1-Acetyl-2-diacetylamin-5,5-dimethyl-3-cyano-4,5,6,7-tetrahydropyrrolo[2,3-c]pyran (VI). A mixture of 1.15 g (5 mmoles) aminonitrile IV and 8 ml (0.08 mole) acetic anhydride was heated at reflux for 1 h, cooled and 30 ml ethanol was added. The precipitate was filtered off, washed with ethanol and dried to yield 1.1 g (72.3%) VI with mp 117-118°C (from ethanol). R_f 0.62 (4:1:1 ethanol—chloroform—ether). IR spectrum 2250 (C≡N), 1720-1740 cm^{-1} (C = O). PMR spectrum (in pyridine-d_5): 4.85 (2H, s, CH_2), 2.70 (11H, s, CH_2, $3CH_3$), 1.35 ppm (6H, s, $2CH_3$). M 317 (mass spectroscopy). Found: C, 60.5; H, 6.1; N, 13.8%. Calculated from $C_{16}H_{19}N_3O_4$: C, 60.6; H, 6.0; N, 13.2%.

1-Acetyl-2-acetylamin-5,5-dimethyl-3-cyano-4,5,6,7-tetrahydropyrrolo[2,3-c]pyran (VII). A mixture of 1.15 g (5 mmoles) aminonitrile IV, 75 ml absolute benzene, and 0.5 ml (5 mmoles) acetic anhdride was heated at reflux for 3 h and cooled. The precipitate was filtered off, washed with methanol and ether, and dried to yield 1.0 g (75.6%) VII with mp 152-153°C (from methanol), R_f 0.70 (2:1:2 ethanol—chloroform—petroleum ether). IR spectrum: 3120, 3230, 3310 (NH 2230 (C≡N), 1720-1740 cm^{-1} (C=O). PMR spectrum (in pyridine-d_5): 7.90 (1H, s, NH), 4.70 (2H, s, CH_2), 2.40 (5H, s, CH_2 and $NCOCH_3$), 1.50 (3H, s, $NHCOCH_3$), 1.20 (6H, s, $2CH_3$). Found: C, 61.2; H, 6.3; N, 15.3%. Calculated for $C_{14}H_{17}N_2O_3$: C, 61.1; H, 6.2; N, 15.3%.

LITERATURE CITED

1. R. P. Carr, A. H. Jackson, G. W. Kenner, and G. S. Sach, J. Chem. Soc., C, No. 3, 487 (1971).
2. A. L. Mndzhoyan (editor), Synthesis of Heterocyclic Compounds [in Russian], Vol. 8, Izd. Akad. Nauk Arm. SSR, Erevan (1969), p. 30.

ARYLATION OF HETEROCYCLES IN THE REACTION OF HETEROCYCLIC MERCURY DERIVATIVES IN THE PRESENCE OF PALLADIUM COMPLEXES

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A convenient method is proposed for the synthesis of aryl derivatives of heterocyclic compounds by the coupling reaction of heterocyclic mercury derivatives and tin derivatives with aryl and heteryl iodides in the presence of palladium complexes. In the case of organotin compounds, the reaction proceeds without the formation of side-products although mercury derivatives are usually more available.

The Gomberg—Bachmann—Hey reaction [1] is most often used to prepare aryl derivatives of heterocyclic compounds. However, this reaction requires the use of a large excess of one of the reagents. A mixture of isomers formed and the yield of the desired product is usually low. These disadvantages have recently been eliminated by the discovery of the coupling reaction of organic halides with organometallic compounds catalyzed by transition metal complexes [2-6]. We have previously shown that the introduction of organic mercury and tin derivatives instead of Grignard reagents permits expansion of the synthetic scope of the reaction and the use of organic halides containing various functional groups [7, 8]. In the present work, this reaction is used for the preparation of arylated hyterocycles.

