *n*-BuI, the reaction mixtures contain three products at the end of the process. In all cases, the major products isolated were the corresponding C-dialkylated ketones **3** (58-83% of the reaction mixtures, the secondary products were O-mono- **5** (10-16%) and C,O-dialkylated derivatives **6** (7-24%). In these cases, the pure compounds **3** were isolated by vacuum distillation in 32-59% yields.

Alkylation of 2-acetylfuran and 2-acetylthiophene by benzyl bromide under phase-transfer catalysis conditions is C-regioselective and leads to the corresponding 2-benzyl-1-(2-hetaryl)-3-phenylpropanones in 45-50% yields. The NMR spectra of these ketones have several characteristic features. First of all, the chemical shifts of the CH_2 groups (2.80-2.83 ppm and 3.11-3.13 ppm) show that the protons of the methylene groups of the benzyl substituents are nonequivalent. This can be explained if we hypothesize that in 2-benzyl-3-phenyl-1-(2-furyl and 2-thienyl)propanones, reaction of the phenyl rings with other moieties of the molecule leads to complete inhibition of rotation about the $CH–CH_2$ single bonds. We should also note the upfield shift of the ring protons of the furan and thiophene rings of these compounds (from -0.13 ppm to -0.33 ppm) compared with signals observed in the spectra of C-dialkylated ketones with alkyl substituents. Some similar features were observed recently in dibenzylated acetophenone [5].

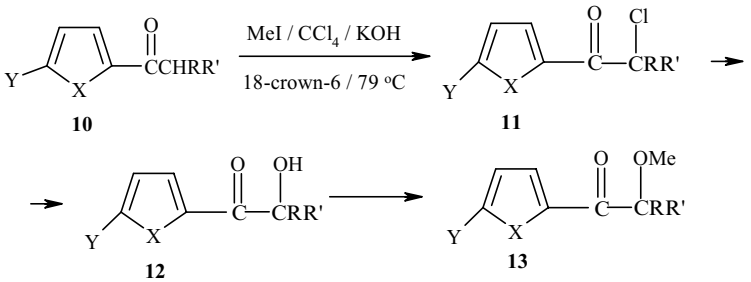
Thus in alkylation of methyl ketones **1**, in all cases the major products are the C-dialkylated derivatives; and in the cases of methylation and benzylation, these are the only products. When using other alkylating agents, we observe partial O-alkylation of the enol form of the ketones. In all cases, the regioselectivity of C-alkylation regularly decreases as the chain length of the alkylating agent increases.

At elevated temperature, the sterically hindered furan and thiophene ketones **3** in the system CCl_4/solid KOH/18-crown-6 give the corresponding α-hydroxy ketones **9** in 28-44% yields. Formation of compounds **9** occurs through intermediate chlorination products **8**, completely disappearing from the reaction mixtures by the end of the process [6].

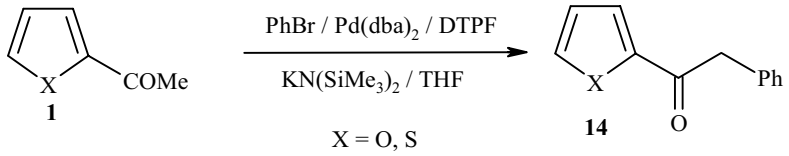


X = O, S; R = Me, Et

We know that α-alkoxycarbonyl compounds are of interest because of their photoactivity, and also are used as intermediates in organic synthesis. We have developed a new selective phase-transfer catalysis (PTC) one-pot method for α-methoxylation of sterically hindered ketones. Furan and thiophene ketones **10** in the system MeI/CCl_4/solid KOH/18-crown-6 give the corresponding α-methoxy ketones **13** in 30-57% yields. Formation of ketones **13** occurs through the intermediates **11** and **12**, completely disappearing from the reaction mixtures by the end of the process. This method is also effective in synthesis of aromatic sterically hindered ketones [7]. The reaction of ketones **10** with electrophiles which are softer than MeI (EtI and *n*-PrI) in the phase-transfer catalysis system CCl_4/solid KOH/18-crown-6 leads to a complex mixture of products [8].

