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Buchwald–Hartwig Amination Approach for the Synthesis of Functionalized 1,2,3,4-Tetrahydroacridine Derivatives

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Electrophilic 1,2,3,4-tetrahydroacridin-9-yl trifluoromethanesulfonates have been prepared and applied for the first time in the synthesis of functionalized tacrines with high efficacy by using the Buchwald–Hartwig amination reaction. Remarkably, secondary, poor nucleophilic, and functionalized amines also reacted efficiently by using our conditions. The versatility and convenience of these highly reactive derivatives is illustrated through their application in other valuable C–C (Sonogashira, Suzuki, and cyanation cross-coupling), C–S, and C–O bond-forming reactions under palladium catalysis.

Introduction

Nitrogen-containing heterocycles are key functional components of many drugs and other biologically active molecules. Tacrines, such as 1,2,3,4-tetrahydroacridine-9-amine (tacrine: THA, **1**), is arguably a key structural motif in bioorganic chemistry, medicinal chemistry and drug discovery (Figure 1).[1] However, THA (**1**) is not naturally occurring and has therefore attracted interest as a target for synthesis and further modifications.[2]

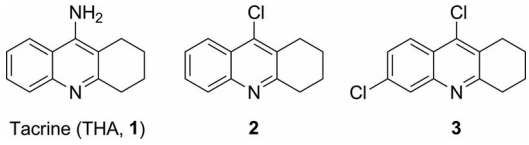
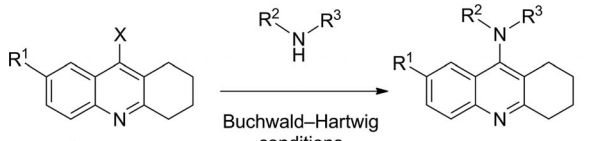


Figure 1. Structure of Tacrine (**1**), 9-chloro-1,2,3,4-tetrahydroacridine (**2**), and 6,9-dichloro-1,2,3,4-tetrahydroacridine (**3**).

Tacrine (Cognex®) was the first approved cholinesterase inhibitor by the Food and Drug Administration agency in 1993 for the palliative treatment of Alzheimer diseases, related loss of memory and cognitive functions.[3] Owing to its potent inhibition of acetylcholine esterase (AChE) and butylcholinesterase (BuChE),[4] the chemical modification of tacrine is of great interest for the development of multipotent drugs prepared by conjugation of the THA scaffold with other medicinally relevant groups.[5] Recently, numerous multifunctional tacrine homo- and heterodimer co-drugs have been designed and synthesized with the aim of enlarging and improving its pharmacological profile beyond its ability to serve as an AChE or BuChE inhibitor.[6] In this context, the development of the multi-target-directed ligand strategy requires reliable and selective synthetic methods possessing broad substrate scope to assemble tacrines, and 1,2,3,4-tetrahydroacridines.[7] Traditional strategies based on direct acylation or alkylation of poorly nucleophilic 9-aminotacrine with appropriate electrophiles usually suffer from restricted substrate scope and require harsh and hazardous experimental conditions.[8,9] Alternatively, functionalization of the 9-position can be effected either by nucleophilic aromatic substitution (S_NAr),[10] or Buchwald–Hartwig amination (BHA)[11] of 9-chloro-1,2,3,4-tetrahydroacridine (**2**, Figure 1). A significant breakthrough has been recently disclosed by Renard and co-workers, and by Carlier et al.[12] in the development of a Pd-catalyzed amination reaction of 9-chloro-tetrahydroacridine (**2**) and 6,9-dichloro-1,2,3,4-tetrahydroacridine (**3**) for the preparation of *N*-alkyltacrines (Figure 1, Scheme 1).



4: R^1 = Cl, X = Cl
5: R^1 = Cl, X = Br
6: R^1 = H, X = OTf
7: R^1 = Cl, X = OTf

R^2, R^3 = H, alkyl, aryl, heteroaryl, C(O)Ph, S(O)*t*Bu, $P(O)(OEt)_2$

Scheme 1. Buchwald–Hartwig amination reactions of tetrahydroacridine derivatives **4**–**7**.

Notwithstanding the efficiency of these recent accounts for the cross-coupling of **2** and **3**, a broadly applicable method enabling the use of aromatic, heteroaromatic, secondary, non-nucleophilic nitrogen coupling partners, as well

