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SYNTHESIS OF 3'- OR 4'-ALKENYLBENZOCROWN ETHERS[1)]

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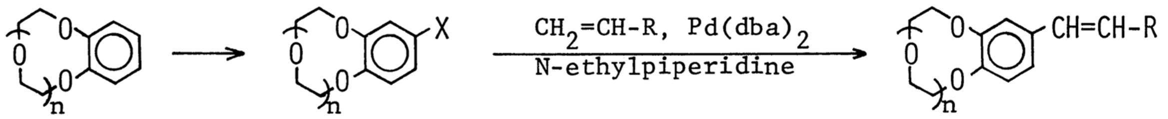
Palladium(0) catalyzed alkenylation of 3'- or 4'-iodo- (or bromo-) benzocrown ethers are found to be a convenient procedure for the introduction of alkenyl groups (-CH=CH-R; R=Ph, COOEt and COOH). Iodination at 3'-position of benzocrown ethers could be achieved in good yield by the use of 4'-*t*-butyl derivatives.

Functionalized benzocrown ethers have received much attention through not only their modified nature of complexation with cations, but also their specialized utility for analytical[2)] and pharmaceutical applications,[3)] and as potential intermediates for other functionalized crown ethers, such as polymer-bound crown ethers or bis(crown ether)s. Various substituted benzocrown ethers have been prepared by either electrophilic substitution to benzocrown ethers(1) or crown ring-forming cyclization of substituted catechols. Although the former method is used successfully for nitration or halogenation, the reactions carried out under metal salts catalysis frequently encounter with deactivation of catalysts[4)] and complexity in the isolation of the product owing to the formation of complexes.[5)] The latter method is considered to be restricted by the availability of starting catechols and variable yields in the cyclization. Now we wish to report a convenient preparation of 3'- or 4'-alkenylbenzocrown ethers from corresponding halobenzocrown ethers under palladium(0) catalysis.

A mixture of a 4'-iodobenzocrown ether(3)[5)] (1 mmol), an olefinic compound (5 mmol), N-ethylpiperidine (2 mmol) and bis(dibenzylideneacetone)palladium(0)(Pd(dba)$_2$) (0.02 mmol) was stirred at 120-125 °C for 1 h (eq. 1). The reaction mixture was washed with hydrochloric acid and extracted twice with benzene. Pure 4 and 5 were isolated by silica gel column ($CHCl_3$). A recrystallization of crude 6 precipitated by acidification of aq. basic extracts from methanol gave pure products. Slightly severe reaction conditions (130-140 °C, 1.5 h) were required for 4'-bromobenzocrown



(1)

1a(n=3)
1b(n=4)

2a(X=Br, n=3)
2b(X=Br, n=4)
3a(X=I, n=3)
3b(X=I, n=4)

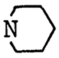
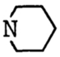
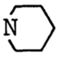
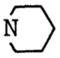
4a(R=Ph, n=3)
4b(R=Ph, n=4)
5a(R=COOEt, n=3)
5b(R=COOEt, n=4)
6a(R=COOH, n=3)
6b(R=COOH, n=4)

ethers(2) with use of combined catalyst ($Pd(OAc)_2$-PPh_3) (a conventional catalyst system of the Heck arylation with aryl bromides[6]). Better yields in the alkenylation were obtained from 3 than 2 as shown in Table. Since both 2 and 3 are easily available from 1 with comparable yields (~80%), the use of 3 as the starting material is preferable. In the present system, the zero valent palladium catalyst, $Pd(dba)_2$, gave better yields than $Pd(OAc)_2$ did. Tributylamine (frequently used base in the Heck arylation) can be used for acidic products(6). The amine, however, caused complexity in the isolation of neutral products(4 and 5) with column treatment, and extraction with hot heptane from the concentrate gave pure materials with a considerable loss of the products. The alternative routes for 4a or 6a from 4'-formylbenzocrown ether by the reaction with diethyl benzylphosphonate (Wittig-Horner reaction)[7] or malonic acid[3] are reported to give relatively low yields (43% for 4a and 21% for 6a).

