# Allylic alkylation of benzoimidazole catalyzed by palladium complexes

*E. A. Petrushkina* and N. B. Polonik*

*A. N. Nesmeyanov Institute of Organoelement Compounds, Russian Academy of Sciences, 28 ul. Vavilova, 117813 Moscow, Russian Federation. Fax: +7 (095) 135 5085. E-mail: dir@ineos.ac.ru*

Bis(dibenzylidenacetone)palladium is an efficient and highly selective catalyst for the formation of *N*-(2,7-dimethylocta-2,7-dienyl)benzoimidazole in the allylation of benzoimidazole with *N*-(2,7-dimethylocta-2,7-dienyl)-*N*-methylpiperidinium iodide in the presence of NaH.

**Key words**: allylation, benzoimidazole, palladium complexes.

*N*-Substituted benzoimidazoles have a broad spectrum of biological activity. For example, active juvenoids have been found among *N*-terpenyl derivatives.[1,2] Nonsubstituted imidazoles react with alkyl halides in alkaline media to give the target products in unsatisfactory yields.[3,4] To successfully allylate benzoimidazole in acetone at room temperature, a twofold excess of allylic halide is required.[5] Allylation in the presence of such bases as NaOMe, NaOEt, or NaH at 100—110 °C is also low-yielding.[6,7] If allylic halides are replaced by allylic acetates, carbonates, sulfones, or similar compounds, allylation can occur only in the presence of transition metal complexes. In the literature, much attention has been given to palladium-catalyzed allylation of heterocycles containing the imidazole ring, mostly, adenine and guanine. In particular, this is the basis for the synthesis of carbocyclic analogs of nucleosides such as carbovir and its adenine analog[8] with the use of cyclopentenyl acetates as allylic components because they prevent the formation of products of allylic rearrangement. Usually, LiH or NaH have been used as bases in the reactions catalyzed by $Pd(Ph_3P)_4$.[8—13] For allylation of adenine and guanine with allylic acetates or allyl phenyl ethers, the $Pd(dba)_2$—dppe (dba is dibenzylidenacetone and dppe is bis(diphenylphosphino)ethane) and $Pd_2(dba)_3$—dppb (dppb is bis(diphenylphosphino)-butane) systems have also served as catalysts.[14,15] Earlier,[8] it was shown that imidazole is satisfactorily allylated with cyclopentenyl acetates upon mixing together substrates, a base, and a catalyst, while in the case of adenine, one should first obtain its sodium salt and then add allyl acetate and a catalyst. The use of vinyloxiranes allows allylation in neutral media, but the reaction can be accompanied by the formation of considerable amounts of a product of allylic rearrangement.[16] Literature data on the catalyzed alkylation of *N*-heterocycles with acyclic allylic compounds are lacking. There are some data on the allylation of aliphatic amines with allylic acetates and allyl phenyl ethers in the $Pd(acac)_2$—$Ph_3P$ [17] and $(Ph_3P)_2PdCl_2$—PhONa [18] catalytic systems, respectively. Earlier,[19] it was shown that (neryl)- and (geranyl)trialkylammonium halides are convenient reagents for the catalyzed allylic alkylation of C-nucleophiles, in particular, sodium ethyl malonate.

The set of allylation reagents of the monoterpene series having the 2,7-dimethyloctane skeleton is limited, because chlorides and iodides are rather difficult to isolate in the pure state,[20,21] and acetate can be obtained as a result of a multistage synthesis from a telomer of isoprene with *N*-methylaniline.[21] Therefore, we studied *N*-(2,7-dimethylocta-2,7-dienyl)-*N*-methylpiperidinium iodide (**1**) as a possible allylating agent. This compound can be easily obtained by quaternization of *N*-(2,7-dimethylocta-2,7-dienyl)piperidine (**2**), synthesized according to the known procedure[22] by telomerization of isoprene with piperidine in MeCN in the presence of the $Pd(acac)_2$—$Ph_3P$ catalytic system.

Amine **2** is quaternized faster than (geranyl)- and (neryl)diethylamines to give *N*-methylpiperidinium iodide **1** as a white powder (m.p. 128—129 °C), which is used in the allylation of benzoimidazole without additional purification.

The allylation of sodium benzoimidazolide with salt **1** was carried out in the $Pd(acac)_2$—$2Ph_3P$ (**A**), $(Ph_3P)_4Pd$ (**B**), and $Pd(dba)_2$ (**C**) catalytic systems to give products **3** and **4** (Scheme 1).

The mode in which the reaction is carried out affects substantially the yield and ratio of the reaction products. Thus the method including preliminary preparation of sodium benzoimidazolide (method *A*) requires high temperature (no lower than 100 °C) and a highly polar solvent (such as DMF). The allylation of benzoimidazole in a THF—DMF system in the presence of NaH was found to be more convenient (method *B*).