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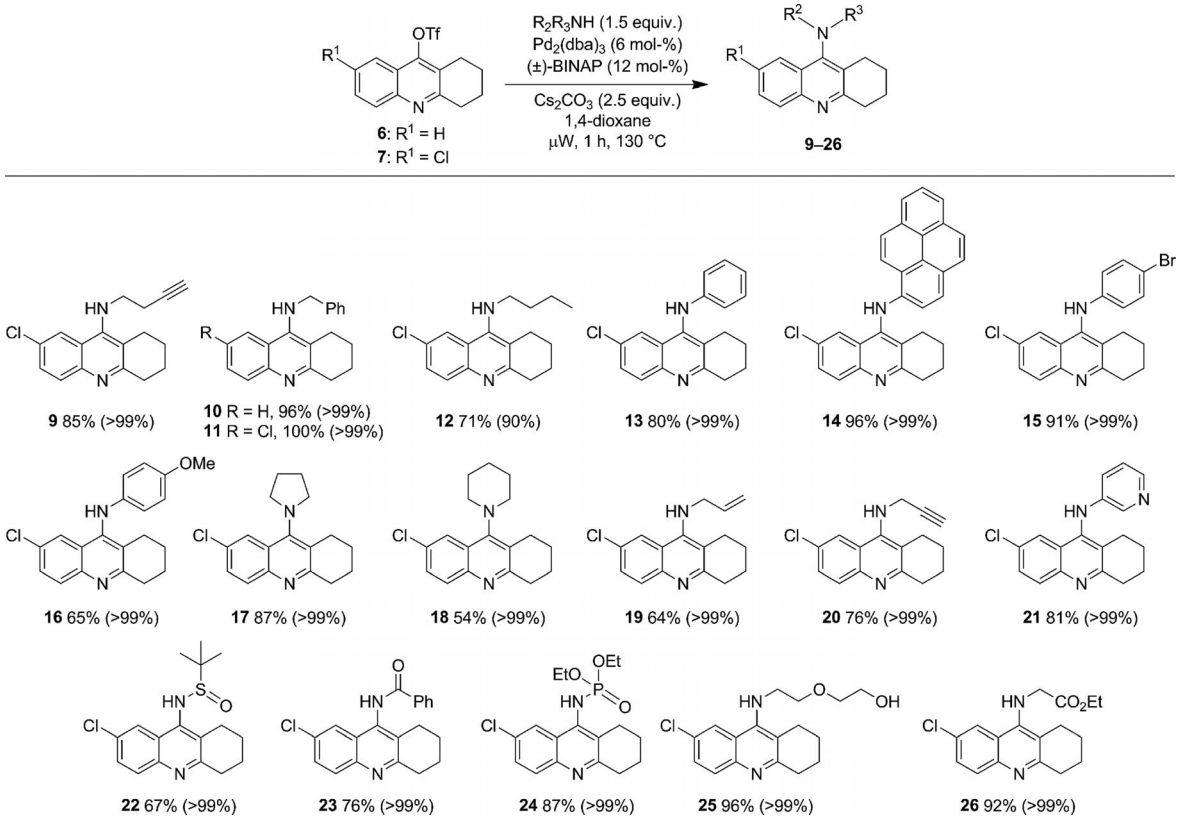
as functionalized amine-containing substrates, is still lacking. Given the importance of the tacrine pharmacophore in medicinal chemistry,[1–6] and in the framework of our synthetic efforts towards medicinally relevant tacrine-hybrids for the reactivation of phosphylated AChE,[13] we recognized the need for tetrahydroacridine derivatives with enhanced electrophilicity for application in BHA. More highly activated derivatives such as 9-bromo-, and 9-OTf-1,2,3,4-tetrahydroacridines **5**–**7** could fulfill this requirement, resulting in increased efficiency of the BHA reactions with a wider scope of application (Scheme 1). Our specific interest in the development of more reactive tetrahydroacridines **5**–**7** for use in BHA is driven by the failure of 7,9-dichlorotetrahydroacridine (**4**) to react selectively and efficiently with certain functionalized amines of interest during the synthesis of tacrine hybrids by using the reported protocols.[12] Herein we report the synthesis of 9-bromo-7-chloro-1,2,3,4-tetrahydroacridine (**5**) and 1,2,3,4-tetrahydroacridin-9-yl trifluoromethanesulfonates **6**–**7**, and their use in the microwave-assisted Buchwald–Hartwig amination reaction with various amines.

Results and Discussion

Prior to embarking on BHA reactions, our initial efforts focused on the synthesis of 9-bromo-7-chloro-1,2,3,4-tetrahydroacridine (**5**), 1,2,3,4-tetrahydroacridin-9-yl trifluoromethanesulfonate (**6**) and 7-chloro-1,2,3,4-tetrahydroacridin-9-yl trifluoromethanesulfonate (**7**, Scheme 1). To this end, **5** was obtained in modest unoptimized yield (23%) by $P(O)Br_3$-mediated cyclodehydration reaction of 5-chloroanthranilic acid with cyclohexanone.[14] With the aim of analyzing the reactivity of 9-halo-tetrahydroacridines derivatives in BHA reactions, the synthesis of 9-iodo-7-chloro-1,2,3,4-tetrahydroacridine was initially considered. However, owing to the inefficiency of the reported procedure in our hands,[15] our attention moved to the preparation of acridin-9-yl trifluoromethanesulfonates. Accordingly, tetrahydroacridines **6** and **7** were prepared on a gram-scale in 78% and 87% isolated yields, respectively, as stable white crystalline solids from commercially available 1,2,3,4-tetrahydroacridin-9(10*H*)-one and 7-chloro-1,2,3,4-tetrahydroacridin-9(10*H*)-one (**8**), respectively.[16] With substrate **4**[14] and new electrophiles **5**–**7** in hand we next evaluated their reactivity in the BHA reaction.

In an initial experiment the direct reactions of unprotected 1-amino-3-butyne, a bifunctional linker, and 1,2,3,4-tetrahydroacridines **4**–**7** were explored. Four electrophiles **4**–**7** were reacted by using a modified BHA procedure, under microwave irradiation in dioxane in the presence of a tris(dibenzylideneacetone)dipalladium(0) [$Pd_2(dba)_3$] and 2,2′-bis(diphenylphosphino)-1,1′-binaphthalene [(±)-BINAP] catalyst system, with Cs_2CO_3 as the base.[12] After 1.5 h of reaction at 130 °C, the conversion of starting electrophiles **4**–**7** was determined by analyzing the crude reaction mixtures by ^{1}H NMR spectroscopy. Although the use



Scheme 2. Substrate scope for the microwave-assisted Buchwald–Hartwig Amination reaction with **6** and **7** (isolated yields after column chromatography are given, and conversion of starting triflates are given in brackets and were determined by ^{1}H NMR spectroscopy).

