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Copper-Catalyzed Cross-Coupling of (*Z*)-Allyl Phenyl Ethers with Grignard Compounds in the Synthesis of Insect Pheromones

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Abstract— (8*Z*)-Dodec-8-en-1-yl acetate (pheromone of oriental fruit moth *Grapholita molesta*) and (9*Z*)-dodec-9-en-1-yl acetate (pheromone of grape berry moth *Paralobesia viteana*) containing impurities of isomeric structures were synthesized via copper-catalyzed cross-coupling of (*Z*)-1-phenoxyhex-2-ene and (*Z*)-1-phenoxypent-2-ene, respectively, with Grignard compounds in the key stage.

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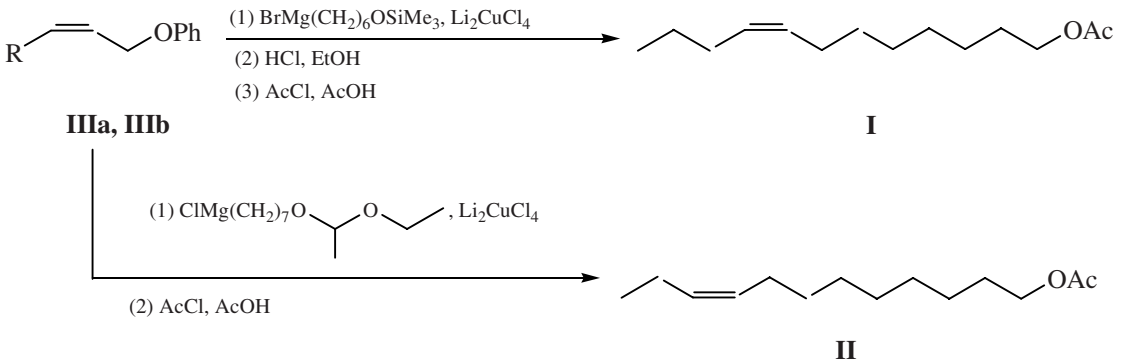
Copper-catalyzed cross-coupling of allyl compounds with Grignard reagents provides a useful tool for building up carbon–carbon bond [1]. We previously showed that this procedure ensures highly selective preparation of pheromones having an *E*-alkene moiety from (2*E*)-1-phenoxyocta-2,7-diene [2, 3]. However, isomerization of *Z*-double bond in the synthesis of some conjugated diene alcohols and acetates has also been reported [4, 5]. We made an attempt to effect copper-catalyzed cross-coupling of *Z*-alkenyl phenyl ethers with an isolated double bond with a view to obtain known (8*Z*)- and (9*Z*)-dodecenyl acetates **I** and **II** that are pheromones of *Lepidoptera* insects, oriental fruit moth *Grapholita molesta* [6] and grape berry moth *Paralobesia viteana* [7], respectively (Scheme 1).

The required hydrocarbon chains containing a *Z*-configured double bond were built up by reacting (*Z*)-1-phenoxyhex-2-ene (**IIIa**) and (*Z*)-1-phenoxypent-2-ene (**IIIb**) (Scheme 1) with the Grignard compounds obtained from 6-bromohexan-1-ol and 7-chloroheptan-1-ol (which were preliminarily protected at the hydroxy group). The reactions were carried out in the presence of Li_2CuCl_4 as catalyst. The latter is rapidly reduced *in situ* to copper(I) salt ($CuCl \cdot 2LiCl$) by the action of Grignard compound [8, 9]. The mechanism of this reaction remains a matter of extensive discussions. Up to now, two main reaction paths have been proposed [10–12]. The first of these involves intermediate π-allyl Cu^{III} complexes and leads to the formation of three products: *cis*- and *trans*-isomeric α-substitution products and γ-substitution product. The

Scheme 1.



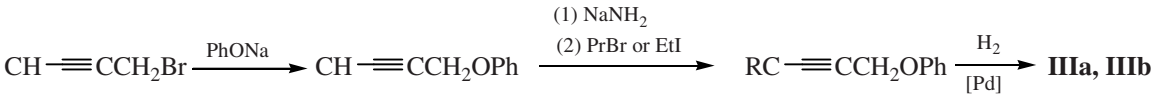
III, R = Pr (**a**), Et (**b**).

second path implies direct replacement in intermediate σ-allyl Cu^I complexes to give only two products: α-substitution product with the same geometry of the double bond and γ-substitution product. Conditions ensuring selective substitution at the α- or γ-position were found, and structural factors in the substrate responsible for the reaction direction were determined [10–12]. In keeping with published data on the use of the above reaction in the synthesis of natural compounds, *trans*-configured double bond as a rule does not change during the process, while *cis*-double bond may undergo isomerization or not depending on the substrate structure. The presence of a conjugated system favors isomerization of *Z*-double bond [4, 5, 13, 14], whereas in the alkylation with dialkylcuprates ($LiCuMe_2$) of allyl carboxylates with an isolated double bond, in particular geranyl or neryl acetates, the corresponding α-substituted derivatives are formed without change in the double bond configuration [15]. As allylating agents we used phenyl ethers in which the departing group is inactive. In this case the corresponding α-substituted products are formed preferentially [11, 12]. To a solution of Li_2CuCl_4 and compound **IIIa** or **IIIb** in THF, cooled to –20°C, a solution of the corresponding Grignard reagent in THF was quickly added to exclude formation of γ-substituted product. The Grignard reagents were prepared from 6-bromo-1-trimethylsilyloxyhexane [16] and acetaldehyde 6-chloroheptyl ethyl acetal [17].