In the case of phosphine-containing palladium catalysts **A** and **B**, $Ph_3P$ is oxidized into $Ph_3PO$, the yield of the latter being increased as the temperature is increased and the reaction time is prolonged, and the yields of products **3** and **4** are decreased. Elimination of $Ph_3P$ from the catalytic cycle (*i.e.*, the formation of $Ph_3PO$),

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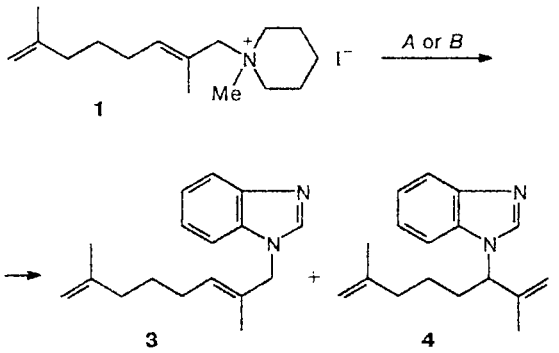
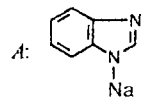
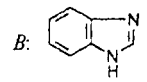
**Scheme 1**




**Reagents and conditions:**

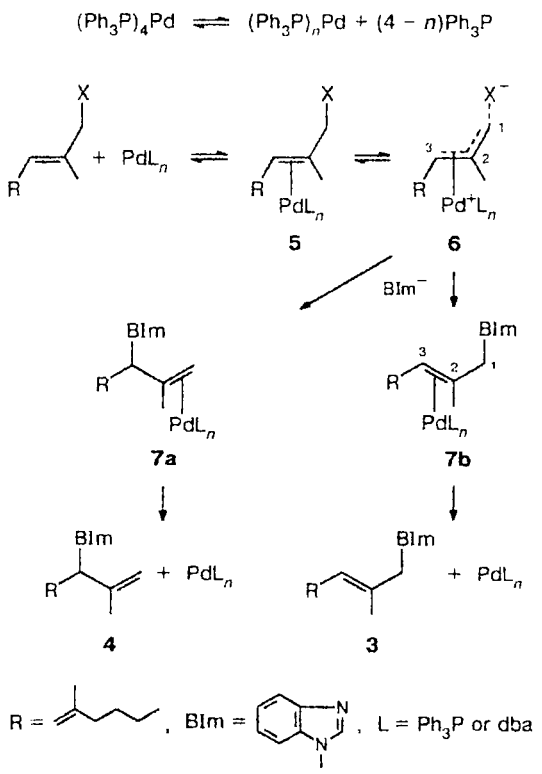



and the use of complex **A** with a lesser amount of $Ph_3P$ also reduce the yields of products **3** and **4**. A larger amount of catalyst **B** (10 mol. % $(Ph_3P)_4Pd$) favors the yield of **3** and **4**. However, the best results were obtained using method *B* in the presence of $Pd(dba)_2$ (complex **C**), isomer **3** being formed virtually without admixture of isomer **4**, which is a rare phenomenon for catalyzed allylation. The mechanism proposed earlier[23] for the allylation of nucleophiles catalyzed by the palladium(0) complex **B** can explain our experimental data. The first stage of reaction is the dissociation of ligands from $(Ph_3P)_4Pd$ or $Pd(dba)_2$ with subsequent formation of an olefin—palladium π complex (**5**) (Scheme 2).

The oxidative addition of the metal yields a π-allylic palladium complex (**6**). The regiochemical outcome of the nucleophilic attack[23] depends on the steric accessibility for the nucleophile and stability of an intermediate π-olefin complex (**7**) that formed on alkylation. Usually, a nucleophile (especially, a sterically hindered one) attacks the least hindered terminus of the π-allylic complex. However, in the case of bulky phosphine or dba ligands at the palladium atom, steric hindrances for the formation of complexes **7** increase the energy of the transition state, so that the nucleophilic attack at the more substituted C atom, resulting in the least hindered olefin—palladium π-complex **7a**, is preferential. Palladium complexes **B** or **C** did not affect significantly the regioselectivity of a reaction involving a little hindered nucleophile, such as diethyl malonate, which had been used earlier,[19] while this influence was crucial in the case of benzoimidazole, a bulkier nucleophile. The absence of the isomer with the inverted double bond (as followed from comparison with authentic *E*- and *Z*-isomers of compound **3**) suggests that the nucleophilic attack at the π-allylic complex **6** occurs much more rapidly than its *syn—anti* isomerization.