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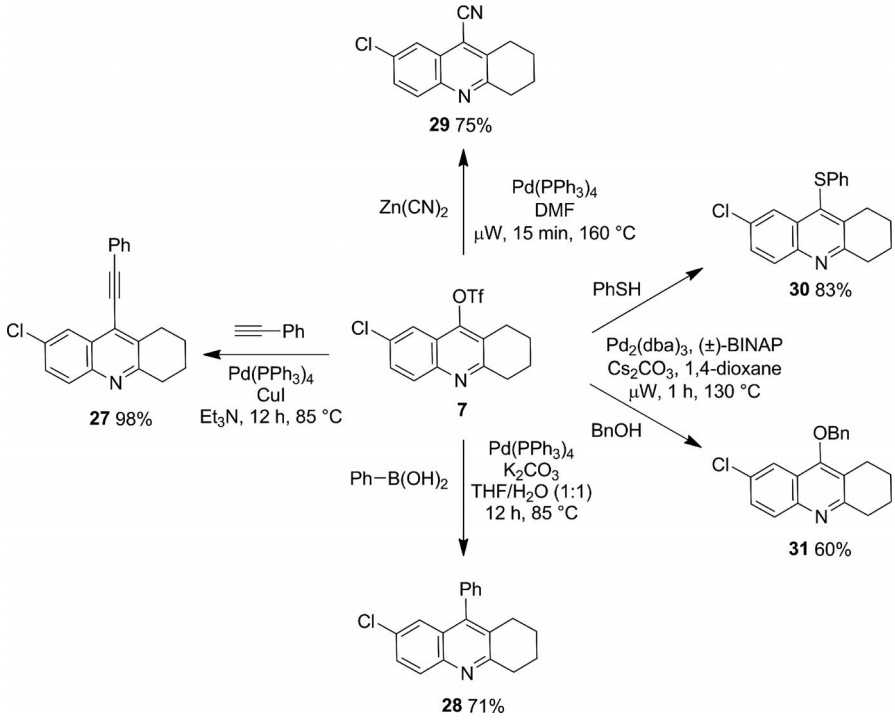
of chloride **4** resulted in moderate conversion (40–60%), we were pleased to observe that bromide **5** and the analogous triflate **7** underwent complete conversion (>99%) forming the desired adduct **9** in excellent isolated yield (92% and 85%, respectively) after column chromatography on silica gel (Supporting Information and Scheme 2). In view of these promising preliminary results, demonstrating the high reactivity of triflate **7** combined with its ease of preparation, the scope of the amination reaction was evaluated by using additional selected amines. A brief survey of temperature and reaction conditions, revealed that smooth arylation of benzylamine in 1,4-dioxane with either **6** or **7** occurred at 100–130 °C after 1 h, to furnish benzylated tacrines **10** and **11** in quantitative yield (Scheme 2). Gratifyingly, exposure of primary amines, such as *n*-butylamine, aniline, and bulky 1-aminopyrene, resulted in the formation of expected alkylated tacrines **12**–**14** in excellent isolated yields (Scheme 2), which constituted a substantial improvement relative to previous reports that used chloride **4**.[12]

Significantly, the method is compatible with both electron-rich and electron-poor anilines bearing a variety of synthetically valuable functional groups (Scheme 2). Indeed, 4-bromoaniline is suitable and cross-coupling product **15** was obtained selectively in excellent yield (91%), highlighting the high reactivity of triflate **7** in BHA reactions. Electron-rich anilines, such as *p*-anisidine, exhibited good reactivity and gave **16** in 65% yield. Secondary cyclic amines, such as pyrrolidine and piperidine, also underwent coupling (87 and 54% for **17** and **18**, respectively) under otherwise identical reaction conditions. These results suggest that the cross-coupling of **7** with secondary amines is less sensitive to steric hindrance in contrast to previous reports that used chloro derivative **4**, in which cyclic secondary amines were inferior cross-coupling partners.[12a] Attempts to further expand the scope of BHA to include allylamine and propargylamine were fruitful and expected adducts **19** and **20** were isolated in acceptable chemical yields (64 and 76%, respectively). Notably, the use of a heteroaromatic nucleophile, such as 3-aminopyridine, also led to cross-coupled product **21** in excellent isolated yield (81%). Other nitrogen nucleophiles, such as *tert*-butylsulfinamide, benzamide and diethyl phosphoramidate, also successfully engaged in BHA reactions under our optimized conditions. To our delight, the reactions displayed, unexpectedly, not only total conversion of reagent **7** but also a high chemical efficiency; the sulfinylated, acylated and phosphorylated tacrines were obtained in good to excellent isolated yields (67, 76 and 87% for **22**, **23** and **24**, respectively). Amine substrates containing additional functional groups, such as 2-(2-aminothoxy)ethanol and glycine ethyl ester, were also subjected to the Pd-catalyzed BHA reaction with triflate **7** to give aminated adducts **25** and **26** in excellent yields (96 and 92%, respectively).

It is noteworthy that total conversion of triflates **6** and **7** was observed for the majority of the reactions, with significantly reduced reaction times and lower temperature. Furthermore, lower quantities of reduced byproducts were formed under BHA conditions by using the triflates; this is a significant drawback of the existing BHA protocols which use less reactive substrates, such as **2**–**4**.[12] Besides these features, a wide range of functionality was tolerated, including unprotected alkynes, free alcohols, olefins, bromo- and chloroarenes, ethers and ester groups. Additionally, in the cross-coupling reactions, complete chemoselectivity of the



Scheme 3. Versatility of triflate **7** in C–C, C–S and C–O bond-forming reactions; THF = tetrahydrofuran.

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triflate group versus the chloro substituent was always observed. Consequently, this method provides efficient access to new tacrine derivatives containing functionality suitable for further potential ligation to a variety of other valuable building blocks through Pd cross-coupling (**9**, **15**, **19**, **20**), click chemistry (**9**, **20**), metathesis (**19**), thiol-ene reaction (**9**, **19**, **20**), and ester- and amide-bond formation (**25**, **26**).

To extend the scope of the cross-coupling methodology to other 1,2,3,4-tetrahydroacridines, the application of triflate **7** in other synthetically useful Pd-catalyzed C–C bond forming reactions, such as Sonogashira, Suzuki, and cyanation cross-couplings, was investigated (Scheme 3).

