Palladium Catalyzed Cross-Methylation of Bromoheterocycles with Intramolecularly Stabilized Dimethyl Indium Reagents

Nimer Jaber [a], Herbert Schumann [b] and Jochanan Blum*[a]

[a] Department of Organic Chemistry, Hebrew University, Jerusalem 91904, Israel,
[b] Institut für Chemie, Technische Universität, Berlin, Strasse des 17. Juni 135, D-10623 Berlin, Germany

Received January 21, 2003

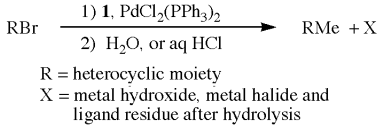
Although the intramolecularly stabilized [(3-dimethylamino)propyl]dimethylaluminum (**1a**) fails to undergo palladium-catalyzed cross-coupling with bromopyridines and with bromofuran derivatives, the analogous gallium and indium reagent **1b** and **1c** smoothly cross-methylate these and other bromoheterocycles. The cross-coupling can be performed also with the dimeric indium and gallium compounds bis(μ-[2-(dimethylamino)ethanolato-*N,O:O*]tetramethyldigallium and –diindium (**2b** and **2c**, respectively). The indium reagent is fairly air-stable and the reactions can be carried out under ambient conditions. The yields are generally very high but are influenced by steric and electronic effects.

J. Heterocyclic Chem., **40**, 565(2003).

Although aluminum alkyls have been synthesized already in 1865 [1] the application of R_3Al to lab-scale cross-coupling operations is limited owing to the pyrophoric nature of the aluminum compounds. Upon replacement of one of the alkyl groups by a chelating ligand such as the (3-dimethylamino)propyl group [2,3], the dialkylaluminum complexes, so formed, are safe enough for handling under standard laboratory conditions. [(3-Dimethylamino)propyl]dimethylaluminum (**1a**) was successfully utilized in the alkylation of various carbonyl compounds [4], as well as in palladium- and nickel-catalyzed cross-methylation of carbocyclic aryl halides and triflates [5-9]. However, in all but one case [6] this mononuclear methylating reagent failed to couple with *heterocyclic* substrates, probably because of its tendency to form highly stable adducts *via* the lone pairs of the heteroatoms [10]. In this paper we report a way to overcome this shortcoming by replacing of **1a** by either the analogous gallium or the indium reagent (**1b** or **1c**) [11].

Under our standard reaction conditions for the cross-methylation of carbocyclic aryl and benzyl bromides [5] 1 mmole of substrate, 1 mmole of the methylating reagent **1a**, 4 x 10^{-2} mmoles of dichlorobis(triphenylphosphine)-palladium, and 10 ml of anhydrous benzene heated under nitrogen atmosphere at 80 °C followed by quenching with water or 5% aqueous hydrochloric acid] (see Scheme below) neither bromopyridine derivatives nor bromofurans

Scheme



R = heterocyclic moiety
X = metal hydroxide, metal halide and ligand residue after hydrolysis

yielded methylated products, even after 24 hours. The analogous gallium complex [3-(dimethylamino)-propyl]dimethylgallium (**1b**), however, did react under these conditions both with 3-bromopyridine and with

Table 1
Cross-Methylation of Some Heterocyclic Bromides with Stabilized Group 13-Metal Methylating Reagents **1** and **2** [a]