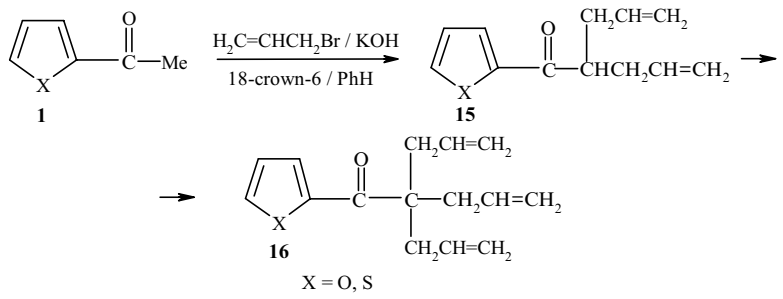


Sterically hindered furan and thiophene ketones can also be obtained by arylation of methyl ketones by bromobenzene in the presence of a complex Pd catalyst containing dibenzylideneacetone (dba) residues as ligands. So 2-acetylfuran and 2-acetylthiophene **1** in the system bromobenzene/$Pd(dba)_2$/1,1-bis(di-*o*-tolylphosphino)ferrocene (DTPF)/$KN(SiMe_3)_2$/tetrahydrofuran give 1-(2-furyl or thienyl)-2-phenylethanones **14** in 57 and 68% yields. The arylation reactions occur with good selectivity under the given conditions [9].

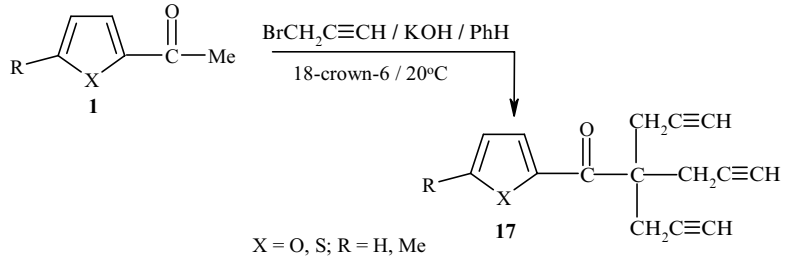


1.2. Synthesis of Furan and Thiophene Unsaturated Ketones

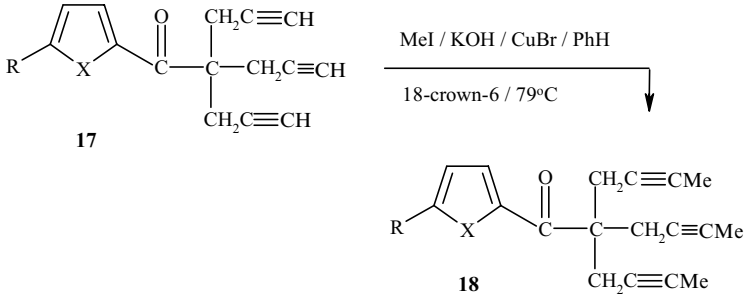
2-Acetylfuran and 2-acetylthiophene on the whole react with allyl bromide and propargyl bromide just as with alkyl halides. Generally the selectivity of these reactions is higher than in the case of alkyl halides (EtI, *n*-PrI, and *n*-BuI). Varying the ratio of the reagents and the reaction conditions makes it possible to obtain the C-di- and C-triallylated products from ketones **1** and allyl bromide. So the reaction of 2-acetylfuran and 2-acetylthiophene **1** with allyl bromide in the phase-transfer catalysis system solid KOH/18-crown-6/benzene (mole ratio **1**:CH_2=$CHCH_2$Br:KOH:18-crown-6 1:2.1:6:0.05) at room temperature gives the C-diallylated products **15** in 36-48% yields. C-triallylated (17-45%), O-mono- (0-4%), C,O-di- (0-4%), and C,C,O-triallylated derivatives (0-5%) are also formed. Allylation of ketones **1** by allyl bromide at elevated temperature in the presence of solid KOH and 18-crown-6 in benzene (mole ratio **1**:CH_2=$CHCH_2$Br:KOH:18-crown-6 1:5:6:0.1) allows us to obtain C-triallylated products **16** in 54-64% yields.