We have found that organomercury and organotin derivatives of thiophene and furan react under mild conditions with aryl iodides in the presence of 1% palladium complex to give high yields of the corresponding derivatives of these heterocycles (see Table 1). The reactions of the organomercury compounds were carried out in the presence of two or three equivalents of iodide ion (Bu_4NI in HMPTA and THF and NaI in acetone), which acts as a nucleophilic catalyst accelerating the exchange of the organomercury compounds with palladium complex, which

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TABLE 1. Reaction Conditions and Yields of the Products of the Coupling of Organomercury and Organotin Compounds with Aryl and Heteryl Iodides[a]

Compound	Iodide	Solvent	Catalyst[b]	Reaction time, h	Yield, %: coupling product	Yield, %: oxidative demercuration product
I	IV b	Acetone (2)[d]	A	4	85	15
I	IV d	HMPTA (2)	A	1,5	86	14
I[e]	V	HMPTA (2)	A	7	70	29
I[e]	VI	HMPTA (2)	A	15	74	26
I[f]	VI	HMPTA (3)	B	5	87	10
I[f]	VII	HMPTA (3)	B	1,5	88	8
II	IV a	Acetone (3)	A	0,5	98	—
II	IV b	Acetone (3)	A	1	85	15
II	IV c	Acetone (3)	A	2	71	29
III	IV a	THF (3)	A	0,25	90	—
XI[e]	V	HMPTA (0)	C	24	80	—
XI[e, g]	VII	HMPTA (0)	D	2	96	—
Ph_2Hg	V	HMPTA (2)	A	1	75	25

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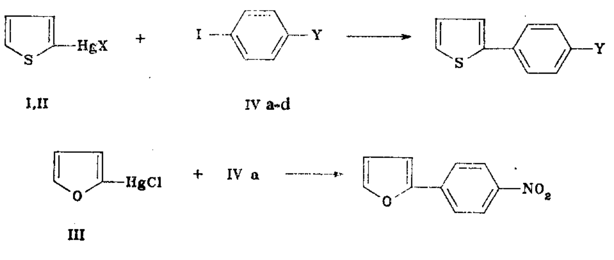
[a] The reaction was carried out at 20°C; the starting iodide concentration was 0.25 mole/liter. The catalyst was 1% palladium catalyst. [b] A) $PhpdI(PPh_3)_2$, B) $PdCl_2(PPh_3)_2$, C) $(CH_3CN)_2PdCl_2$, D) $PdCl_2$. [c] The yields were found by thin-layer chromatography and UV spectroscopy using standard compounds. [d] The number of equivalents of iodide ion are given in parentheses. [e] The starting iodide concentration was 0.5 mole/liter. [f] Bu_4NBr was used as the nucleophilic catalyst. [g] The reaction was carried out at 70°C.

is one of the steps of the catalytic cycle [2]. As a result, the reaction rate is significantly increased and the yield of the coupling product is enhanced. Oxidiative demercuration [9] leading to the formation of the corresponding biheteryls is a side reaction in the case of organomercury compounds. In the presence of atmospheric oxygen, the amount of the oxidative demercuration product increases significantly, while the rate of the coupling reaction decreases. Thus, the reaction should be carried out in an inert atmosphere for organomercury compounds.

Both symmetrical organomercury compounds and organomercury salts may be used in the coupling reaction with organic halides. Bis(2-thienyl)mercury (I), 2-thienylmercuric bromide (II), and 2-furylmercuric chloride (III) react with aryl iodides at 20°C to give good yields of the coupling products.



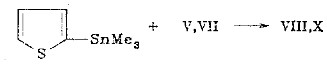
I X= 2-thienyl; II X=Br; IVa Y=NO_2, b, Y=CN, c Y=CO_2CH_3, d Y=$COCH_3$

The heterocyclic fragment may be introduced into the coupling reaction not only from the organomercury compound but from a heteryl halide. For example, the coupling of I with 3-iodopyridine (V) and 2-iodopyridine (VI) yields 3-(2-thienyl)pyridine (VIII) and 2-(2-thienyl)-pyridine (IX), respectively. The bromide ion may also be used as the nucleophilic catalyst, in addition to the iodide ion. Thus, the use of tetrabutylammonium bromide in the reaction of I with iodide VI and 4-iodopyridine (VII) gives the corresponding thienylpyridines IX and X in even higher yields than in the previous case, while the oxidative demercuration product (2,2'-bithienyl) is not formed in more than 10% yield.

V–VII VIII–X

Thienylpyridines were previously obtained by rather complicated methods and the yields were usually extremely low [10, 11].