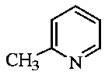
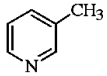
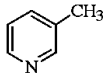
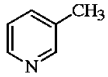
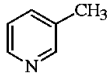
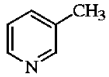
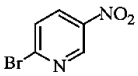
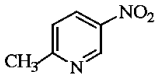
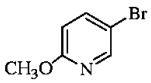
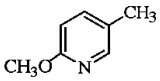
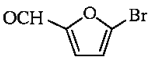
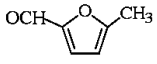
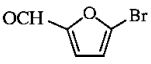
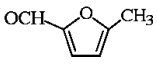
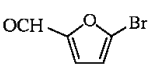
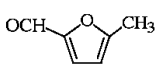
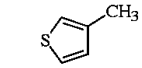
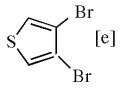
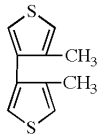
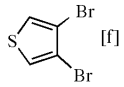
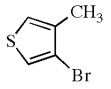
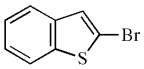
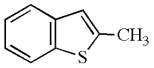
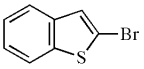
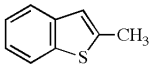
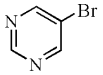
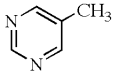
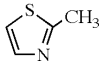
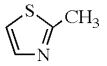
Entry	Substrate	Alkylating reagent	Time (houres)	Product	Yield (%) [b]
1		**2c**	24		68
2		**1b**	24		82
3		**1c**	19		99 [c]
4		**2a**	19		70
5		**2b**	24		78
6		**2c**	24		98 [d]
7		**2c**	24		83
8		**2c**	24		68
9		**1b**	24		90
10		**1c**	12		97
11		**2c**	24		95
12		**2c**	24		93

Table 1 (continued)

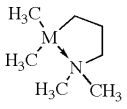
Entry	Substrate	Alkylating reagent	Time (houres)	Product	Yield (%) [b]
13	 [e]	**2c**	24		99
14	 [f]	**2c**	24		67
15		**1c**	19		98
16		**2c**	24		91
17		**2c**	24		95
18		**1c**	19		94
19		**2c**	24		84

[a] Reaction conditions as specified in the Experimental section; [b] In the experiments with the gallium and indium reagents, the missing percentage reflects on the unreacted bromides; [c] 85% after 15 hours; [d] 84% after 15 hours; [e] A 1:2 ratio of substrate:reagent was used; [f] In the presence of 0.1 mmole of 2,5-di-*tert*-butylhydroquinone.

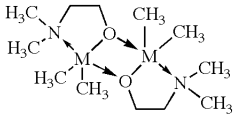
5-bromofurfural to give within 24 hours at 80 °C, 82 and 90% of the corresponding methylated products (see Table 1, entries 2 and 9). Even better results were obtained when the indium reagent **1c** was employed. This compound coupled with 3-bromopyridine and with 5-bromofurfural to give 3-picoline and 5-methylfurfural in quantitative yield within 12-19 hours (entries 3 and 10). Further cross-coupling experiments of **1c** with 2-bromobenzo[*b*]thiophene and with 2-bromothiazole furnished after 19 hours, under the aforementioned conditions, 98 and 94% of the corresponding methylated compounds (entries 15 and 18).

Although a wide range of palladium compounds can be employed in cross-coupling processes [12] the most efficient ones in the reactions with **1c** are tetrakis(triphenylphosphine)palladium and dichlorobis(diphenylphosphine)palladium. Since the latter catalyst is more stable than the palladium(0) complex and easier to handle, it was used throughout this study.

Dimeric stabilized group 13-metal alkylating reagents have a lower tendency to form adducts with heteroatom-containing compounds. Thus, in various cases bis[μ-[2-(dimethylamino)ethanolato-*N,O:O*]]tetramethyldialuminum (**2a**) [13] could be used successfully in cross-coupling with bromoheterocyclics. E.g., 3-bromopyridine reacted with this reagent at 80 °C to give after 19 hours 70% of 3-methylpyridine (entry 4). In this regard it should be recalled that the dimeric, highly pyrophoric, trimethylaluminum is also capable of coupling with 3-bromopyridine and with some other haloheterocycles [14]. A somewhat faster cross-methylation of 3-bromopyridine took placed when **2a** was replaced by the analogous gallium complex **2b** [15]. Under the conditions given in the Experimental section, it afforded 78% of the methylated product within 24 h (entry 5).