Sonogashira reaction of **7** with phenyl acetylene afforded desired product **27** in excellent isolated yield (98%).[2a] Furthermore, it was also possible to access 9-phenyltetrahydroacridine derivative **28** in 71% yield under Suzuki cross-coupling conditions, along with a minor bisarylated product (28%) which resulted from secondary arylation of the 7-chloro group. Synthetically valuable 9-CN-tetrahydroacridine derivative **29** was obtained in 75% yield through cyanation of triflate **7** by using $Zn(CN)_2$ under Pd-catalysis in dry dimethylformamide (DMF), along with a minor amount of biscyanated product (25%). Finally, we explored C–S and C–O bond-formation by using thiophenol and benzyl alcohol, respectively. Gratifyingly, mercaptotetrahydroacridine and benzyloxytetrahydroacridine derivatives **30** and **31** were formed after 1 h under our optimized microwave conditions in 83 and 60% yields, respectively.

Conclusions

In summary, we have demonstrated 1,2,3,4-tetrahydroacridin-9-yl trifluoromethanesulfonates **6** and **7** to be superior substrates in Buchwald–Hartwig amination reactions, which display broader substrate scope and applicability relative to previously employed 9-chloro derivatives. A variety of amines (alkylamines, anilines, heteroarylamines) were shown to react smoothly under microwave conditions to give corresponding *N*-substituted tacrines in reasonable to excellent yields. Even secondary and poorly nucleophilic amines, such as *tert*-butylsulfinamide, benzamide and diethyl phosphoramidate, were shown to react efficiently, and functional groups, including terminal alkynes, alcohols, bromo- and chloro-arenes, ethers, esters, and olefins, were tolerated. Investigation of other Pd-catalyzed C–C, C–O and C–S bond-forming reactions also show promise for the development of practical routes to 9-substituted 1,2,3,4-tetrahydroacridines, which extends the application of this heterocycle in drug design.

Experimental Section

General Procedure A for the Palladium-Catalyzed Amination Reaction under Microwave Irradiation: A microwave tube (0.5–2 mL) containing a magnetic stirrer bar was charged with 1,2,3,4-tetrahydroacridine trifluoromethanesulfonate derivative (1 equiv., 0.137 mmol), $Pd_2(dba)_3$ (8 mg, 6 mol-%), (±)-BINAP (11 mg, 12 mol-%) and Cs_2CO_3 (2.5 equiv., 0.343 mmol). The vessel was sealed with a microwave septum and purged with argon. Degased 1,4-dioxane (1.7 mL) and amine (1–1.5 equiv.) were introduced through the septum. The resulting mixture was heated by using a Biotage® Initiator Microwave Synthesizer Apparatus to 130 °C for 1 h. After cooling, the reaction mixture was concentrated and purified by column chromatography.

***N*-(But-3-yn-1-yl)-7-chloro-1,2,3,4-tetrahydroacridin-9-amine (9):** Following general procedure A, 1-amino-3-butyne (17 μL, 0.205 mmol) gave **9** as a yellow oil (31 mg, 80%). R_f (petroleum ether/EtOAc/MeOH, 6:4:0.02) = 0.33. IR (neat): $\tilde{\nu}$ = 3301, 2934, 2861, 1581, 1555, 1487, 1433, 1349, 1338, 1126 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.95 (d, J = 2.33 Hz, 1 H), 7.83 (d, J = 8.96 Hz, 1 H), 7.48 (dd, J = 2.24, 8.85 Hz, 1 H), 4.22 (t, J = 6.87 Hz, 1 H), 3.57 (q, J = 6.37 Hz, 2 H), 3.04 (t, J = 5.96 Hz, 2 H), 2.79 (t, J = 6.41 Hz, 2 H), 2.46 (dt, J = 2.68, 6.20 Hz, 2 H), 2.14 (t, J = 2.61 Hz, 1 H), 1.96–1.90 (m, 4 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 159.30, 149.21, 145.97, 130.67, 129.76, 129.25, 121.95, 121.72, 118.90, 81.63, 71.15, 47.53, 34.17, 24.84, 23.02, 22.82, 21.01 ppm. HRMS (ESI): calcd. for $C_{17}H_{17}ClN_2$ $[M + H]^+$ 285.1153; found 285.1159.

***N*-Benzyl-1,2,3,4-tetrahydroacridin-9-amine (10):** Following general procedure A, 1,2,3,4-tetrahydroacridin-9(10*H*)-one (50 mg, 0.151 mmol) and benzylamine (25 μL, 0.227 mmol) gave **10** as a yellow oil (42 mg, 96%). R_f (petroleum ether/EtOAc/MeOH, 1:1:0.02) = 0.15. IR (neat): $\tilde{\nu}$ = 3317, 3060, 2932, 2859, 1581, 1561, 1495, 1452, 1418, 1349, 1123, 1028 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.96 (q, J = 8.64 Hz, 2 H), 7.57 (t, J = 7.58 Hz, 1 H), 7.39–7.30 (m, 6 H), 4.61 (s, 2 H), 4.15 (br. s, 1 H), 3.07 (t, J = 6.27 Hz, 2 H), 2.64 (t, J = 6.31 Hz, 2 H), 1.94–1.82 (m, 4 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 159.93, 150.51, 147.77, 139.92, 129.09, 129.00 (2 C), 128.47, 127.86, 127.76 (2 C), 124.09, 122.88, 120.59, 117.12, 53.78, 34.29, 24.94, 23.14, 22.93 ppm. HRMS (ESI): calcd. for $C_{20}H_{20}N_2$ $[M + H]^+$ 289.1699; found 289.1696.