The reaction of trimethyl-2-thienyltin (XI) with iodide V was stopped after 24 h to give 80% thienylpyridine VIII and 2,2'-bithienyl was virtually not formed. The yield of product X in the analogous reaction with iodide VII over 2 h at 70°C was 96%.



XI

Thus, organotin compounds have definite advantages over organomercury compounds: 1) the reaction with the tin derivatives occurs without the formation of side-products, 2) a nucleophilic catalyst is not required, 3) an inert atmosphere is not necessary, and 4) "ligandless" palladium, i.e., palladium complexes not containing ligands strongly bound to the palladium atom such as $(CH_3CN)_2PdCl_2$, $LiPdCl_3$, or, simply, $PdCl_2$ (see Table 2), may be used as the catalyst. On the other hand, in the case of organomercury compounds, such catalysts are rapidly converted into an inactive form and, as a result, approximately equal amounts of the coupling product and the oxidative demercuration product are formed.

On the other hand, organomercury compounds are more available and may be obtained not only using organomagnesium and organolithium compounds but also by the direct mercuration of thiophene and furan. Furthermore, only one organic group reacts in the case of the organotin compounds (for example, the Ar group in $ArSnMe_3$) while the other three groups are wasted. On the other hand, both organic groups take part in the reaction in the case of organomercury compounds.

EXPERIMENTAL

Samples of the organomercury and organotin compounds [12, 13], palladium complexes A [14], B [15], and C [16], organic halides IVa [17], IVb [18], IVc [19], IVd [20], V [21], VI [20], and VII [22] were prepared by known procedures.

Pure-grade samples of tetrabutylammonium iodide and tetrabutyl ammonium bromide were used. A sample of pure-grade sodium iodide was dried for 2 h at 150°C and 10 mm. A sample of hexamethylphosphorotriamide was maintained over 13X molecular sieves for 24 h, twice distilled over calcium hydride at 37°C (0.008 mm) and stored over 4A molecular sieves. A sample of tetrahydrofuran was maintained over KOH and distilled over lithium aluminum hydride immediately before use. High-purity acetone was used without further purification.

The UV spectra were taken on a Hitachi-124 spectrophotometer. The product yields were found by thin-layer chromatography on Silufol UV-254 plates using UV spectroscopy. The bands observed in UV light were cut and eluted with methanol. The reaction products were identified by comparison of R_f values and the UV spectra with the R_f values and UV spectra of standard compounds. The yields were calculated using the extinction coefficients found for the standard compounds.

2-(4-Nitrophenyl)furan. A mixture of 0.1515 g (0.5 mmole) 2-furylmercuric chloride (III), 0.554 g (1.5 mmole) Bu_4NI, 0.1245 g (0.5 mmole) iodide IVa, 2 ml THF, and 0.0042 g (5 μmoles) catalyst A was prepared in a flask equipped with a magnetic stirrer in an argon stream. After 15 min, thin-layer chromatography and UV spectroscopy indicated that 0.085 g (90%) coupling product had formed in the reaction mixture. Without further treatment, the reaction mixture was transferred to a silica gel plate and eluted with 3:1 hexane–chloroform to yield 0.079 g (84%) product with mp 134-135°C (134-135°C [23]).

4-(2-Thienyl)acetophenone. A mixture of 0.092 g (0.25 mmole) bis(2-thienyl)mercury (I), 0.123 g (0.5 mmole) iodide IVd, 0.186 g (0.5 mmole) Bu_4NI, 2 ml HMPTA, and 0.0042 g (5 μmoles) catalyst A was prepared in a flask equipped with a magnetic stirrer in an argon stream. After 90 min, thin-layer chromatography and UV spectroscopy indicated formation of 0.087 g (86%) of the desired product and 0.0058 g (14%) 2,2'-bithienyl. A sample of 20 ml water was added to the reaction mixture and extracted with four 10-ml portions of ether. The extracts were washed with three 20-ml portions of water. The organic layer was dried over $MgSO_4$. Thin-layer chromatography on silica gel with 3:1 hexane–chloroform eluent was used to separate 0.077 g (76%) 4-(2-thienyl)acetophenone with mp 116-117°C (115-116°C [24]).

By analogy, we obtained 2-(4-nitrophenyl)thiophene [25], 4-(2-thienyl)benzonitrile [26], methyl 4-(2-thienyl)benzoate [27], thienylpyridines VIII, IX, and X [10], and 3-phenylpyridine [28]. All the compounds isolated had physical constants in accord with literature values.