The reactions of furan and thiophene methyl ketones **1** with propargyl bromide in the phase-transfer catalysis system solid KOH/18-crown-6/benzene (mole ratio **1**: $HC{\equiv}CCH_2Br$:KOH:18-crown-6 1:5:5:0.05) at room temperature proceed selectively and lead to C-tripropargyl derivatives **17** in 63-78% yields [11].

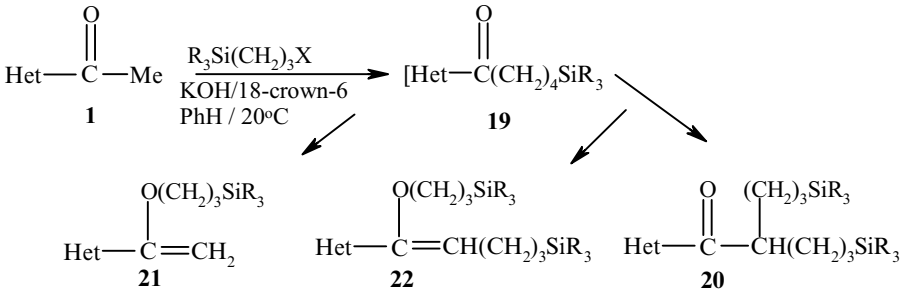


The C-tripropargyl ketones **17** obtained then were selectively modified in the phase-transfer catalysis system MeI/solid KOH/18-crown-6/CuBr/benzene (mole ratio **17**:MeI:KOH:18-crown-6:CuBr 1:6:6:0.2:0.1). The trimethylated products **18** were isolated by column chromatography in 36-58% yields.



1.3. Synthesis of Sterically Hindered Silicon-containing Furan and Thiophene Ketones

We have developed a new phase-transfer catalysis method for synthesis of sterically hindered ketones **20** containing silyl groups, from 2-acetylfuran and 2-acetylthiophene **1** in the system $R_3Si(CH_2)_3X$ (R = Me, Et; X = Br,I)/solid KOH/18-crown-6/benzene (mole ratio ketone:$R_3Si(CH_2)_3X$:KOH:18-crown-6 1:4:4:0.2) at room temperature [12].



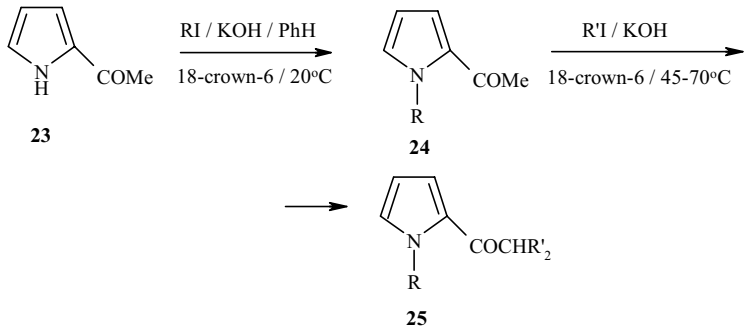
Het = 2-furyl, 2-thienyl; R = Me, Et

Alkylation of ketones **1** by $Me_3Si(CH_2)_3I$ in the system solid KOH/18-crown-6/benzene at room temperature gives as the major products the corresponding C-dialkylated ketones **20** (selectivity 49-70%) in up to 48% yield. In addition to the major products, the reaction mixtures contain various amounts of two types of products of alkylation of the enol form: O-mono- **21** (12-18%) and C,O-dialkylated **22** (18-33%).

The reaction of 2-acetylthiophene with $Et_3Si(CH_2)_3Br$ under similar phase-transfer catalysis conditions is less selective. In these cases, at the end of the process the reaction mixtures, in addition to the expected compounds **20**, **21**, and **22**, also contained desilylated products. Ketone **20** (R = Et) was isolated by column chromatography in 18% yield.

