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$AgNO_2$-mediated direct nitration of the quinoxaline tertiary benzylic C–H bond and direct conversion of 2-methyl quinoxalines into related nitriles†

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A unique method for $AgNO_2$-mediated direct nitration of the quinoxaline tertiary C–H bond and direct conversion of 2-methyl quinoxalines into 2-quinoxaline nitriles under oxidative conditions has been developed. This protocol provides an efficient way to access quinoxaline containing nitroalkanes and nitriles depending on different substrate selection.

Nitro compounds are widely used in the chemical industry as well as in the academic research.[1–3] In contrast to the easy nitration of aromatic C–H bonds by nitrating agents, the selective nitration of aliphatic C–H bonds is very difficult. The nitration process of aliphatic hydrocarbons usually requires high temperatures (>200 °C) which will cause undesired C–C bond scissions, thus leading to poor selectivities and adding difficulties for the product separation.[4] As a consequence, the preparation of nitroalkanes generally relies on methods other than the direct C–H nitration.[5] In last decades, despite several more mild processes for the nitration of aliphatic hydrocarbons being reported,[6] selectivity has remained a big problem. Therefore, it is still desirable to develop methods for highly selective nitration of aliphatic C–H bonds.

On the other hand, aryl nitrile compounds as versatile synthetic intermediates are widely used in the synthesis of natural products, functional materials, medicines, agricultural chemicals, and dyes.[7] Besides, they also serve as important precursors for the preparation of a variety of molecules including acids, aldehydes, amines, amides, and N-containing heterocycles.[8] Some representative methods for the synthesis of aryl nitriles include the Sandmeyer reaction,[9] the Rosenmund–von Braun reaction,[10] transition-metal-catalyzed cross-coupling reactions of aryl halides with metallic[11] or nonmetallic cyano-group sources,[12] and the dehydration of primary aromatic amides.[13] However, most of these methods suffer from one or more limitations with respect to the use of toxic reagents, the need for prefunctionalization of coupling partners, and the generation of a large amount of organic or inorganic wastes. Owing to the abundance of methyl arenes, the direct conversion of methyl arenes into the related aromatic nitriles has become an important and practical route to access aryl nitriles.[14] However, such a procedure using NH_3 as the N-source for the formation of the cyano group usually requires very high temperature (>350 °C). Recently, Jiao[15] and Wang[16] reported two mild methods for the conversion of methyl arenes into aryl nitriles by using NaN_3 and *tert*-butyl nitrite (*t*BuONO), respectively, as the N-source for the formation of the cyano group. Overall, the synthetic methods involving the direct transformation of methyl arenes into aryl nitriles remain largely under-explored. As part of our continued interest in the transition metal-involved sp^3 C–H bond functionalizations,[17–19] we herein present a unique $AgNO_2$-mediated direct nitration of the quinoxaline tertiary C–H bond and direct conversion of 2-methyl quinoxalines into 2-quinoxaline nitriles in the presence of $K_2S_2O_8$.

The present finding originated from our recent study on the regiospecific preparation of nitroarenes *via* palladium-catalyzed chelation-assisted nitration of aromatic C–H bonds.[20] When 2-isopropylquinoxaline **1a** was subjected to the same reaction conditions (10 mol% $Pd(OAc)_2$, 2.0 equiv. $AgNO_2$ and $K_2S_2O_8$, 130 °C, 48 h) for the *ortho*-nitration of 2-arylquinoxalines described in our previous work[20] (entry 1, Table 1), we expected that the methyl C–H bond in **1a** could also be nitrated to yield **3a**. It was found that no target product **3a** was formed while a benzylic C–H bond nitrated product **2a** was unexpectedly obtained in 63% yield (entry 1). Control experiments showed that in the absence of $Pd(OAc)_2$ or $K_2S_2O_8$, **2a** was produced in 64% and 5% yields, respectively (entries 2 & 3), indicating that $Pd(OAc)_2$ did not participate in the nitration process while $K_2S_2O_8$ was indispensable. Further experiments disclosed that 110 °C was a more suitable temperature for getting a good yield of **2a** (entry 4 *vs.* 2). Note that using 1.2 equivalents of $AgNO_2$ and $K_2S_2O_8$ was enough for the reaction to be completed (entry 5). Among several solvents (entries 5–15) and oxidants (entries 5 and 16–22) examined, it was proven that DCE was the best choice of solvent and $K_2S_2O_8$ was the best choice of oxidant. Attempting to

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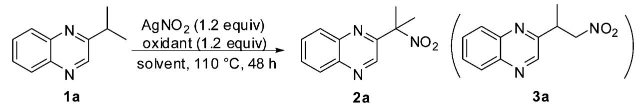
† Electronic supplementary information (ESI) available: Detailed experimental procedure, charts of the mechanistic studies, and analytical data for all products. See DOI: 10.1039/c4cc01327a

Table 1 Optimization of reaction conditions[a]