1a: M = Al
1b: M = Ga
1c: M = In



2a: M = Al
2b: M = Ga
2c: M = In

Bis[μ-[2-(dimethylamino)ethanolato-*N,O:O*]]tetramethyldiindium (**2c**) [16] proved to react faster than both **2a** and **2b** and has the advantage of being less sensitive to air. It can usually be employed under an ambient atmosphere [17]. Thus, we cross-coupled this reagent with some further representative bromoheterocycles listed in Table 1. With most bromoheterocycles including the pyrimidine derivative with two nitrogen atoms (entry 17), the cross coupling with **2c** proceeded without difficulty. The differences between the activity of 2- and 3-bromopyridine (entries 1 and 6) is attributed to the steric hindrance in the former substrate. The electronic nature of the bromide has also a marked effect on the process. The electron attracting nitro group in 3-nitro-2-bromopyridine increases the activity and outweighs the negative effect of the steric hindrance (compare entries 1 and 7). On the other hand, the electron-attracting function in 2-methoxy-5-brompyridine reduces the activity of 3-bromopyridine (compare entries 6 and 8). The reaction of **2c** with 3,4-dibromothiophene is notable. Unlike the monobromothiophene it undergoes both cross- and homocoupling to give 4,4'-dimethyl-3,3'-bithiophene [18] as the only product in quantitative yield. The homocoupling has been shown to result from a free radical chain reaction. Addition of the free radical scavenger 2,5-di-*tert*-butylhydroquinone to the reaction mixture (substrates hydroquinone ratio 1:10) completely eliminates the homocoupling and furnishes the expected 3-bromo-4-methylthiophene (*c.f.*, entries 13 and 14).

In conclusion, the palladium-catalyzed cross-coupling of bromoheterocyclic compounds with the monomeric [3-(dimethylamino)propyl]dimethylgallium (**1b**) and -indium (**1c**) proceeds well despite the fact that the corresponding aluminum complex **1a** is unable to take part in the process.

Within the series **1a**, **1b** and **1c** the indium reagent **1c** gives the highest yields. Dimeric bis[μ-[2-(dimethylamino)-ethanolato-*N,O:O*]tetramethyl digallium (**2b**) and –diindium (**2c**) react somewhat slower than **1b** and **1c**, but ultimately afford high yields. The diindium complex has the advantage of being fairly air insensitive and easy to handle. The cross-methylation of the bromohetrocycles is not associated with hydrodebromination processes observed frequently during palladium- and nickel-catalyzed cross-coupling of carbocylic bromoarenes with **1a**. Even in the reactions of the carbocyclic substrates the undesired hydrodehalogenation could be diminished or eliminated by replacement of the aluminum complex by an indium reagent [8,19].

EXPERIMENTAL

General Procedure for Cross-methylation of Bromoheterocyclics with Compounds **1** and **2**.

A thick walled glass tube was charged with 1 mmole of the heterocyclic bromide, 1 mmole of the methylation reagent, 28.5 mg (0.04 mmoles) of dichlorobis(triphenylphosphine)-palladium and 10 ml of anhydrous benzene. Except for those cases in which **2c** was employed the tube was sealed under nitrogen atmosphere. The reaction vessel was heated at 80 °C for the desired length of time. The cooled reaction mixture was worked up by one of the following methods: The nitrogen containing substrates were either concentrated and flash chromatographed on silica gel or treated with 10 ml water, and the dried organic phase concentrated and chromatographed. The furan derivative and the sulfur containing compounds were quenched with 5% aqueous hydrochloric acid prior to their purification by chromotography. The reaction products were analyzed by gas chromatography and their mass spectra and nmr compared with those of authentic samples. The picolines, 2-methylthiazole, 5-methylfurfural and 3-methylthiophene were compared directly with commercial compounds. 5-Nitro-2-picoline [20], 5-methoxy-3-picoline [21], 4,4-dimethyl-3,3'-bithiophene [18], 3-methylbenzo[*b*]thiophene [22], 3-bromo-4-methylthiophene [23] and 5-methylpyrimidine [24] were compared with samples prepared according to literature procedures.

Acknowledgement.

We thank the United States-Israel Binational Science Foundation (BSF grant No. 2000013), the Fonds der Chemischen Industrie (H.S.), the Deutsche Forschungsgemeinschaft (H.S.) and the Exchange Program between the Hebrew University of Jerusalem and the Technische Universität Berlin for financial support of this study.

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* Author to whom correspondence should be addressed; e-mail: jblum@chem.ch.huji.ac.il

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