Palladium-Catalyzed Coupling Reactions of *N*-Methoxy-*N*-methylcarbamoyl Chloride for the Synthesis of *N*-Methoxy-*N*-methylamides

Masahiro Murakami,* Yujiro Hoshino, Hajime Ito,# and Yoshihiko Ito*
Department of Synthetic Chemistry and Biological Chemistry, Graduate School of Engineering, Kyoto University, Yoshida, Kyoto 606-01

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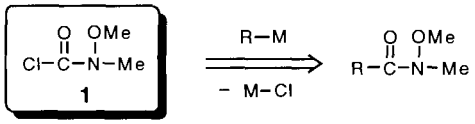
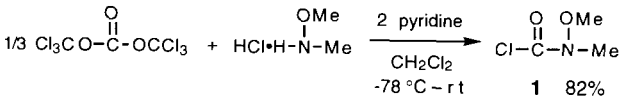
A new synthetic method of *N*-methoxy-*N*-methylamides is developed. The palladium-catalyzed coupling reaction of *N*-methoxy-*N*-methylcarbamoyl chloride furnished *N*-methoxy-*N*-methylamide in moderate to good yield, wherein a carbonyl equivalent was appended to *sp* and sp^2 carbon atoms as a versatile synthetic basis for further manipulation.

A carboxylic acid component is often used as a key functionality for multistep syntheses. In particular, *N*-methoxy-*N*-methylamides are practically useful precursors.[1,2] Various synthetic operations on the main chain skeleton are possible prior to the manipulation of the carbamoyl group, which is easily transformed into an aldehyde or a ketone at an later stage. Mostly, *N*-methoxy-*N*-methylamides have been prepared from carboxylic acids or from their derivatives.[2-4] Due to the established synthetic usefulness and versatility of *N*-methoxy-*N*-methylamides, it is of current interest to develop a new preparative method. *N*-Methoxy-*N*-methylcarbamoyl chloride (**1**) is considered as a promising synthetic block to construct *N*-methoxy-*N*-methylamides. However, examples of C–C bond forming reactions of **1** still remain very rare.[5] The fact that the known preparative procedure of **1**, described in French patents,[6] utilizes notoriously toxic phosgene gas might be relevant to the paucity of its application to C–C bond formation.



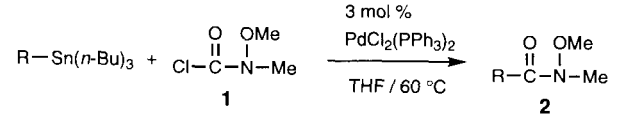
On the other hand, the palladium-catalyzed coupling reactions have proved to be especially powerful tools for C–C bond formation with a high tolerance for other functional groups.[7,8] We now report (i) a modified preparative method of **1** using solid bis(trichloromethyl) carbonate (triphosgene)[9] in place of phosgene, and (ii) the synthesis of *N*-methoxy-*N*-methylamides by the palladium-catalyzed coupling reactions of **1**. A useful synthetic C1 basis ready for further manipulation is efficiently appended to *sp* and sp^2 carbon atoms.

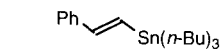
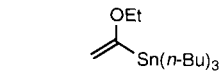
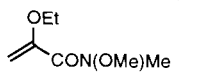
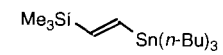
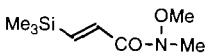
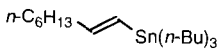
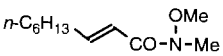
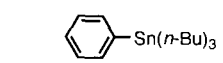
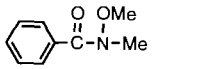
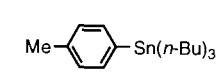
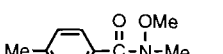
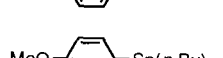
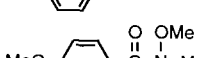
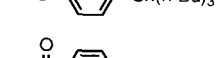
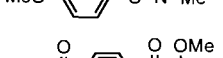
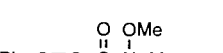
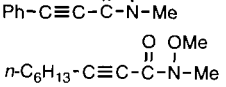
N-Methoxy-*N*-methylcarbamoyl chloride (**1**) was synthesized by the following procedure using bis(trichloromethyl) carbonate: To a mixture of (MeO)NHMe•HCl (2.93 g, 30.0 mmol) and bis(trichloromethyl) carbonate (2.97 g, 10.0 mmol) in CH_2Cl_2 (20 mL) at -78 °C was added a solution of pyridine (4.75 g, 60 mmol) in CH_2Cl_2 (10 mL) over 90 min. The reaction mixture was stirred overnight with the temperature being allowed to rise to room temperature, and then subjected to extractive workup (ether–water). The ethereal solution was successively washed with aqueous solutions of $NaHCO_3$ and NaCl, and dried over $MgSO_4$. Kugelrohr distillation (bath temperature: 70 °C/32 mmHg) afforded **1** (3.04 g, 82%) as colorless liquid. Notably, the carbamoyl chloride (**1**) is quite stable toward water.