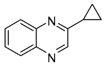
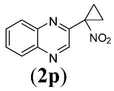
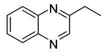
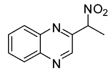
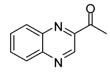
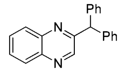
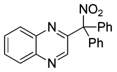
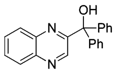
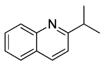
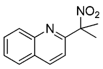
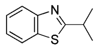
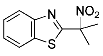
Entry	Nitro source	Oxidant	Add.	Solvent	Yield of **2a**[b] (%)
1	$AgNO_2$[c]	$K_2S_2O_8$[c]	$Pd(OAc)_2$[d]	DCE	63[e]
2	$AgNO_2$[c]	$K_2S_2O_8$[c]	—	DCE	64[e]
3	$AgNO_2$[c]	—	—	DCE	5[e]
4	$AgNO_2$[c]	$K_2S_2O_8$[c]		DCE	75, 68[f]
5	**$AgNO_2$**	**$K_2S_2O_8$**		**DCE**	**82**
6	$AgNO_2$	$K_2S_2O_8$		CH_2Cl_2	78
7	$AgNO_2$	$K_2S_2O_8$		Toluene	16
8	$AgNO_2$	$K_2S_2O_8$		MeCN	70
9	$AgNO_2$	$K_2S_2O_8$		DMF	53
10	$AgNO_2$	$K_2S_2O_8$		Et_2O	16
11	$AgNO_2$	$K_2S_2O_8$		THF	8
12	$AgNO_2$	$K_2S_2O_8$		Acetone	27
13	$AgNO_2$	$K_2S_2O_8$		HOAc	61
14	$AgNO_2$	$K_2S_2O_8$		EtOAc	Trace
15	$AgNO_2$	$K_2S_2O_8$		$MeNO_2$	77
16	$AgNO_2$	$Cu(OAc)_2$		DCE	Trace
17	$AgNO_2$	$CuCl_2$		DCE	10
18	$AgNO_2$	$PhI(OAc)_2$		DCE	12
19	$AgNO_2$	DDQ		DCE	Trace
20	$AgNO_2$	CAN		DCE	16
21	$AgNO_2$	^{t}BuOOBu^t		DCE	41
22	$AgNO_2$	TBHP		DCE	6
23	KNO_2	$K_2S_2O_8$		DCE	18
24	$AgNO_2$[g]/KNO_2[h]	$K_2S_2O_8$		DCE	50

[a] Reaction conditions: **1a** (0.15 mmol), $AgNO_2$ (1.2 equiv.), oxidant (1.2 equiv.), solvent (1.5 mL), 110 °C for 48 h unless otherwise noted. [b] Isolated yield. [c] The amount is 2.0 equiv. [d] The amount is 10 mol% of **1a**. [e] The reaction was conducted at 130 °C. [f] The reaction was conducted at 100 °C. [g] The amount is 0.2 equiv. [h] The amount is 1.2 equiv.

use the cheap KNO_2 as the nitro source resulted in a low yield of **2a** (18%, entry 23). However, a combination of 0.2 equiv. $AgNO_2$ with 1.2 equiv. KNO_2 as the nitro source could give an acceptable yield of **2a** (50%, entry 24).

With the optimized reaction conditions in hand, we set out to investigate the scope of substrates (Table 2). For substrates possessing a tertiary benzylic carbon, the corresponding benzylic C–H bond could be successfully nitrated to afford nitroalkane **2** in moderate to good yields (**2a–2o**). Unfortunately, the benzylic C–H bond in 2-cyclopropylquinoxaline **1p** failed to be nitrated and the starting material was recovered. When a substrate **1q** bearing a secondary benzylic carbon was used, the reaction failed to give the corresponding nitrated product while the benzylic C–H bond ketonized product **2q′** was obtained in 70% yield. An attempt to conduct the reaction of **1q** in a degassed solvent under an argon atmosphere still gave **2q′** in similar yield whereas no formation of **2q** was detected. Note that **1** substituted with a phenyl group at the 3-position resulted in decreased yields of **2** compared with those without a substituent due to the low conversion of the starting substrates (**2l–2o** *vs.* **2a–2e**). When **1r** having a *gem*-diphenyl substituted benzylic C–H bond was used, the reaction gave a hydroxylated product **2r′** in 60% yield while no formation of **2r** was detected. The nitration of the tertiary benzylic C–H bond of N-containing heterocycles **4** and **6** was not successful under the present reaction conditions while the starting substrate was recovered.