In the synthesis of compound **I**, the hydroxy group was protected via conversion into trimethylsiloxy group which was readily removed by heating in boiling ethanol. The subsequent treatment with acetyl chloride in acetic acid at 40°C gave the corresponding acetate. To reduce the number of steps in the synthesis of compound **II**, the hydroxy group in 7-chloroheptan-1-ol was protected by conversion into mixed acetal, taking into account that the subsequent reaction of the acetal with acetyl chloride in acetic acid could directly produce the desired acetate. However, the transformation of the acetal into acetate **II** required severe conditions, heating in boiling acetic acid. Compounds **I** and **II** were formed with different selectivities. Compound **I** was isolated as a single isomer which was identified by GLC using an authentic sample. In the synthesis of **II**, the acetylation stage gave a mixture of three isomers at a ratio of 1:15:2, the major isomer being the target product (GLC). Predominant formation of the α-substituted products in the synthesis of **I** and **II** indicates that the reaction involves mainly Cu^I complexes as intermediates. The presence of an insignificant amount of the *trans* isomer of **II** implies some contribution of the reaction path involving intermediate Cu^{III} complexes. Thus the selectivity of copper-catalyzed cross-coupling of alkenyl phenyl ethers with alkyl Grignard compounds is determined not only by reaction conditions but also by the structure of both reactants. Presumably, C_6+C_6 alkyl chain coupling is preferred to C_5+C_7.

Esters **IIIa** and **IIIb** were synthesized according to Scheme 2, via transformation of prop-2-yn-1-yl bromide into 3-phenoxyprop-1-yne (**V**) [18], alkylation of the latter with propyl bromide or ethyl iodide, and subsequent reduction of the triple bond in ethers **VIa** and **VIb** with hydrogen over Lindlar catalyst poisoned with quinoline.

Scheme 2.



R = Pr (**a**), Et (**b**).

EXPERIMENTAL

The reagents used had a purity of 99%; solvents and liquid reagents were distilled prior to use and were stored under argon. All reactions were carried out under argon. GLC analysis was performed on an LKhM-8MD (5) chromatograph equipped with a steel column, 2000×3 mm, packed with 15% of SKTFT-50 on Chromaton N-AW; carrier gas helium. The IR spectra were recorded from thin films on an UR-20 spectrometer.

1-Phenoxyhex-2-yne (VIa). 3-Phenoxyprop-1-yne (**V**), 22.7 g, was treated with an equimolar amounr of

metallic sodium in 150 ml of liquid ammonia at –60 to –63°C. The resulting sodium derivative was alkylated with 21.2 g of propyl bromide at –40 to –45°C. Yield 12.3 g (41%), bp 80°C (1 mm Hg). Found, %: C 82.21; H 8.07. $C_{12}H_{14}O$. Calculated, %: C 82.71; H 8.09.

(*Z*)-1-Phenoxyhex-2-ene (IIIa). Compound **VIa**, 6.57 g, was hydrogenated at room temperature over Lindlar catalyst poisoned with 1 ml of quinoline. Yield 6.62 g (99%), bp 125–127°C (12 mm Hg). Found, %: C 82.00; H 9.09. $C_{12}H_{16}O$. Calculated, %: C 81.77; H 9.15.

1-Phenoxypent-2-yne (VIb) was synthesized as described above for compound **VIa** from 32.18 g of ether **V** and 31.3 g of ethyl iodide. Yield 16.31 g (42%), bp 115–116°C (8 mm Hg). Found, %: C 82.72; H 7.49. $C_{11}H_{12}O$. Calculated, %: C 82.46; H 7.55.

(*Z*)-1-Phenoxypent-2-ene (IIIb). Hydrogenation of 16.31 g of compound **VIb** in 90 ml of hexane over 1 g of Lindlar catalyst poisoned with 1 ml of quinoline gave 11.54 g (68%) of *Z*-alkene **IIIb** with bp 116–117°C (23 mm Hg). Found, %: C 81.21; H 8.49. $C_{11}H_{14}O$. Calculated, %: C 81.44; H 8.70.