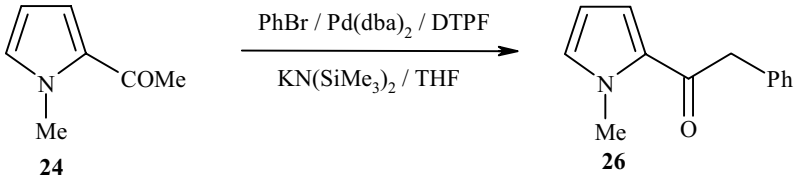
2. STERICALLY HINDERED PYRROLE KETONES

The use of phase-transfer catalysis systems of the liquid/solid type allows us, by altering the conditions, to carry out both N-alkylation of 2-acetylpyrrole and subsequent C-alkylation of the side chain. The reactions of 2-acetylpyrrole **23** with alkyl iodides in the system solid KOH/18-crown-6/benzene (mole ratio **23**:RI:KOH:18-crown-6 1:5:5:0.01) at room temperature proceed N-regioselectively and lead to 2-acetyl-1-alkylpyrroles **24** in 78-82% yields. But at elevated temperature in the presence of alkyl iodide (R'I), solid KOH and 18-crown-6, ketones **24** can be alkylated to the corresponding C-dialkylated derivatives **25** (mole ratio **24**:R'I:KOH:18-crown-6 1:8:4:0.1). The reaction products **25** are isolated by vacuum distillation in 51-73% yields [13].



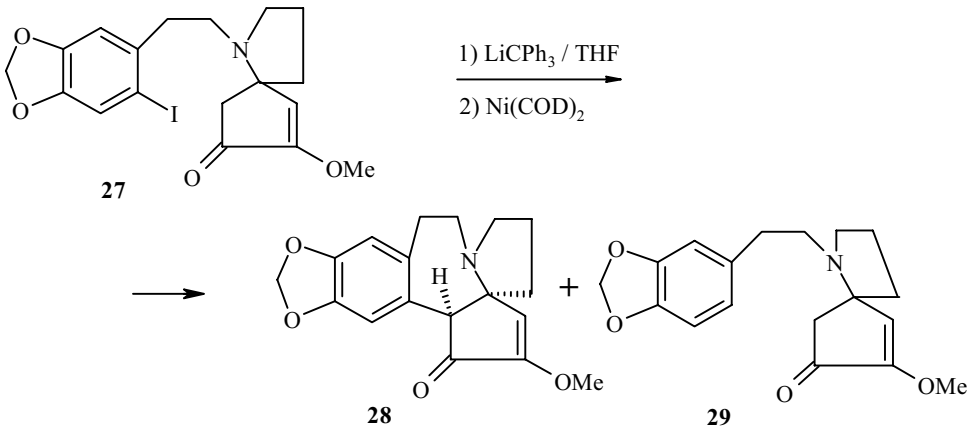
R = Me, Et, *n*-Pr; R' = Me, Et

2-Acetyl-1-methylpyrrole **24** in the system bromobenzene/$Pd(dba)_2$/1,1-bis(di-*o*-tolylphosphino)-ferrocene (DTPF)/$KN(SiMe_3)_2$/tetrahydrofuran at elevated temperatures gives 1-(1-methyl-2-pyrrolyl)-2-phenylethanone **26** in 79% yield [9].



24 **26**

Intramolecular arylation, catalyzed by nickel complexes, is used in synthesis of derivatives of the natural anti-cancer alkaloid cephalotaxine. So reaction of 1-aza-8-methoxyspiro[4.4]non-8-en-7-one **27** with lithium triphenylmethide in tetrahydrofuran followed by treatment of the reaction mixture with a $Ni(COD)_2$ complex gives a mixture of cyclic **28** (30%) and dehalogenated product **29** (30%) [14, 15]. This cyclization has also been accomplished by irradiation in the presence of KNH_2/Na/K or *t*-BuOK.



