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Greater variety in Groebke–Blackburn type 3-arylaminoimidazo[1,2-*a*]azines accessed via Pd-catalyzed arylation of a primary amine precursor

Yuri Sandulenko [a], Alexander Komarov [a], Konstantin Rufanov [a], Mikhail Krasavin [a,b,*]

[a] Chemical Diversity Research Institute, 2a Rabochaya St., Moscow Region, Khimki 141400, Russia
[b] Department of Organic and Biological Chemistry, L. N. Tolstoy State Pedagogical University, 125 Lenin Av., Tula 300026, Russia

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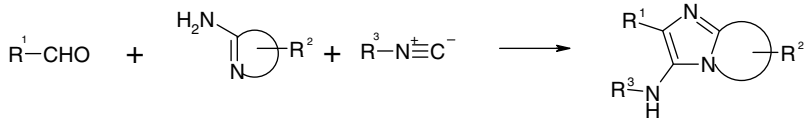
ABSTRACT

The scope of the Groebke–Blackburn reaction of 2-aminoazines is limited by the availability of isocyanides. To prepare the Groebke–Blackburn type 2-phenyl-3-(hetero)arylaminoimidazo[1,2-*a*]azines, for which the respective (hetero)arylisocyanides are scarce or unavailable, a general Pd-catalyzed protocol has been developed that is useful for the arylation of known 2-phenylimidazo[1,2-*a*]pyridin-3-amine and 2-phenylimidazo[1,2-*a*]pyrazin-3-amine with various electron-deficient aryl and heteroaryl halides.

Four-center, three-component reactions involving 2-aminoazines and 2-aminoazoles leading to the formation of the respective fused imidazoles (Scheme 1) were disclosed independently in 1998 by three research groups.[1–3] This reaction is referred to[4] as the Groebke–Blackburn reaction to signify the earlier submissions from the Hoffmann–La Roche[1] and Millennium[2] groups, respectively. This novel reaction was very well received, especially, by the drug discovery research community as witnessed by several related patents and patent applications,[5] and by an increasing number of journal publications[6] that have appeared over the last 10 years. We have been actively utilizing isocyanide-based multi-component reactions (MCRs) in our research program aimed at identifying biologically active heterocyclic compounds. Specifically, the atom economy and the technical simplicity of the Groebke–Blackburn reaction prompted us to propose some improvements to the reaction protocol for 2-aminopyrimidines,[7] which have inspired an analogous reaction design that has resulted in a new approach to prepare quinoxalines.[8]

The obvious limitation one faces in designing combinatorial arrays based on the Groebke–Blackburn reaction (or any other isocyanide-based process) is the commercial scarcity or synthetic inaccessibility of certain isocyanides. More precisely, a number of heteroaromatic isocyanides are either difficult to prepare or have not been described in the literature (2-pyridyl, 4-pyridyl, 2-pyrazinyl, 2-pyrimidinyl, and 4-pyrimidinyl isocyanides being notable examples). As we required such heteroaromatic groups as appendages on 3-aminoimidazo[1,2-*a*]azine scaffolds, we considered an alternative approach to their preparation.

We reasoned that if the requisite scaffolds were constructed using the Groebke–Blackburn reaction of a 2-aminoazine (e.g., 2-aminopyridine) with an aldehyde and a convertible isonitrile, we could then use the resulting products to liberate the primary amino group and use it as the reactive center for arylation with the aromatic and heteroaromatic groups of interest (Scheme 2). A similar approach involving acylation, reductive alkylation, and carbamoylation of 3-amino-2-arylimidazo[1,2-*a*]azines has already



Scheme 1. Four-center, three-component reactions of 2-aminoazines and -azoles with aldehydes and isocyanides (the Groebke–Blackburn reaction).

* Corresponding author. Tel.: +7 495 995 4944; fax: +7 495 926 9780.
E-mail address: myk@chemdiv.com (M. Krasavin).

