

New DNA Intercalating Acridinic Ligands: Comparative Copper-Catalyzed *N*-Arylation Reactions of 4-Aminoacridine with Organobismuth, Organoboron and Organolead Compounds

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Abstract: Copper diacetate catalyzed phenylation of 4-aminoacridine afforded the *N*-phenyl derivative in good yields with triphenylbismuth diacetate, moderate yields with phenylboronic acid and failed with *in situ* generated phenyllead triacetate. All systems gave high yields of the *N*-monophenyl derivative in their reaction with 3,4-dimethylaniline.

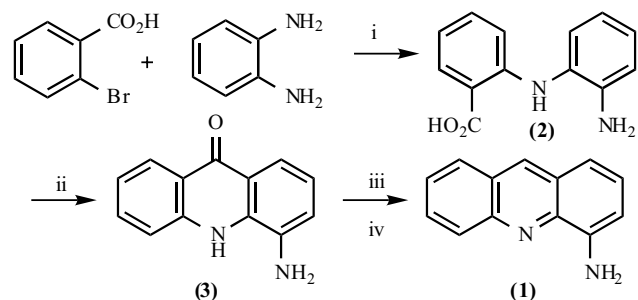
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Derivatives of acridine constitute a group of anticancer agents interacting with DNA by intercalation, or through action on topoisomerase or telomerase [1]. Among them, the 3-amino derivatives have been recently reported as a new family of anticancer agents [2]. As part of our program on the synthesis of functionalized acridines [3], we were interested in the preparation of arylaminoacridine derivatives as potential intercalating ligands. In this letter, we report our observations on the arylation of 4-aminoacridine by copper diacetate-catalyzed *N*-arylation systems using either triarylbismuth diacetate, arylboronic acid or aryllead triacetate as carrier agent for the aryl ligand transfer. In view of our interest in the application of these new and efficient systems to the arylation of heteroatoms such as oxygen, sulfur or nitrogen [4], and in particular the *N*-arylation of aromatic and heteroaromatic amines [5], we decided to compare the reactivity of various Cu(OAc)₂ catalyzed arylation systems towards 4-aminoacridine : Ph₃Bi(OAc)₂ - catalytic Cu(OAc)₂ system, PhB(OH)₂ - stoichiometric or catalytic Cu(OAc)₂ systems, and *in situ* generated PhPb(OAc)₃ - catalytic Cu(OAc)₂.

4-Aminoacridine (**1**) was selected as typical substrate for our model studies. It was prepared in four steps by Ullmann reaction between *ortho*-bromobenzoic acid and *ortho*-phenylenediamine, followed by H₂SO₄ catalyzed cyclization, reduction-dehydration and air oxidation to afford (**1**) [6] (Scheme 1).

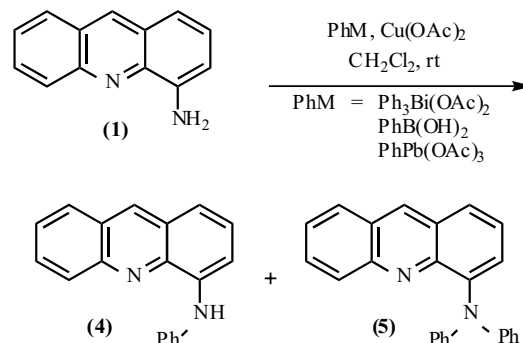
Reaction of 4-aminoacridine (**1**) with the phenylating systems led to the corresponding monophenyl and diphenyl derivatives (**4**) and (**5**) [7] (Scheme 2). However, a comparative study with the various phenylating systems showed a significant difference of reactivity. When (**1**) was

treated with triphenylbismuth diacetate and a catalytic amount of copper (II) diacetate in methylene dichloride at room temperature, high yields of the *N*-monophenyl or the *N*-diphenyl derivatives were selectively obtained, depending on the amount of bismuth reagent used. When 1.1 equivalent of the bismuth reagent was used, the *N*-monophenyl derivative (**4**) was isolated in 72% yield after 2 h at room temperature, and when 2.2 equivalents of bismuth reagent were used, the *N*-diphenyl derivative (**5**) was obtained in 85% yield after 3 h (Table 1).



i) Cu, K₂CO₃, DME, reflux, 3 h, 83%; ii) H₂SO₄, 110°C, 1 h, 31%; iii) Na, BuOH; iv) O₂, NaOH, H₂O, 80°C, 12 h, 41%

Scheme 1. Synthesis of 4-aminoacridine (**1**).