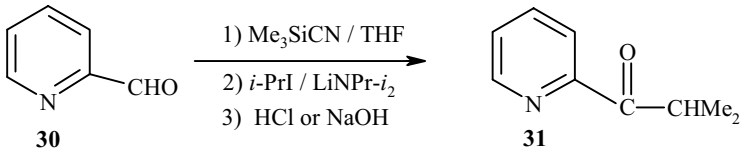
27 **28** **29**

3. STERICALLY HINDERED PYRIDINE KETONES

3.1 Synthesis of Pyridine Saturated Ketones

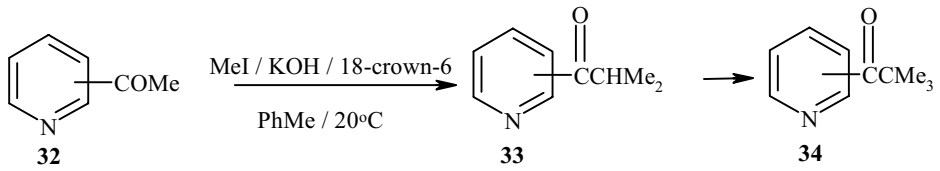
Only a few classical methods are known for synthesis of sterically hindered pyridine ketones ($Py–COCH_2R$, $Py–COCHR_2$ or $Py–COCR_3$, where R = alkyl, aryl). One of the most widely used methods is addition of Grignard reagents to pyridine nitriles. This method obtains 2-pyridyl isopropyl ketone from 2-cyanopyridine and isopropylmagnesium bromide [16].

2-Pyridyl isopropyl ketone **31** was also obtained by reaction of 2-pyridinecarbaldehyde **30** with trimethylcyanosilane followed by treatment with lithium diisopropylamide and an alkylating agent. Hydrolysis of the reaction mixture led to formation of ketone **31** in 75% yield [17].

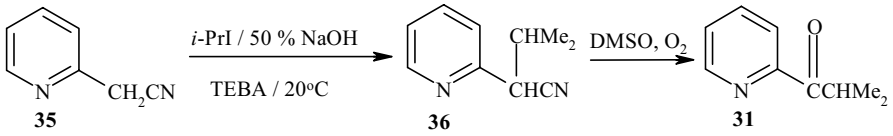


30 **31**

Using phase-transfer catalysis significantly simplifies synthesis of sterically hindered pyridine ketones. Varying the ratio of the reagents and the reaction conditions allows us to obtain from 2-, 3-, and 4-acetylpyridines **32** the corresponding isopropyl pyridyl **33** and *tert*-butyl pyridyl ketones **34** [18] in 13-67% yield. But attempts to obtain *tert*-butyl 3-pyridyl ketone in pure form were unsuccessful due to the instability of this compound.

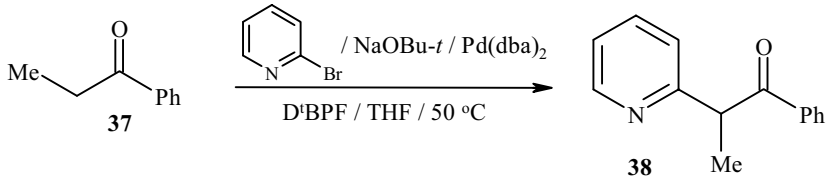


2-Methyl-1-(2-pyridyl)propanone **31** was obtained by oxidative decyanation of the corresponding nitrile. Alkylation of 2-pyridylacetonitrile **35** by isopropyl iodide in the phase-transfer catalysis system TEBA/50% aq. NaOH at room temperature gives nitrile **36**. Treatment of compound **36** with oxygen in dimethylsulfoxide leads to ketone **31** in 51% yield [19].



Later it was shown that oxidative decyanation of pyridine, quinoline, pyrazine, and pyrimidine nitriles under phase-transfer catalysis conditions is a universal method for synthesis of the corresponding aryl hetaryl ketones [20].