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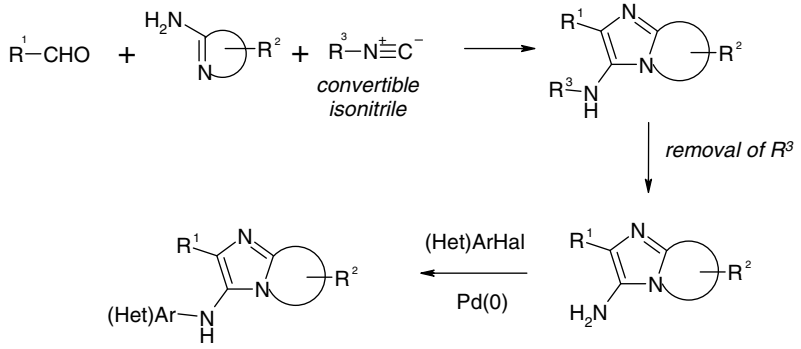
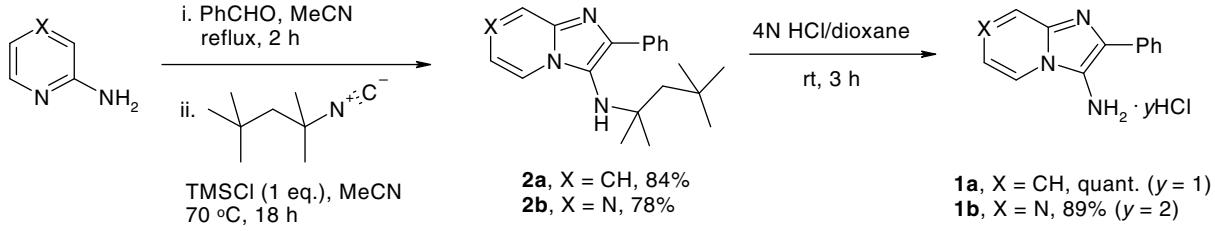
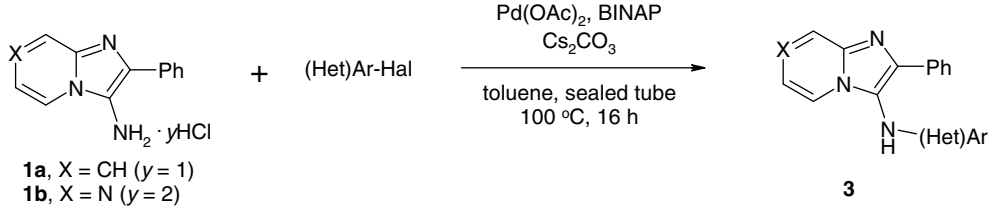


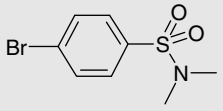
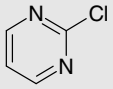
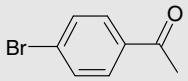
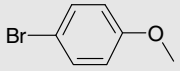
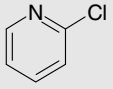
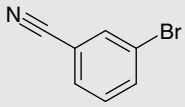
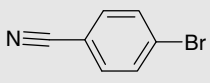
Scheme 2. General approach to the 3-(hetero)arylaminoimidazo[1,2-*a*]azines investigated in this work.



Scheme 3. Preparation of the primary amine scaffolds **1a** and **1b**.

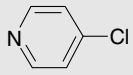
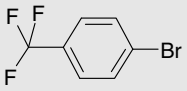
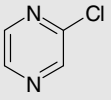
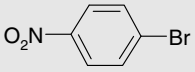
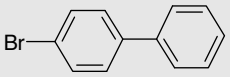
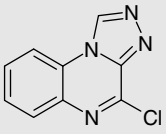
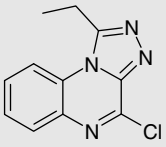
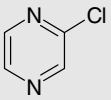
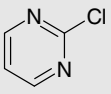
Table 1
Buchwald–Hartwig arylation of 2-phenylimidazo[1,2-*a*]azin-3-amines **1a** and **1b**



Entry	Starting amine	(Het)Ar-Hal	Product	Yield (%)
1	**1a**		**3a**	72
2	**1a**		**3b**	66
3	**1a**		**3c**	27
4	**1a**		**3d**	<5[a]
5	**1a**		**3e**	44
6	**1a**		**3f**	53
7	**1a**		**3g**	69

(*continued on next page*)

Table 1 (*continued*)

Entry	Starting amine	(Het)Ar-Hal	Product	Yield (%)
8	**1a**		**3h**	44
9	**1a**		**3i**	32
10	**1a**		**3j**	67
11	**1a**		**3k**	86
12	**1a**		**3l**	<5[a]
13	**1a**		**3m**	64
14	**1a**		**3n**	71
15	**1b**		**3o**	82
16	**1b**		**3p**	78

[a] Product yield was estimated by LCMS analysis of the crude reaction mixture; the product was not isolated.

been described in the literature.[9] However, no reports on arylation of such primary amines have been published to-date. Herein, we report on the preparation of N-arylated Groebke–Blackburn type 3-aminoimidazo[1,2-*a*]azines via, a Buchwald–Hartwig reaction[10] with various aryl and heteroaryl halides.