***N*-Benzyl-7-chloro-1,2,3,4-tetrahydroacridin-9-amine (11):** Following general procedure A, benzylamine (22 μL, 0.205 mmol) gave **11** as a yellow wax (44 mg, quant.). R_f (petroleum ether/EtOAc, 1:1) = 0.23. IR (neat): $\tilde{\nu}$ = 3065, 3028, 2930, 2859, 1580, 1554, 1484, 1452, 1427, 1346, 1118, 1078 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.97 (d, J = 2.33 Hz, 1 H), 7.87 (d, J = 9.01 Hz, 1 H), 7.50 (dd, J = 2.31, 9.01 Hz, 1 H), 7.39–7.28 (m, 5 H), 4.58 (s, 2 H), 4.11 (br. s, 1 H), 3.04 (t, J = 6.37 Hz, 2 H), 2.59 (t, J = 6.31 Hz, 2 H), 1.92–1.81 (m, 4 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 159.18, 149.83, 146.04, 139.56, 130.62, 129.73, 129.36, 129.08 (2 C), 128.04, 127.81 (2 C), 122.18, 121.28, 117.99, 53.84, 34.12, 24.83, 22.98, 22.77 ppm. HRMS (ESI): calcd. for $C_{20}H_{19}ClN_2$ $[M + H]^+$ 323.1310; found 323.1313.

***N*-Butyl-7-chloro-1,2,3,4-tetrahydroacridin-9-amine (12):** Following general procedure A, *n*-butylamine (20 μL, 0.205 mmol) gave **12** as a yellow oil (28 mg, 71%). R_f (petroleum ether/EtOAc, 1:1) = 0.24. IR (neat): $\tilde{\nu}$ = 3339, 2927, 2860, 1578, 1556, 1487, 1431, 1359, 1263, 1115, 1081 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.93 (d, J = 2.32 Hz, 1 H), 7.82 (d, J = 9.03 Hz, 1 H), 7.47 (dd, J = 2.33, 9.01 Hz, 1 H), 3.87 (br. s, 1 H), 3.46 (t, J = 7.13 Hz, 2 H), 3.05–3.01 (m, 2 H), 2.70–2.66 (m, 2 H), 1.93–1.89 (m, 4 H), 1.65 (quint, J = 7.28 Hz, 2 H), 1.43 (sext, J = 7.39 Hz, 2 H), 0.96 (t, J = 7.32 Hz, 3 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 158.96, 150.21, 146.11, 130.59, 129.22, 129.15, 122.25, 121.09, 116.84, 49.39, 34.17, 34.02, 24.84, 23.10, 22.84, 20.24, 13.99 ppm. HRMS (ESI): calcd. for $C_{17}H_{21}ClN$ $[M + H]^+$ 289.1466; found 289.1462.

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***N*-Phenyl-7-chloro-1,2,3,4-tetrahydroacridin-9-amine (13):** Following general procedure A, aniline (19 μL, 0.205 mmol) gave **13** as a yellow solid (34 mg, 80%). R_f (petroleum ether/EtOAc, 7:3) = 0.39. IR (neat): $\tilde{\nu}$ = 3247, 3041, 2948, 2869, 1669, 1579, 1558, 1496, 1435, 1404, 1374, 1199, 1131 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.92 (d, J = 9.03 Hz, 1 H), 7.76 (d, J = 2.32 Hz, 1 H), 7.52 (dd, J = 2.35, 9.01 Hz, 1 H), 7.24–7.19 (m, 2 H), 6.92 (t, J = 7.39 Hz, 1 H), 6.67 (d, J = 8.13 Hz, 2 H), 5.83 (br. s, 1 H), 3.13 (t, J = 6.51 Hz, 2 H), 2.72 (t, J = 6.42 Hz, 2 H), 2.00–1.80 (m, 4 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 160.50, 145.89, 144.30, 142.55, 130.99, 130.60, 129.70, 129.52 (2 C), 124.82, 124.24, 122.25, 121.05, 116.56 (2 C), 34.15, 25.61, 22.87, 22.70 ppm. HRMS (ESI): calcd. for $C_{19}H_{17}ClN_2$ $[M + H]^+$ 309.1153; found 309.1151.

***N*-(Pyren-2-yl)-7-chloro-1,2,3,4-tetrahydroacridin-9-amine (14):** Following general procedure A, 1-aminopyrene (45 mg, 0.206 mmol) gave **14** as a green solid (57 mg, 96%). R_f (petroleum ether/EtOAc, 8:2) = 0.14. IR (neat): $\tilde{\nu}$ = 3361, 3037, 2920, 2853, 1601, 1551, 1512, 1482, 1466, 1370, 1333, 1272, 1089 cm^{-1}. ^1H NMR (500 MHz, DMSO): δ = 8.86 (br. s, 1 H), 8.68 (d, J = 9.29 Hz, 1 H), 8.22–8.18 (m, 3 H), 8.09 (d, J = 2.27 Hz, 1 H), 8.04–7.99 (m, 3 H), 7.96–7.94 (m, 2 H), 7.66 (dd, J = 2.27, 9.13 Hz, 1 H), 6.96 (d, J = 8.60 Hz, 1 H), 3.08–3.04 (m, 2 H), 2.72–2.67 (m, 1 H), 2.35–2.31 (m, 1 H), 1.91–1.59 (m, 4 H) ppm. ^{13}C NMR (125 MHz, DMSO): δ = 160.51, 145.60, 143.54, 139.59, 131.54, 131.21, 130.71, 129.40, 129.11, 127.44, 126.41, 126.06, 125.91, 125.33, 124.86, 124.77, 124.48, 124.45 (2 C), 124.30, 123.94, 122.40, 122.35, 119.56, 115.16, 33.46, 25.59, 22.31, 21.99 ppm. HRMS (ESI): calcd. for $C_{29}H_{21}ClN_2$ $[M + H]^+$ 433.1466; found 433.1475.