Reaction of trimethyl-2-thienyltin (XI) with 3-iodopyridine (V). A mixture of 0.124 g (0.5 mmole) XI, 0.102 g (0.5 mmole) iodide V, 1 ml HMPTA, and 0.0013 g (5 μmoles) catalyst C was prepared in a flask equipped with a magnetic stirrer and maintained for 24 h. Thin-layer chromatography and UV spectroscopy indicated 0.065 g (80%) VII in the reaction mixture.

LITERATURE CITED

1. W. E. Bachmann and R. A. Hofmann, in: Organic Reactions [Russian translation], Collection 2, Izd. Inostr. Lit., Moscow (1950), p. 244.
2. M. Kumada, Pure Appl. Chem., 52, 669 (1980).
3. L. N. Pridgen, J. Heterocycl. Chem., 12, 443 (1975).
4. K. Tamao, S. Kodama, I. Nakajima, T. Nokatsuka, A. Minato, and M. Kumada, Heterocycles, 3, 1133 (1975).
5. E. D. Thorsett and F. R. Stermitz, J. Heterocycl. Chem., 10, 243 (1973).
6. A. Minato, K. Tamao, T. Hayashi, K. Suzuki, and M. Kumada, Tetrahedron Lett., 22, 5319 (1981).
7. A. N. Kashin, I. G. Bumagina, N. A. Bumagin, and I. P. Beletskaya, Zh. Org. Khim., 17, 21 (1981).
8. N. A. Bumagin, I. O. Kalinovskii, and I. P. Beletskaya, Izv. Akad. Nauk SSSR, Ser. Khim., No. 10, 2431 (1981).
9. K. Takagi, N. Hayama, T. Okamoto, Y. Sakakibara, and S. Oka, Bull. Chem. Soc. Jpn., 50, 2741 (1977).
10. H. Wynberg, T. J. Van Bergen, and R. M. Kellog, J. Org. Chem., 34, 3176 (1969).
11. H.-S. Ryang and U. Sakurai, Chem. Commun., No. 10, 594 (1972).
12. A. G. Makarova and A. N. Nesmeyanov, Methods in Heteroorganic Chemistry, Mercury [in Russian], Izd. Nauka, Moscow (1965), p. 101.
13. J. R. Pratt, F. H. Pinkerton, and S. F. Thames, J. Organomet. Chem., 38, 29 (1972).
14. P. Fitton and E. A. Rick, J. Organomet. Chem., 28, 287 (1971).
15. A. O. King and E. Negishi, J. Org. Chem., 43, 358 (1978).
16. J. P. Haudegond, Y. Chauvin, and D. Commereuc, J. Org. Chem., 44, 3063 (1979).
17. R. Linsted, J. Elvidge, M. Wally, and J. Wilkinson, Modern Research Methods in Organic Chemistry [Russian translation], Izd. Inostr. Lit., Moscow (1959), p. 279.
18. K. Kindler, Ann. Chem., 450, 1 (1926).
19. G. E. K. Branch and A. C. Nixon, J. Am. Chem. Soc., 58, 2499 (1936).
20. K. Takagi, N. Hayama, and T. Okamoto, Chem. Lett., No. 2, 191 (1978).
21. A. Binz and C. Rath, Ann. Chem., 486, 101 (1931).
22. E. Gergely and T. Iredale, J. Chem. Soc., No. 10, 3226 (1953).
23. A. W. Johnson, J. Chem. Soc., No. 3, 895 (1946).
24. F. Friquelli, G. Marino, and A. Taticchi, J. Chem. Soc. Perkin Trans. II, No. 2, 158 (1972).
25. M. Nilsson and C. Ullenius, Acta Chem. Scand., 24, 2379 (1970).
26. Farbwerke Hoechst AG, Netherlands Patent No. 6,611,004 (1967); Chem. Abstr., 67, 33840 (1967).
27. L. Fisera, J. Kovac, and E. Komanova, Chem. Zvesti, 30, 499 (1976).
28. H. Rappoport, M. Look, and G. J. Kelly, J. Am. Chem. Soc., 74, 6293 (1952).