In our approach, 1,1,3,4-tetramethylbutylisocyanide (Walborsky reagent[11]) was used as a convertible isonitrile that has been reported[9] to be easily removed under treatment with a Brønsted acid. Two primary amine scaffolds, 2-phenylimidazo[1,2-*a*]pyridin-3-amine (**1a**) and 2-phenylimidazo[1,2-*a*]pyrazin-3-amine (**1b**), were prepared in two steps via (i) Groebke-Blackburn reaction of 2-aminopyridine or 2-aminopyrazine with benzaldehyde and the Walborsky reagent using TMSCl as a promoter[4] to ensure high yields of the *N*-isooctyl imidazo[1,2-*a*]azin-3-amines **2a** and **2b** (after chromatography) with unambiguous regiochemistry;[12] and (ii) removal of the isooctyl group by treatment with 4 N HCl solution in dioxane (Scheme 3). The target amines **1a** and **1b** were isolated as hydrochloride salts by filtration.

The Buchwald–Hartwig arylation of **1a** and **1b** was performed as described in the general procedure. Crude reaction mixtures were analyzed by LCMS to establish the presence of the target arylation products **3**. The crude products were purified by column chromatography on silica gel using appropriate gradients of ethyl acetate in dichloromethane as eluent to provide moderate to excellent yields of **3** (Table 1).[13] Several observations emerge from these results. The N-arylation approach appears to be generally applicable to electron-deficient (hetero)aryl halides. This, in our view, is a very valuable aspect of the present methodology as it complements the relative scarcity of isocyanides containing such groups (and, thus, the inaccessibility of the respective Groebke–Blackburn products via a direct, multi-component approach). The Buchwald–Hartwig arylation of **1a** and **1b** is unproductive for electron-rich or non-activated aryl halides (entries **d** and **l**). Finally, entry **c** demonstrates that the present approach broadens the functional group tolerance in the target products compared to the direct MCR approach (as the ketone functionality would interfere with the Groebke–Blackburn reaction).

In conclusion, we have developed a general protocol that allows efficient N-arylation of various Groebke–Blackburn type imidazo[1,2-*a*]azin-3-amines with various electron-deficient (hetero)-aryl halides. Thus, the present methodology broadens the scope of the Groebke–Blackburn MCR with regard to peripheral group design in the final products.

General procedure: A round-bottomed 15 mL flask was charged with a mixture of **1a** or **1b** (0.4 mmol), (hetero)aryl halide (0.4 mmol), and Cs_2CO_3 (0.8 mmol [**1a**] or 1.2 mmol [**1b**]) in

toluene (1.5 mL). The vial was flushed with nitrogen and sealed with a septum top. The catalyst solution was prepared by mixing $Pd(OAc)_2$[14] (0.008 mmol) and BINAP (0.016 mmol) in toluene (0.5 mL). After shaking at 80 °C for 2 min, the catalyst solution was added to the reaction vial via a syringe. The mixture was heated at 100 °C under vigorous stirring for 16 h after which the mixture was cooled to rt and the solvent was removed in vacuo. The residue was partitioned between ethyl acetate (3 mL) and water (2 mL). The organic layer was separated, dried over anhydrous Na_2SO_4, filtered, and concentrated to give the crude product. The latter was purified by column chromatography on silica gel using an appropriate gradient of ethyl acetate in dichloromethane as eluent.