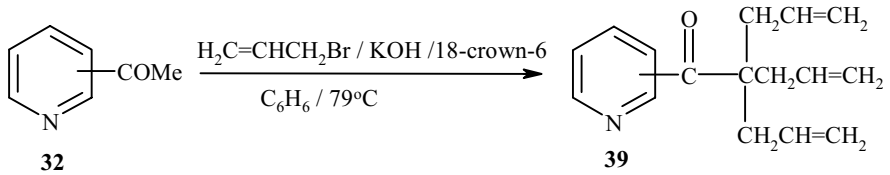
The sterically hindered 1-phenyl-2-(3-pyridyl)propanone **38** was successfully obtained by Pd-catalyzed arylation of propiophenone **37** at 50°C in the system 3-bromopyridine/$Pd(dba)_2$/1,1'-bis(di-*tert*-butylphosphino)-ferrocene (DtBPF)/NaOBu-*t*/tetrahydrofuran (mole ratio 2-bromopyridine:**37**:$Pd(dba)_2$:D^tBPF:NaOBu-*t* 1:1.1:0.02:0.025:1.5). Under these conditions, product **38** was selectively obtained in 87% yield. The high catalytic activity of this system is probably explained by formation of chelate complexes of palladium in the catalytic cycle [21].



We should note two more methods for synthesis of pyridine ketones. First of all, the heteroaromatic ketones Het–COCHMeR (where Het = 3-pyridyl etc.; R = H, alkyl) are obtained from the corresponding unsaturated ketones which contain at least two geminal hydrogen atoms in the α-position, and MeOH in the gas phase at 300-350°C in the presence of Mn oxides, Ce, Cr, Fe, or Mg [22]. 3-(3-Pyridyl)-2-butanone is obtained from 3-bromopyridine and 3-chloro-2-butanone by electrochemical reaction on an Al or Zn anode in the presence of a $NiBr_2$bpy complex [23].

3.2. Synthesis of Pyridine Unsaturated Ketones

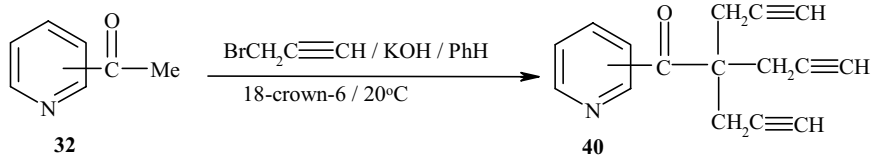
Allylation of 2- and 3-acetylpyridines **32** by allyl bromide at elevated temperature in the presence of solid KOH and 18-crown-6 in benzene (mole ratio **32**:CH_2=$CHCH_2Br$:KOH:18-crown-6 1:5:6:0.1) allows us to selectively obtain the C-triallylated products **39** in 54-64% yields [10].



32 **39**

But allylation of 2- and 3-acetylpyridines by allyl bromide in the system solid KOH/18-crown-6/benzene at room temperature proved to be ineffective, since it led to a complex mixture of products in low yields.

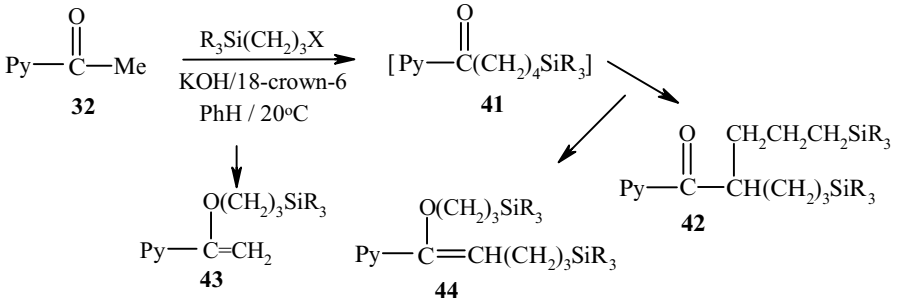
The reactions of acetylpyridines **32** with propargyl bromide in the phase-transfer catalysis system solid KOH/18-crown-6/benzene (mole ratio **32**:HC≡CCH$_2$Br:KOH:18-crown-6 1:5:5:0.05) at room temperature proceed selectively and lead to the C-tripropargyl derivative **40** in 34-46% yields [11].