**Scheme 2**




Thus, the method of catalyzed allylation is quite convenient and effective for the allylation of benzoimidazole. Here, the choice of a catalyst is decisive for the course of the reaction.

## Experimental

All reactions were carried out in an atmosphere of argon (99% purity) with the use of Schlenk equipment. For the synthesis, 99%-purity monomers were used. Tetrahydrofuran was dried by distillation over $LiAlH_4$ and stored under argon. Dimethylformamide was distilled over CaO and, repeatedly, over $CaH_2$ at 80 Torr. The content of water was 0.02% according to the Fischer analysis. Benzoimidazole was recrystallized from toluene and dried at 1 Torr. $Pd(Ph_3P)_4$ and $Pd(dba)_2$ were synthesized according to the known procedures.[24,25] GLC analysis was performed on a Chrom-5 chromatograph with a glass capillary column ($l$ = 30 m) and an OV-101 phase. The temperature was programmed from 80 to 230 °C at a rate of 20 deg $min^{-1}$ and then was maintained at 230 °C for 20 min. $n$-$C_{24}H_{50}$ was used as the standard. Compounds **3** and **4** were identified by comparing their GLC retention times with those for the specimens obtained by the known procedure.[26]

**Preparation of salt 1.** MeI (8.37 g, 59 mmol) was added to a solution of amine **2** (6.55 g, 29.5 mmol) in 5 mL of benzene. The reaction mixture was kept in the dark at room temperature for 24 h. The precipitate that formed was filtered off and washed with hexane to give salt **1** (10.28 g, 96%), m.p.

**Table 1.** Allylation of benzoimidazole

| Catalyst (mol. %) | Solvent | $T$/°C (τ/h) | Reaction product ratio | | Yield of **3**+**4** (%) |
|---|---|---|---|---|---|
| | | | $Ph_3PO$ : (**3**+**4**) | **3** : **4** | |
| | | Method *A* | | | |
| **A** (5) | DMF | 100 (15) | 64 : 36 | 84 : 16 | 6.3 |
| **B** (5) | DMF | 100 (8)<br>150 (0.75) | 40 : 60 | 47 : 53 | 33.0 |
| **B** (10) | DMF | 100 (8) | 19 : 81 | 49 : 51 | 85.3 |
| | | Method *B* | | | |
| **A** (5) | THF—DMF (6 : 1) | 76 (49) | 46 : 54 | 91 : 9 | 12.6 |
| **B** (5) | THF—DMF (3 : 2) | 77 (54) | 50 : 50 | 69 : 31 | 22.0 |
| **C** (2.5) | THF—DMF (8 : 1) | 69 (52) | — | 97.5 : 2.5 | 87.0 |
| **C** (5) | THF—DMF (6 : 1) | 72 (35) | — | 96 : 4 | 80.0 |
| **C** (10) | THF—DMF (6 : 1) | 69 (35) | — | 97 : 3 | 85.0 |

128—129 °C. Found (%): C, 52.88; H, 8.37; N, 3.52. $C_{16}H_{30}IN$. Calculated (%): C, 52.89; H, 8.32; N, 3.85.

**Allylation of benzoimidazole (general procedure). Method *A*.** Solid NaH (0.072 g, 3 mmol) was added to a solution of benzoimidazole (0.342 g, 2.89 mmol) in DMF (10 mL). The homogeneous solution that formed after 30 min at 100 °C was added to a solution of salt **1** (1.0 g, 2.75 mmol) and a catalyst (Table 1) in DMF (15 mL). The formation of allylated products **3** and **4** was monitored by TLC (silica gel; ethanol—benzene, 1 : 3). Palladium black was filtered off, and the solvent was removed. The residue was diluted with benzene, and the precipitate that formed was filtered off. The benzene solution was concentrated, and the residue was chromatographed on a column with $SiO_2$, elution with heptane or hexane. The products were analyzed by GLC following distillation at 186—194 °C (1 Torr).

**Method *B*.** To a mixture of salt **1** (2.75 mmol), benzoimidazole (0.32 g, 2.75 mmol), and a catalyst, 30 mL of a mixture of THF and DMF was added (see Table 1). Dry NaH (0.07 g, 3 mmol) was added to the homogeneous solutions that formed. The reaction mixture was stirred at room temperature until complete dissolution of NaH and then refluxed; the solution gradually darkened. The white precipitate that formed was filtered off, and the solvent removed *in vacuo*. The residue was diluted with water, and the products were extracted with benzene. The benzene extract was concentrated on a rotary evaporator to give an oil, which was chromatographed on a column with silica gel; the eluent was hexane. Following distillation at 186—191 °C (1 Torr), the products were analyzed by GLC.

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