Scheme 2. Copper diacetate catalyzed phenylation of 4-aminoacridine (**1**).

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To evaluate the relative reactivity of some of the recently reported copper-catalyzed phenylating systems, we decided to compare the bismuth-mediated phenylation of (**1**) with the reactions involving the copper diacetate-phenylboronic acid and the copper diacetate-phenyllead triacetate systems. In the reaction implying phenylboronic acid as the phenyl ligand carrier, two sets of conditions were considered: the stoichiometric [8] and the catalytic [9] reactions. When a mixture of (**1**), PhB(OH)₂ (2.2 equiv), Cu(OAc)₂ (2.25 equiv) and Et₃N (8 equiv) in CH₂Cl₂ was stirred for 24 h at room temperature, only the monophenyl derivative (**4**) was isolated in a poor 18% yield. Slightly better yields were obtained when the catalytic system of Antilla-Buchwald [9] was used. The mixture of (**1**) with PhB(OH)₂ (1.5 equiv), Cu(OAc)₂ (0.1 equiv), myristic acid (0.2 equiv) and 2,6-lutidine (1 equiv) stirred in toluene for 24 h at room temperature afforded a 22% yield of (**4**), and this yield rose to 35% when a larger excess of PhB(OH)₂ (5 equiv) was used.

Table 1. Copper Diacetate Catalyzed Phenylation of 4-Aminoacridine (1)

Reaction conditions	4 (%)	5 (%)
Bismuth reagent		
Ph ₃ Bi(OAc) ₂ (1.1 equiv), Cu(OAc) ₂ (0.1 equiv), CH ₂ Cl ₂ , rt, 2 h	72	0
Ph ₃ Bi(OAc) ₂ (2.2 equiv), Cu(OAc) ₂ (0.1 equiv), CH ₂ Cl ₂ , rt, 3 h	0	85
Boron reagent		
PhB(OH) ₂ (2.2 equiv), Cu(OAc) ₂ (2.25 equiv), Et ₃ N (8 equiv), CH ₂ Cl ₂ , rt, 24 h	18	0
PhB(OH) ₂ (1.5 equiv), Cu(OAc) ₂ (0.1 equiv), myristic acid (0.2 equiv), 2,6-lutidine (1 equiv), toluene, rt, 24 h	22	0
PhB(OH) ₂ (5 equiv), Cu(OAc) ₂ (0.1 equiv), myristic acid (0.2 equiv), 2,6-lutidine (1 equiv), toluene, rt, 24 h	35	0
Lead reagent		
i) PhB(OH) ₂ , Pb(OAc) ₄ , Hg(OAc) ₂ (0.1 equiv), CHCl ₃ , 40°C, 1 h ii) (1) and Cu(OAc) ₂ (0.1 equiv), rt, 96 h	0	0

Aryllead triacetates are generally prepared and used as pure reagents. However, they can be prepared *in situ* by boron-lead exchange [10]. Therefore we decided to investigate a new system, in which the aryllead reagent is generated *in situ*, as an alternative approach to the aryllead triacetate-copper catalyzed arylation reaction systems [11]. The boron-lead exchange was performed by stirring a mixture of PhB(OH)₂, Pb(OAc)₄ and Hg(OAc)₂ (0.1 equiv)

in CHCl₃ for 1 h at 40°C. The aminoacridine (**1**) (0.9 equiv) and Cu(OAc)₂ (0.1 equiv) were then added and the mixture was stirred at room temperature for 96 h. However, only an intractable mixture was formed. When (**1**) was treated with pure 4-methoxyphenyllead triacetate and copper diacetate in CHCl₃ for 96 h, the *N*-anisyl analog of (**4**) was not detected.

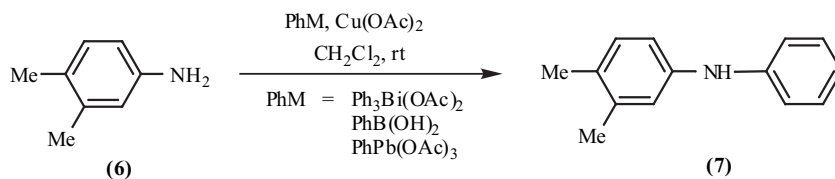
However when, after the boron-lead exchange was performed, the mixture was treated with 3,4-dimethylaniline (**6**) in the presence of copper diacetate (0.1 equiv) in CHCl₃ for 5 h at 40°C, an 85% yield of the 3,4-dimethyldiphenylamine (**7**) was obtained (Scheme 3 and Table 2). Similarly, when 3,4-dimethylaniline was treated with the boronic - copper system [PhB(OH)₂ (1.4 equiv), Cu(OAc)₂ (1.5 equiv) and Et₃N (4 equiv)] for 72 h at room temperature, a 60% yield of the corresponding diarylamine was isolated. If, in the case of 3,4-dimethylaniline, we compare these systems with the bismuth mediated system [*in situ* generated Ph₃Bi(OAc)₂ (1 equiv), Cu(OAc)₂ (0.1 equiv) for 2 h at room temperature, 86% yield] [12], the latter system appears as systematically the mildest and most efficient one.