***N*-(4-Bromophenyl)-7-chloro-1,2,3,4-tetrahydroacridin-9-amine (15):** Following general procedure A, 4-bromoaniline (24 mg, 0.137 mmol) was introduced before sealing the vessel and gave **15** as a bright yellow solid (48 mg, 91%). R_f (petroleum ether/EtOAc, 75:25) = 0.29. IR (neat): $\tilde{\nu}$ = 3244, 3108, 2927, 2855, 1669, 1577, 1506, 1487, 1404, 1200, 1181, 1132 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.48 (br. s, 1 H), 8.12 (d, J = 9.14 Hz, 1 H), 7.89 (d, J = 4 Hz, 1 H), 7.52–7.49 (m, 3 H), 6.93 (d, J = 8.55 Hz, 2 H), 3.26 (t, J = 6.23 Hz, 2 H), 3.39 (t, J = 6.31 Hz, 2 H), 1.93–1.81 (m, 4 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 155.33, 150.93, 139.53, 136.38, 133.24, 132.67, 132.60, 129.18, 128.37, 125.44, 123.84, 122.16, 119.92, 118.82, 117.80, 28.67, 26.30, 21.72, 20.60 ppm. HRMS (ESI): calcd. for $C_{19}H_{16}BrClN_2$ $[M + H]^+$ 387.0257; found 387.0258.

***N*-(4-Methoxyphenyl)-7-chloro-1,2,3,4-tetrahydroacridin-9-amine (16):** Following general procedure A, *p*-anisidine (25 mg, 0.205 mmol) was introduced before sealing the vessel and gave **16** as a yellow solid (30 mg, 65%). R_f (petroleum ether/EtOAc, 75:25) = 0.18. IR (neat): $\tilde{\nu}$ = 3271, 3108, 2947, 2840, 1779, 1667, 1581, 1559, 1507, 1436, 1404, 1245, 1198, 1170, 1134 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.46 (br. s, 1 H), 7.95 (d, J = 9.03 Hz, 1 H), 7.69 (d, J = 2.12 Hz, 1 H), 7.49 (dd, J = 2.16, 8.93 Hz, 1 H), 6.97 (dd, J = 8.72, 69.25 Hz, 4 H), 3.82 (s, 3 H), 3.11 (t, J = 5.92 Hz, 2 H), 2.48 (t, J = 5.92 Hz, 2 H), 1.88–1.81 (m, 4 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 159.09, 153.65, 152.26, 136.99, 133.57, 132.25, 131.74, 126.03 (2 C), 123.93, 122.19, 117.42, 115.30 (2 C), 114.59, 55.81, 28.50, 24.37, 21.73, 20.63 ppm. HRMS (ESI): calcd. for $C_{20}H_{19}ClN_2O$ $[M + H]^+$ 339.1259; found 339.1260.

7-Chloro-9-(pyrrolidin-1-yl)-1,2,3,4-tetrahydroacridine (17): Following general procedure A, pyrrolidine (57 μL, 0.206 mmol) gave **17** as a pale yellow wax (34 mg, 87%). R_f (petroleum ether/EtOAc, 9:1) = 0.20. IR (neat): $\tilde{\nu}$ = 2929, 2858, 1667, 1476, 1450, 1427, 1380, 1150, 1101 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.89–7.87 (m, 2 H), 7.48 (dd, J = 2.33, 9.00 Hz, 1 H), 3.38 (t, J = 6.46 Hz, 4 H), 3.09 (t, J = 6.63 Hz, 2 H), 2.81 (t, J = 6.32 Hz, 2 H), 2.15–2.08 (m, 4 H), 1.98–1.91 (m, 2 H), 1.87–1.81 (m, 2 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 160.77, 150.30, 146.29, 130.67, 130.59, 129.95, 129.08, 127.36, 123.02, 51.28 (2 C), 34.05, 26.62 (2 C), 26.57, 22.99 (2 C) ppm. HRMS (ESI): calcd. for $C_{17}H_{19}ClN_2$ $[M + H]^+$ 287.1310; found 287.1310.

7-Chloro-9-(piperidin-1-yl)-1,2,3,4-tetrahydroacridine (18): Following general procedure A, piperidine (16 μL, 0.164 mmol) gave **18** as a colorless oil (22 mg, 54%). R_f (petroleum ether/EtOAc/MeOH, 9:1:0.02) = 0.32. IR (neat): $\tilde{\nu}$ = 2932, 2854, 1567, 1479, 1450, 1428, 1388, 1099 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.09 (d, J = 2.36 Hz, 1 H), 7.86 (d, J = 8.89 Hz, 1 H), 7.49 (dd, J = 2.36, 8.92 Hz, 1 H), 3.23 (t, J = 5.02 Hz, 4 H), 3.09 (t, J = 6.69 Hz, 2 H), 2.90 (t, J = 6.37 Hz, 2 H), 1.96–1.89 (m, 2 H), 1.88–1.74 (m, 8 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 160.80, 153.62, 146.26, 130.61, 130.40, 129.15, 128.23, 127.00, 123.29, 52.08 (2 C), 34.16, 27.11 (2 C), 27.07, 24.70, 23.11, 22.91 ppm. HRMS (ESI): calcd. for $C_{18}H_{21}ClN_2$ $[M + H]^+$ 301.1466; found 301.1472.