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12. Under traditional conditions (methanol, Brønsted or Lewis acid catalyst), the Groebke–Blackburn reaction has been noted to lead also to regioisomeric 2-amino-3-phenylimidazo[1,2-*a*]azines: (a) Mandair, G. S.; Light, M.; Russell, A.; Hursthouse, M.; Bradley, M. *Tetrahedron Lett.* **2002**, *43*, 4267–4269; (b) Ref. 6e.
13. Compound **3b**: Brown sticky solid; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.67 (d, J = 4.8 Hz, 2H), 8.43 (d, J = 4.3 Hz, 1H), 8.27 and 8.51 (m, 1H), 7.90–8.00 (m, 3H), 7.47–7.60 (m, 1H), 7.38–7.46 (m, 2H), 7.29 (t, J = 4.8 Hz, 1H), 6.96 (t, J = 4.8 Hz, 1H); ^{13}C NMR (75 Hz, DMSO-d_6) δ 159.9, 159.1, 159.0, 138.0, 126.6, 130.1, 129.3, 129.0, 127.2, 125.8, 118.0, 116.9, 114.1, 112.9; LCMS (M+H$^+$) 288; calcd for $C_{17}H_{13}N_5$: C, 71.07; H, 4.56; N, 24.37. Found: C, 70.98; H, 4.49; N, 24.31.
Compound **3c**: Sticky solid; ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.29 (s, 1H), 8.36 (d, J = 6.8 Hz, 1H), 8.03 (d, J = 8.9 Hz, 1H), 7.88–7.94 (m, 3H), 7.81 (d, J = 8.7 Hz, 2H), 7.51 (m, 3H), 7.40 (t, J = 6.8 Hz, 1H), 6.80 (d, J = 8.4 Hz, 2H), 2.44 (s, 3H); ^{13}C NMR (75 Hz, DMSO-d_6) δ 195.9, 149.1, 138.9, 132.3, 131.1, 130.7, 129.8, 129.2, 128.9, 127.6, 126.9, 124.7, 119.1, 116.5, 113.7, 113.1, 26.2; LCMS (M+H$^+$) 328; calcd for $C_{21}H_{17}N_3O$: C, 77.04; H, 5.23; N, 12.83. Found: C, 77.98; H, 5.22; N, 12.79.
Compound **3h**: Sticky brown solid; ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.79 (s, 1H), 8.49 (unresolved d, 1H), 8.30 (t, J = 8.5 Hz, 1H), 8.26 (unresolved d, 1H), 7.84–7.91 (m, 3H), 7.63 (t, J = 8.5 Hz, 1H), 7.39–7.52 (m, 4H), 7.19 (t, J = 6.6 Hz, 1H), 6.60 (d, J = 7.6 Hz, 1H); ^{13}C NMR (75 Hz, DMSO-d_6) δ 158.5, 158.3, 158.0, 157.0, 145.9, 144.6, 141.5, 135.6, 130.5, 129.1, 128.7, 126.7, 123.9, 116.0, 114.8, 114.6; LCMS (M+H$^+$) 287; calcd for $C_{18}H_{14}N_4$: C, 75.51; H, 4.93; N, 19.57. Found: C, 75.58; H, 4.94; N, 19.62.
Compound **3o**: Off-white solid, mp = 169–171 °C (decomp.); ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.08 (d, J = 1.0 Hz, 1H), 8.24 (d, J = 1.0 Hz, 1H), 7.96–8.06 (m, 5H), 7.88 (d, J = 4.0 Hz, 1H), 7.43 (d, J = 7.0 Hz, 2H), 7.35 (d, J = 7.0 Hz, 1H), 6.30 (br s, NH + bound H_2O); ^{13}C NMR (75 Hz, DMSO-d_6) δ 158.3, 157.8, 152.9, 142.3, 141.8, 140.2, 137.3, 135.0, 133.1, 128.6, 128.4, 128.2, 127.0, 116.9; LCMS (M+H$^+$) 289; calcd for $C_{16}H_{12}N_6$: C, 66.66; H, 4.20; N, 29.15. Found: C, 66.72; H, 4.25; N, 29.21.
Compound **3p**: Off-white solid, mp = 137–139 °C (decomp.); ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.10 (s, 1H), 8.37 (d, J = 4.0 Hz, 2H), 8.05 (d, J = 1.0 Hz, 1H), 8.03 (m, 2H), 7.89 (d, J = 4.0 Hz, 1H), 7.43 (t, J = 7.0 Hz, 2H), 7.34 (dd, J = 1.0, 7.0 Hz, 1H), 6.85 (t, J = 4.0 Hz, 1H), 6.80 (br s, NH + bound H_2O); ^{13}C NMR (75 Hz, DMSO-d_6) δ 161.1, 158.5, 158.4, 157.9, 142.1, 140.2, 137.0, 132.8, 128.9, 128.2, 127.0, 119.4, 116.9, 113.3; LCMS (M+H$^+$) 289; calcd for $C_{16}H_{12}N_6$: C, 66.66; H, 4.20; N, 29.15. Found: C, 66.65; H, 4.21; N, 29.17.
14. In a control experiment, arylation of **1a** was attempted with 2-chloropyrazine in the absence of the palladium catalyst which resulted in virtually no conversion (as evidenced by LCMS analysis of the reaction mixture).