Table 2. Copper Diacetate Catalyzed Phenylation of 3,4-Dimethylaniline (6)

Reaction conditions	7 (%)
i) PhB(OH) ₂ , Pb(OAc) ₄ , Hg(OAc) ₂ (0.1 equiv), CHCl ₃ , 40°C, 1 h ii) (6) and Cu(OAc) ₂ (0.1 equiv), 40°C, 5 h	85
PhB(OH) ₂ (1.4 equiv), Cu(OAc) ₂ (1.5 equiv), Et ₃ N (4 equiv), CH ₂ Cl ₂ , rt, 72 h	60
Ph ₃ Bi(OAc) ₂ (1 equiv), Cu(OAc) ₂ (0.1 equiv), CH ₂ Cl ₂ , rt, 2 h	86 ^a

a – reference [12]

This comparative study of the phenylation reaction with the different systems showed the superior reactivity of the bismuth - mediated system, which afforded easily and selectively in good to high yields the *N*-mono or the *N*-diphenylaminoacridine derivatives, depending on the amount of bismuth reagent which was used. This versatility is generally observed with bismuth reagents. On the other hand, the boron - mediated system afforded only moderate yields of the monophenyl derivative. In the case of the lead reagent, the *in situ* generated PhPb(OAc)₃ - catalytic Cu(OAc)₂ system failed to give any significant amount of the monophenyl derivative. Instead the substrate underwent a competitive oxidation leading to tarry polar products that could not be isolated. However, it must be noted that this new system, with *in situ* generation of the aryllead reagent, can constitute an attractive alternative to the known stoichiometric system, which involves the preparation and isolation of toxic aryllead reagents. Moreover, the variety of commercially available arylboronic acids could considerably extend the scope of the lead-mediated *N*-arylation reaction



Scheme 3 : Copper diacetate catalyzed phenylation of 3,4-dimethylaniline (**6**)

[11]. Further studies are now underway to evaluate the potential of this new method.