A substituent on 3'-position is expected to endow different features on benzocrown ethers from that on 4'-position through its increased proximity to the neighboring crown ether ring. However, preparation of 3'-substituted benzocrown ethers has problems. No electrophilic substitution on 3'-position of 1 has been reported to date. In contrast to catechol or 4-substituted catechols, crown ring-forming cyclization with 3-substituted catechols proceedes in poor yields (~10%).[3]

4'-*t*-Butylbenzo-15-crown-5(7) is chosen as a starting material to block the 4'-position, where electrophilic substitution has been known to occur exclusively (eq. 2). Iodination of 7 could be achieved by the use of excess of silver trifluoroacetate-iodine to give pure 8 (mp; 54.7-57 °C) in 81% yield. Use of an equimolar amount of the reagents gave a mixture of 8 and 7 (9:1, viscous oil, 74%), from which pure 8 could not be obtained by conventional techniques (chromatography or solvent extraction). The alkenylation of 8 was carried out under the same conditions as that for 3 with 2% $Pd(dba)_2$ (Table). The same isolation procedure as that for 6 gave monohydrated

Table. Synthesis of Alkenylated Benzocrown Ethers[a)]

Substrates		Catalysts	Bases	Products[b)]	Yields[c)]	Mp, °C
Crown ethers	CH_2=CH-R				%	
3a	Ph	Pd(dba)$_2$	Et-N	4a	97	108.0-108.6
〃	〃	〃	NBu_3	〃	38	
〃	COOEt	〃	Et-N	5a	98	98.1-99.4
〃	〃	〃	NBu_3	〃	41	
〃	〃	Pd(OAc)$_2$	Et-N	〃	69	
〃	COOH	Pd(dba)$_2$	〃	6a	79	189.7-191.3[d)]
2a[e)]	〃	Pd(OAc)$_2$-5PPh$_3$	〃	〃	41	
3b	Ph	Pd(dba)$_2$	〃	4b	87	97.1-98.2
〃	COOEt	〃	〃	5b	93	99.4-100.6
〃	COOH	〃	〃	6b	80	152.0-153.0
〃	〃	〃	NBu_3	〃	84	
2b[e)]	〃	Pd(OAc)$_2$-5PPh$_3$	Et-N	〃	50	
8	〃	Pd(dba)$_2$	〃	9	63	154.2-156.7[f)]

a) Unless otherwise noted the reactions were performed at 120-125 °C for 1 h with **3** (1 mmol), catalyst (0.02 mmol), unsaturated compound (5 mmol) and base (2 mmol) under nitrogen.

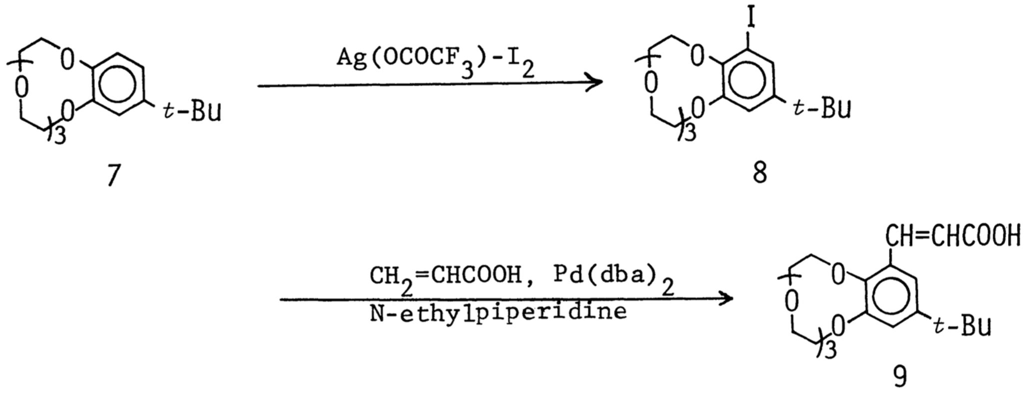
b) All compounds listed here and halobenzocrown ethers have satisfactory elemental analyses (± 0.4%) and spectral features (IR and NMR) for expected structures. Trans configuration of double bond for all products listed here were confirmed by coupling constants (15-16 Hz) of olefinic protons in NMR and the presence of sharp absorption band assignable to trans CH wagging in IR (960-990 cm^{-1}).

c) Isolated and purified yields based on halo benzocrown ether used.

d) Lit.[3)], 192-194 °C.

e) The reaction was performed at 130-140 °C for 1.5 h.

f) Monohydrated crystals showed two melting points at 85.0-85.9 °C and 154.6-159.0 °C



(2)

crystals of 9. Dehydration was accomplished by heating at 100 °C for 5 h *in vacuo*. The hydrated crystals showed a higher carbonyl absorption band at 1702 cm^{-1} than that of the dehydrated one (1678 cm^{-1}). The higher one might be assigned to monomeric form bonded with water, while the lower one to dimeric form.

The product 9 or its saturated form is conceivable as a good model compound for naturally occurring ionophores such as monesine bearing a carboxylic group on the end of the molecule.$^{3)}$

Thus, the palladium catalyzed alkenylation of benzocrown ethers *via* halobenzocrown ethers affords a novel and convenient method for the introduction of a function at 3'-position of 1 as well as at 4'-position.

References

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