32 **40**

3.3. Synthesis of Sterically Hindered Silicon-containing Pyridine Ketones

We have developed a new phase-transfer catalysis method for synthesis of sterically hindered ketones **20** containing silyl groups from acetylpyridines **32** in the system R$_3$Si(CH$_2$)$_3$X (R = Me, Et; X = Br, I)/solid KOH/18-crown-6/benzene (mole ratio ketone:R$_3$Si(CH$_2$)$_3$X:KOH:18-crown-6 1:4:4:0.2) at room temperature [12].



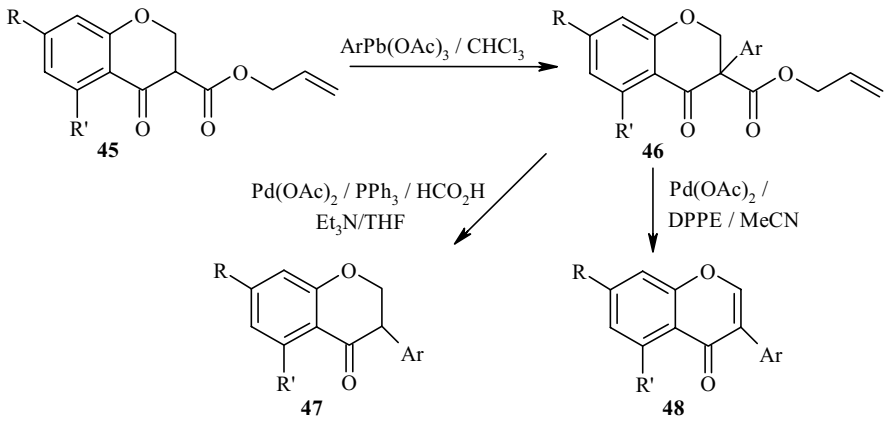
Py = 2-, 3- and 4-pyridyl; R = Me, Et

Alkylation of ketones **32** by Me$_3$Si(CH$_2$)$_3$I in the system solid KOH/18-crown-6/benzene at room temperature gives as the major products the corresponding C-dialkylated ketones **42** (selectivity 46-50%) in up to 43% yield. Furthermore, the reaction mixtures contain various amounts of O-mono **43** (14-36%) and C,O-dialkylated **44** (18-38%) products. The reaction of 2-acetylpyridine with Et$_3$Si(CH$_2$)$_3$Br under similar phase-transfer catalysis conditions is less selective. The ketone **42** (R = Et) is isolated by column chromatography in 20% yield.

4. ARYLATION OF CHROMAN-4-ONES

Derivatives of chroman-4-ones are of interest as biologically active compounds. Recently convenient methods have been developed for arylation of chroman-4-ones and 4-hydroxycoumarins by arylbismuth and aryllead reagents. Reaction of chroman-4-ones with arylbismuth reagents such as Ph_3BiCO_3, $PhBiCl_2$, $PhBi(OAc)_2$, $Ph_4BiOTos$, Ph_5Bi, $Ph_3Bi(OTs)_2$, $Ph_3Bi(NO_3)_2$, *p*-$Tol_3Bi(OAc)_2$, and (*m*-$O_2N–C_6H_4)_3Bi(NO_3)_2$ leads to their 3-diphenyl-substituted derivatives [24]. As a result of arylation of 3-aryl-4-hydroxycoumarins by Bi(V) reagents, 3-aryl-4-hydroxycoumarins are obtained in up to 92% yields.

Arylation of derivatives of 3-allyloxycarbonylchroman-4-ones **45** by aryllead(IV) acetates in the presence of pyridine gives β-keto esters **46**, which when treated with palladium acetate in the presence or absence of HCO_2H are easily converted to the corresponding isoflavanones **47** (79-97% yield) or isoflavones **48** (68-90%) [25].



R, R' = H, OMe; DPPE = $Ph_2PCH_2CH_2PPh_2$

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