***N*-Allyl-7-chloro-1,2,3,4-tetrahydroacridin-9-amine (19):** Following general procedure A, allylamine (16 μL, 0.205 mmol) gave **19** as a white powder (24 mg, 64%). R_f (petroleum ether/EtOAc, 1:1) = 0.16. IR (neat): $\tilde{\nu}$ = 3290, 3089, 2945, 2871, 1669, 1584, 1519, 1417, 1349, 1325, 1199, 1176, 1131 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.91 (d, J = 2.26 Hz, 1 H), 7.85 (d, J = 9.13 Hz, 1 H), 7.48 (dd, J = 2.49, 8.92 Hz, 1 H), 6.05–5.95 (m, 1 H), 5.38 (dd, J = 1.51, 17.03 Hz, 1 H), 5.24 (dd, J = 1.30, 10.26 Hz, 1 H), 4.05 (d, J = 5.43 Hz, 2 H), 3.97 (br. s, 1 H), 3.06–3.03 (m, 2 H), 2.74–2.70 (m, 2 H), 1.95–1.89 (m, 4 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 159.03, 149.89, 145.92, 135.62, 130.53, 129.66, 129.36, 122.11, 121.22, 117.71, 117.36, 51.90, 34.09, 24.86, 23.04, 22.80 ppm. HRMS (ESI): calcd. for $C_{16}H_{17}ClN_2$ $[M + H]^+$ 273.1153; found 273.1146.

***N*-(Prop-2-yn-1-yl)-7-chloro-1,2,3,4-tetrahydroacridin-9-amine (20):** Following general procedure A, propargylamine (10 μL, 0.151 mmol) gave **20** as a white solid (28 mg, 76%). R_f (petroleum ether/EtOAc, 1:1) = 0.19. IR (neat): $\tilde{\nu}$ = 3292, 3112, 2943, 2874, 1669, 1583, 1567, 1517, 1417, 1338, 1199, 1177, 1130 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.20 (d, J = 2.11 Hz, 1 H), 8.14 (d, J = 9.18 Hz, 1 H), 7.61 (dd, J = 2.18, 9.02 Hz, 1 H), 6.61 (br. s, 1 H), 4.58–4.56 (m, 2 H), 3.19 (t, J = 6.20 Hz, 2 H), 2.76 (t, J = 5.57 Hz, 2 H), 2.55 (t, J = 2.45 Hz, 1 H), 1.94–1.87 (m, 4 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 154.23, 153.58, 137.09, 133.33, 132.08, 123.05, 122.60, 117.25, 113.19, 78.62, 75.22, 37.58, 28.48, 24.07, 21.90, 20.63 ppm. HRMS (ESI): calcd. for $C_{16}H_{15}ClN_2$ $[M + H]^+$ 271.0996; found 271.0991.

***N*-(Pyridin-3-yl)-7-chloro-1,2,3,4-tetrahydroacridin-9-amine (21):** Following general procedure A, 3-aminopyridine (19 mg, 0.206 mmol) gave **21** as a yellow solid (34 mg, 81%). R_f (petroleum ether/EtOAc, 6:4) = 0.30. IR (neat): $\tilde{\nu}$ = 3229, 3088, 2935, 2863, 1586, 1557, 1480, 1374, 1286, 1240, 1111, 1092 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.18–8.15 (m, 2 H), 7.93 (d, J = 9.08 Hz, 1 H), 7.73 (d, J = 2.30 Hz, 1 H), 7.54 (dd, J = 2.19, 8.95 Hz, 1 H), 7.12–7.08 (m, 1 H), 6.81–6.78 (m, 1 H), 6.02 (br. s, 1 H), 3.13 (t, J = 6.49 Hz, 2 H), 2.71 (t, J = 6.43 Hz, 2 H), 1.99–1.92 (m, 2 H), 1.87–1.81 (m, 2 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 160.72, 145.93, 141.90, 141.19, 140.90, 138.64, 131.56, 130.84, 129.96, 125.84, 124.30, 123.92, 121.99, 121.81, 34.13, 25.75, 22.80, 22.60 ppm. HRMS (ESI): calcd. for $C_{18}H_{16}ClN_3$ $[M + H]^+$ 310.1105; found 310.1101.

***N*-(7-Chloro-1,2,3,4-tetrahydroacridin-9-yl)-2-methylpropane-2-sulfinamide (22):** Following general procedure A, 2-methyl-2-propanesulfinamide (25 mg, 0.206 mmol) gave **22** as a pale yellow solid

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(31 mg, 67%). R_f (petroleum ether/EtOAc/MeOH, 75:25:0.02) = 0.10. IR (neat): $\tilde{\nu}$ = 3353, 3242, 2932, 2864, 2004, 1650, 1573, 1491, 1445, 1375, 1031 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.83 (d, J = 9.15 Hz, 1 H), 7.68 (d, J = 2.36 Hz, 1 H), 7.49 (dd, J = 2.17, 8.94 Hz, 1 H), 4.68 (br. s, 1 H), 3.01 (t, J = 5.93 Hz, 2 H), 2.61 (t, J = 6.05 Hz, 2 H), 1.99–1.90 (m, 4 H), 1.23 (s, 9 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 158.64, 146.36, 144.46, 130.01, 129.60, 129.53, 119.41, 117.81, 111.20, 55.53, 34.74, 23.81, 22.74, 22.71, 22.26 (3 C) ppm. HRMS (ESI): calcd. for $C_{17}H_{21}ClN_2OS$ $[M + H]^+$ 337.1136; found 337.1136.

***N*-(7-Chloro-1,2,3,4-tetrahydroacridin-9-yl)benzamide (23):** Following general procedure A, benzamide (25 mg, 0.206 mmol) gave **23** as a white solid (35 mg, 76%). R_f (petroleum ether/EtOAc/MeOH, 6:4:0.02) = 0.38. IR (neat): $\tilde{\nu}$ = 3248, 2934, 2862, 1649, 1590, 1511, 1482, 1282, 1082 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.01 (d, J = 7.57 Hz, 2 H), 7.94 (d, J = 9.06 Hz, 2 H), 7.77 (d, J = 2.40 Hz, 1 H), 7.67–7.61 (m, 1 H), 7.58–7.52 (m, 3 H), 3.14 (t, J = 6.55 Hz, 2 H), 2.87 (t, J = 6.54 Hz, 2 H), 2.01–1.95 (m, 2 H), 1.90–1.83 (m, 2 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 165.94, 160.47, 145.40, 137.77, 133.44, 132.72, 132.11, 130.11, 129.95, 129.13 (2 C), 128.98, 127.69 (2 C), 124.97, 121.31, 34.07, 25.79, 22.73, 22.43 ppm. HRMS (ESI): calcd. for $C_{20}H_{17}ClN_2O$ $[M + H]^+$ 337.1102; found 337.1101.