REFERENCES AND NOTES

- [1] Demeunynck, M.; Charmantray, F.; Martelli, A. *Curr. Pharm. Design*, **2001**, 7, 1703.
- [2] Charmantray, F.; Demeunynck, M.; Carrez, D.; Croisy, A.; Lansiaux, A.; Bailly, C.; Colson, P. *J. Med. Chem.*, **2003**, 46, 967.
- [3] Filloux, N.; Galy, J.-P. *Synlett*, **2001**, 1137. Robin, M.; Mialhe, S.; Pique, V.; Faure, R.; Galy, J.-P. *J. Heterocyclic Chem.*, **2002**, 39, 295. Lormier, A.-T.; Boyer, G.; Faure, R.; Galy, J.-P. *Heterocycles*, **2002**, 57, 449. Chiron, J.; Galy, J.-P. *Heterocycles*, **2003**, 60, 1653.
- [4] Finet, J.-P.; Fedorov, A.Yu.; Combes, S.; Boyer, G. *Curr. Org. Chem.*, **2002**, 6, 597.
- [5] a) Boyer, G.; Galy, J.-P.; Barbe, J. *Heterocycles* **1995**, 41, 487. b) Morel, S.; Boyer, G.; Couillet, F.; Galy, J.-P. *Synth. Commun.* **1996**, 26, 2443. c) Boyer, G.; Galy, J.-P. *Molecules* **1998**, 3, M89. (<http://www.mdpi.org/molbank/m0089.htm>). d) Fedorov, A.; Finet, J.-P. *Tetrahedron Lett.* **1999**, 40, 2747. e) Boyer, G.; Chatel, F.; Galy, J.-P. *Arkivoc* **2000**, 1, 563.
- [6] Compound (**1**): mp 104 °C; δ_{H} (CDCl_3 , 300 Mhz) 5.16 (2H, s, NH_2), 6.85 (1H, dd, J 6.1, 2.0, H-3), 7.25 (1H, dbr, J 8.5, H-1), 7.27 (1H, t, J 7.0, H-2), 7.40 (1H, t, J 7.5, H-7), 7.64 (1H, t, J 7.4, H-6), 7.82 (1H, d, J 8.3, H-5), 8.19 (1H, d, J 8.7, H-8) and 8.50 (1H, s, H-9); δ_{C} (CDCl_3 , 75.5 Mhz) 107.94 (C-3), 115.93 (C-1), 125.32 (C-7), 126.52 (C-2), 126.70 (C-8a)*, 126.86 (C-9a)*, 127.77 (C-8), 129.15 (C-6) $^\circ$, 129.37 (C-5) $^\circ$, 135.18 (C-9), 140.44 (C-4), 143.41 (C-4a) and 146.84 (C-10a). Atoms marked (*) or ($^\circ$) can be interchanged.
- [7] Compound (**4**): mp 112 °C; δ_{H} (CDCl_3 , 300 Mhz) 7.09 (1H, m, H-4'), 7.43 (4H, m, H-2, H-3, H-3', H-5'), 7.50 (2H, m, H-2' and H-6'), 7.56 (1H, ddd, J 8.4, 6.7, 1.1, H-7), 7.77 (1H, dd, J 8.0, 1.2, H-1), 7.78 (1H, ddd, J 8.8, 6.8, 1.4, H-6), 8.02 (1H, dd, J 8.7, 0.8, H-8), 8.27 (1H, dd, J 8.7, 0.8, H-5), 8.66 (1H, br s, NH) and 8.72 (1H, s, H-9); δ_{C} (CDCl_3 , 75.5 Mhz) 106.06 (C-3), 116.65 (C-1), 120.41 (C-2' and C-6'), 122.32 (C-4'), 125.91 (C-7), 126.78 (C-2), 127.25 (C-8a), 127.84 (C-9a), 128.09 (C-8), 129.47 (C-3' and C-5'), 129.60 (C-6), 129.75 (C-5), 135.73 (C-9), 139.90 (C-1'), 140.79 (C-4), 142.03 (C-4a) and 146.97 (C-10a).
Compound (**5**): mp 175 °C; δ_{H} (CDCl_3 , 300 Mhz) 6.96 (2H, m, H-4'), 7.15 (4H, m, H-2' and H-6'), 7.21 (4H, m, H-3' and H-5'), 7.48 (1H, ddd, J 8.4, 6.7, 1.0, H-7), 7.49 (1H, t, J 7.8, H-2), 7.62 (1H, ddd, J 8.2, 6.7, 1.4, H-6), 7.64 (1H, dd, J 7.2, 1.3, H-3), 7.86 (1H, dd, J 8.3, 1.1, H-1), 7.87 (1H, dd, J 8.1, 0.7, H-5), 7.94 (1H, br d, J 8.4, H-8) and 8.75 (1H, s, H-9); δ_{C} (CDCl_3 , 75.5 Mhz) 121.72 (C-4'), 123.06 (C-2' and C-6'), 125.33 (C-1), 125.88 (C-7), 125.77 (C-2), 126.50 (C-8a), 127.60 (C-8), 128.20 (C-9a), 128.37 (C-3), 128.72 (C-3' and C-5'), 129.62 (C-6), 130.44 (C-5), 135.76 (C-9), 144.91 (C-4), 145.52 (C-4a), 148.16 (C-10a) and 149.24 (C-1').
- [8] Chan, D.M.T.; Monaco, K.I.; Wang, R.-P.; Winter, M.P. *Tetrahedron Lett.*, **1998**, 39, 2937.
- [9] Antilla, J.C.; Buchwald, S.L. *Organic Lett.*, **2001**, 3, 2077.
- [10] Morgan, J.; Pinhey, J.T. *J. Chem. Soc. Perkin Trans. 1*, **1990**, 715.
- [11] a) Barton, D.H.R.; Yadav-Bhatnagar, N.; Finet, J.-P.; Khamsi, J. *Tetrahedron Lett.*, **1987**, 30, 3111. b) Barton, D.H.R.; Donnelly, D.M.X.; Finet, J.-P.; Guiry, P.J. *J. Chem. Soc. Perkin Trans. 1*, **1991**, 2095.
- [12] Combes, S.; Finet, J.-P. *Tetrahedron*, **1998**, 54, 4313.