Organostannanes, listed in Table 1, were treated with *N*-methoxy-*N*-methylcarbamoyl chloride (**1**) in the presence of a catalytic amount of $PdCl_2(PPh_3)_2$ in tetrahydrofuran (THF).[10,11] An *N*-methoxy-*N*-methylcarbamoyl moiety was successfully appended onto vinyl, aryl, and alkynyl skeletons *via* C–C bond formation to afford the corresponding *N*-methoxy-*N*-methylamides (**2**) in good yield. The mild reaction conditions tolerated the presence of a vinyl ether linkage (entry 2).[12] In cases of entries 4 and 10, the desired amides were obtained in moderate yield due to the competing homocoupling reactions of the organostannanes.[13] The coupling with an aryl ring having an

Table 1. Synthesis of N-methoxy-N-methylamides by palladium-catalyzed coupling reactions of organostannanes with **1**

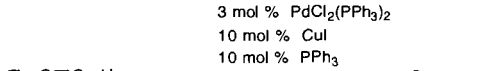


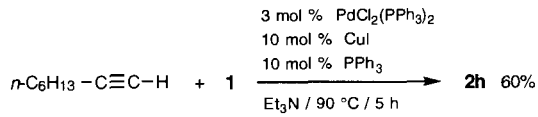
entry	R–Sn(*n*-Bu)$_3$	product	**2**, yield (%)
1			**2a**, 82
2			**2b**, 93
3			**2c**, 85
4			**2d**, 65
5			**2e**, 97
6			**2f**, 81
7			**2g**, 80
8			**2h**, <10
9	Ph–C≡C–Sn(*n*-Bu)$_3$		**2i**, 81
10	*n*-C$_6$H$_{13}$–C≡C–Sn(*n*-Bu)$_3$		**2j**, 60

ester group was sluggish (entry 8), probably due to the electronic reason (*vide infra*).

The coupling reactions of **1** may be envisaged as involving the normal oxidative addition—transmetallation—reductive elimination process common to other palladium-catalyzed cross coupling reactions. The contrasting results with substituted arylstannanes (entries 5–8) suggest that transmetallation is the rate-determining step.[7,14] Positive charge may well be developed on the aryl ring in the transition state of transmetallation under the present conditions.

Next, direct coupling reactions with terminal alkynes were carried out using the Sonogashira conditions.[15] Both aromatic and aliphatic alkynes afforded the corresponding alkynylamides in yields analogous to those observed with alkynylstannanes.





In summary, the palladium-catalyzed coupling reaction of *N*-methoxy-*N*-methylcarbamoyl chloride (**1**) provides a new preparative method of *N*-methoxy-*N*-methylamides. Various possibilities of further transformations of *N*-methoxy-*N*-methylamides signify the agent **1** to be a useful synthetic block which is equivalent to a carbonyl group.

References and Notes

Present address: Department of Chemistry, University of Tsukuba, Tsukuba, Ibaraki 305.

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10 Typical procedure for the cross-coupling reactions with organostannanes: A mixture of $PdCl_2(PPh_3)_2$ (12.6 mg, 18 μmol), tributyl(*p*-methoxyphenyl)stannane (238 mg, 0.60 mmol), and **1** (81.5 mg, 0.66 mmol) in THF (3 mL) was stirred at 60 °C for 6 h. After the mixture was cooled, the solvent was removed under vacuum. The residue was diluted with ether and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, 100 mg, 0.66 mmol)[16] was added. The mixture was passed through a short pad of silica gel to remove insoluble materials, and the eluent was subjected to preparative thin layer chromatography (silica gel, AcOEt : hexane = 1 : 3) to afford **2g** (93.4 mg, 80%).

11 A palladium(0) complex $Pd(PPh_3)_4$ showed a similar catalytic activity. The use of highly dipolar solvents such as 1-methyl-2-pyrrolidinone and *N,N*-dimethylformamide gave inferior results, although they have been frequently used in the cross-coupling reactions of organostannanes.

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13 A considerable amount of urea, $[Me(MeO)N]_2CO$, was formed together with the homocoupling product, being suggestive of **1** as an oxidant.

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