Diethyl (7-Chloro-1,2,3,4-tetrahydroacridin-9-yl)phosphoramide (24): Following general procedure A, diethyl phosphoramidate (32 mg, 0.206 mmol) gave **24** as a pale white solid (44 mg, 87%). R_f (petroleum ether/EtOAc/MeOH, 1:1:0.02) = 0.31. IR (neat): $\tilde{\nu}$ = 3083, 2979, 2931, 2861, 1584, 1549, 1501, 1482, 1389, 1362, 1235, 1203, 1165, 1091, 1033 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.24 (d, J = 2.08 Hz, 1 H), 7.87 (d, J = 8.91 Hz, 1 H), 7.54–7.51 (m, 1 H), 4.87 (br. s, 1 H), 4.20–4.10 (m, 4 H), 3.11–3.00 (m, 4 H), 1.98–1.86 (m, 4 H), 1.36–1.27 (m, 6 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 160.36, 145.56, 131.40, 130.28, 129.74 (2 C), 127.32, 125.42, 122.58, 63.82, 63.76, 34.13, 25.69, 22.71 (2 C), 16.34, 16.27 ppm. ^{31}P NMR (162 MHz, $CDCl_3$): δ = 2.95 ppm. HRMS (ESI): calcd. for $C_{17}H_{22}ClN_2O_3P$ $[M + H]^+$ 369.1129; found 369.1133.

2-{2-[(7-Chloro-1,2,3,4-tetrahydroacridin-9-yl)amino]ethoxy}ethan-1-ol (25): Following general procedure A, 2-(2-aminoethoxy)ethan-1-ol (21 µL, 0.206 mmol) gave **25** as a pale white solid (42 mg, 96%). R_f (EtOAc/MeOH, 97:3) = 0.16. IR (neat): $\tilde{\nu}$ = 3346, 2931, 2861, 1645, 1580, 1558, 1488, 1436, 1341, 1258, 1156, 1117, 1071, 1030 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.97 (d, J = 2.24 Hz, 1 H), 7.84 (d, J = 8.91 Hz, 1 H), 7.48 (dd, J = 2.20, 9.03 Hz, 1 H), 5.48 (br. s, 1 H), 4.63 (br. s, 1 H), 3.83–3.81 (m, 2 H), 3.63–3.60 (m, 6 H), 3.05–3.02 (m, 2 H), 2.76–2.73 (m, 2 H), 1.93–1.88 (m, 4 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 158.07, 150.68, 129.97 (2 C), 129.24, 122.22, 120.91, 117.72, 72.41, 70.31, 61.97, 48.65, 33.18, 24.58, 22.84, 22.52 ppm. HRMS (ESI): calcd. for $C_{17}H_{21}ClN_2O_2$ $[M + H]^+$ 321.1364; found 321.1361.

Ethyl (7-Chloro-1,2,3,4-tetrahydroacridin-9-yl)glycinate (26): Following general procedure A, glycine ethyl ester hydrochloride (29 mg, 0.206 mmol) and triethylamine (29 µL, 0.206 mmol) gave **26** as a pale yellow oil (40 mg, 92%). R_f (petroleum ether/EtOAc/MeOH, 6:4:0.02) = 0.29. IR (neat): $\tilde{\nu}$ = 3386, 2980, 2935, 2862, 1736, 1582, 1557, 1487, 1435, 1373, 1339, 1210, 1161, 1023 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.87 (d, J = 2.35 Hz, 1 H), 7.83 (d, J = 8.87 Hz, 1 H), 7.47 (dd, J = 2.30, 9.09 Hz, 1 H), 4.86 (t, J = 5.04 Hz, 1 H), 4.24 (q, J = 7.17 Hz, 2 H), 4.19 (d, J = 4.94 Hz, 2 H), 3.04–3.01 (m, 2 H), 2.86–2.83 (m, 2 H), 1.92–1.88 (m, 4 H), 1.28 (t, J = 7.15 Hz, 3 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 171.58, 159.22, 149.42, 145.91, 130.66, 129.65, 129.26, 121.81, 120.82, 117.77, 62.01, 50.34, 34.11, 24.63, 22.95, 22.76, 14.26 ppm. HRMS (ESI): calcd. for $C_{17}H_{19}ClN_2O_2$ $[M + H]^+$ 319.1208; found 319.1210.

Supporting Information (see footnote on the first page of this article): Procedures for the synthesis of original compounds are given. ^1H and ^{13}C NMR spectra are also reported.

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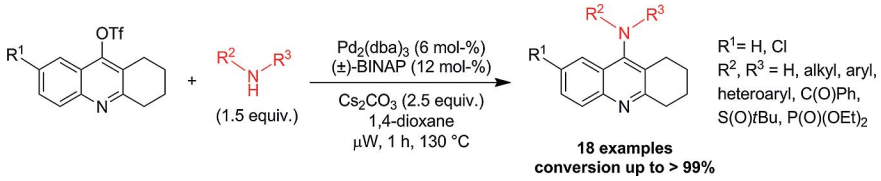
Synthetic Methods



Electrophilic 1,2,3,4-tetrahydroacridin-9-yl trifluoromethanesulfonates have been prepared and applied for the first time in the synthesis of functionalized tacrines with high efficacy by using the Buchwald–Hartwig amination reaction. Secondary, poor nucleophilic, and functionalized amines are well tolerated.

Keywords: Synthetic methods / Cross-coupling / Amination / Nitrogen heterocycles / Medicinal chemistry / Tacrines

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