(8*Z*)-Dodec-8-en-1-yl acetate (I). The Grignard compound prepared from 3.9 g of 1-bromo-6-trimethylsiloxyhexane in 10 ml of THF was added at –20°C to a solution of 2.5 g of phenoxyalkene **IIIa** and 0.6 g of Li_2CuCl_4 in 20 ml of THF, and the mixture was stirred for 2 h at –5 to 0°C. The solvent was distilled off, 50 ml of 80% ethanol was added to the residue, the mixture was heated for 1 h under reflux, 0.4 ml of concentrated hydrochloric acid was added, and the mixture was stirred for 8 h at 20°C, diluted with 30 ml of water, and extracted with diethyl ether. The extract was dried over $MgSO_4$ and evaporated, and the residue was distilled under reduced pressure. Yield of (8*Z*)-dodec-8-en-1-ol 2.1 g (81%), bp 88–90°C (1 mm Hg). IR spectrum, ν, cm^{-1}: 1660 (C=C); 1520, 1615 ($C{=}C_{arom}$); 2960, 2990, 3070 br ($C{-}H_{arom}$); 3440 (NH); 700 ($\delta C{=}CH_2$). Found, %: C 77.72; H 12.80. $C_{12}H_{24}O$. Calculated, %: C 78.19; H 13.13. The product was converted into acetate **I** according to standard procedure (Ac_2O, AcOH).

(*Z*)-Dodec-9-en-1-yl acetate (II). The Grignard compound prepared from 5.2 g of 7-chloro-1-[1-(ethoxy)ethoxy]heptane in 20 ml of THF was added at –20°C to a solution of 3.7 g of phenoxyalkene **IIIb** and 0.99 g of Li_2CuCl_4 in 20 ml of THF, and the mixture was stirred for 2 h at –5 to 0°C. The mixture was then poured into dilute hydrochloric acid, the organic phase was separated and dried over Na_2SO_4, the solvent (THF) was distilled off under reduced pressure, the residue was diluted with hexane and washed with a solution of sodium hydroxide, and the hexane layer was dried over Na_2SO_4 and evaporated to obtain 4.5 g (76%) of (*Z*)-12-[1-(ethoxy)ethoxy]dodec-3-ene. The product was mixed with 1.7 g of acetyl chloride and 24 g of glacial acetic acid, and the mixture was heated for 4 h at 40°C and then heated for 3 h under reflux. Analysis by GLC showed the presence of three compounds.

REFERENCES

1. Knochel, P. and Betzemeier, B., *Modern Organocopper Chemistry*, Krause, N., Ed., Weinheim: Wiley, 2002, p. 45.
2. Zakharkin, L.I. and Petrushkina, E.A., *Izv. Akad. Nauk SSSR, Ser. Khim*., 1982, no. 5, p. 1181.
3. Zakharkin, L.I. and Petrushkina, E.A., *Russ. J. Org. Chem*., 1982, vol. 18, no. 8, p. 1623.
4. Descoins, C.E. and Henrick, C.A., *Tetrahedron Lett*., 1972, vol. 13, no. 30, p. 2999.
5. Gassani, G., Massardo, P., and Piccardi, P., *Tetrahedron Lett*., 1980, vol. 21, no. 36, p. 3497.
6. Holman, G. and O'Keefe, D.F., *Tetrahedron Lett*., 1973, vol. 14, no. 9, p. 673.
7. Roelofs, W.L., Tette, J.P., Taschenberg, E.F., Comeau, A., *Insect Physiol*., 1971, vol. 17, no. 12, p. 2235.
8. Tamura, M. and Kochi, J.K., *Synthesis*, 1971, no. 4, p. 303.
9. Kochi, J.K., *Organometallic Mechanisms and Catalysis*, New York: Academic, 1978, p. 381.
10. Karlström, A.S.E. and Bäckvall, J.-E., *Chem. Eur. J*., 2001, vol. 7, no. 9, p. 1981.
11. Bäckvall, J.-E., Selén, M., and Grant, B., *J. Am. Chem. Soc*., 1990, vol. 112, no. 19, p. 6615.
12. Bäckvall, J.-E. and Sellén, M., *J. Chem. Soc., Chem. Commun*., 1987, no. 11, p. 827.
13. Goering, H.L. and Kantner, S.S., *J. Org. Chem*., 1983, vol. 48, no. 5, p. 721.
14. Samain, D., Descoins, C.E., and Langlois, J., *Nouv. J. Chim*., 1978, vol. 2, no. 3, p. 249.
15. Levisalles, J., Rudler-Chauvin, M., and Rudler, H., *J. Organomet. Chem*., 1977, vol. 136, no. 1, p. 103.
16. Mattes, H. and Benezra, C., *J. Org. Chem*., 1988, vol. 53, no. 12, p. 2732.
17. Caplin, J. and Tyman, J.H.P., *J. Chem. Res., Miniprint*, 1982, no. 1, p. 321.
18. Gaudemar, P.M., *Ann. Chim*., 1956, vol. 13, no. 1, p. 161.