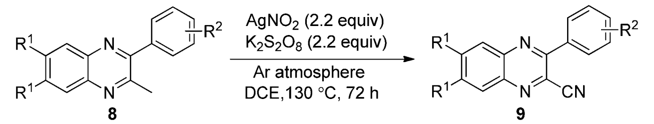
Table 2 $AgNO_2$-mediated nitration of the quinoxaline benzylic C–H bond[a]

Entry	R^1	R^2, R^3	R^4 (**1**)	Product (**2**)	Yield[b] (%)
1	H	H, H	H (**1a**)	**2a**	82 (71[c])
2	H	Me, Me	H (**1b**)	**2b**	64
3	H	Cl, Cl	H (**1c**)	**2c**	61
4	H	NO_2, H	H (**1d**)	**2d**	77
5	H	Br, H	H (**1e**)	**2e**	75
6	Me	H, H	H (**1f**)	**2f**	55[d,e]
7	Me	Me, Me	H (**1g**)	**2g**	77[d,e]
8	Me	Cl, Cl	H (**1h**)	**2h**	74[d,e]
9	Me	NO_2, H	H (**1i**)	**2i**	80[d,e]
10	Me	Br, H	H (**1j**)	**2j**	87[d,e]
11	Me	Cl, H	H (**1k**)	**2k**	82[d,e]
12	H	H, H	Ph (**1l**)	**2l**	62[d,e]
13	H	Me, Me	Ph (**1m**)	**2m**	45[d,e,f]
14	H	Cl, Cl	Ph (**1n**)	**2n**	45[d,e,f]
15	H	Cl, H	Ph (**1o**)	**2o**	43[d,e,f]
16			 (**1p**)	 (**2p**)	Trace[g]
17			 (**1q**)	 (**2q**)  (**2q′**)	0 70 (69[h])
18			 (**1r**)	 (**2r**)  (**2r′**)	0 60
19			 (**4**)	 (**5**)	0[g]
20			 (**6**)	 (**7**)	0[g]

[a] Reaction conditions: **1** (0.3 mmol), $AgNO_2$ (1.2 equiv.), $K_2S_2O_8$ (1.2 equiv.), DCE (1.5 mL), 110 °C for 48 h unless otherwise noted. [b] Isolated yield. [c] The reaction was performed on a 1 mmol scale. [d] The reaction was conducted at 130 °C. [e] The reaction time is 72 h. [f] The use of 1.8 equiv. of $AgNO_2$ and $K_2S_2O_8$, respectively. [g] The starting material was recovered. [h] The reaction was carried out in a degassed solvent under an Ar atmosphere.

To further expand the scope of the present reaction, the nitration of the quinoxaline primary benzylic C–H bond was also carried out. When 2-methyl-3-phenylquinoxaline **8a** was treated with 1.4 equiv. of $AgNO_2$ and $K_2S_2O_8$ in DCE at 130 °C for 72 h, to our surprise, a 2-quinoxalinyl nitrile **9a**, rather than a nitrated product, was unexpectedly isolated in 43% yield (entry 1, Table 3). The yield of **9a** could be increased to 82% by using 2.2 equiv. of $AgNO_2$ and $K_2S_2O_8$, respectively (entry 1, Table 3). Preliminary studies showed that a number of 2-methyl quinoxalines could be converted into the corresponding

Table 3 $AgNO_2$-mediated direct conversion of 2-methyl quinoxalines to the corresponding aromatic nitriles[a]



Entry	R^1	R^2	Sub. (**8**)	Prod. (**9**)	Yield[b] (%)
1	H	H	**8a**	**9a**	43[c], 82
2	H	2-OMe	**8b**	**9b**	65
3	H	3-OMe	**8c**	**9c**	80
4	H	4-Me	**8d**	**9d**	75
5	H	4-F	**8e**	**9e**	78
6	H	4-Cl	**8f**	**9f**	70
7	H	4-Br	**8g**	**9g**	64
8	Me	H	**8h**	**9h**	68

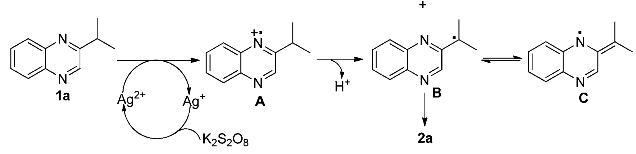
[a] Reaction conditions: **8** (0.3 mmol), $AgNO_2$ (2.2 equiv.), $K_2S_2O_8$ (2.2 equiv.), DCE (4.0 mL), 130 °C under an argon atmosphere for 72 h unless otherwise noted. [b] Isolated yield. [c] The amount of $AgNO_2$ and $K_2S_2O_8$ is 1.4 equiv., respectively.

aromatic nitriles in moderate to good yields (**9a–9h**, 60–82%, Table 3).

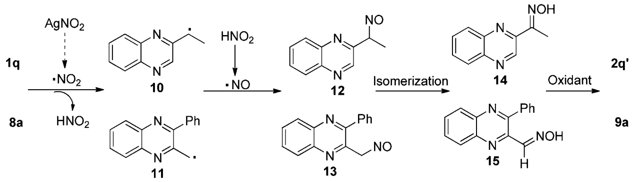
To gain insight into the mechanism of the benzylic C–H nitration process, a mixture of substrates **1a** and [*D*]-**1a** was subjected to determine the intermolecular isotope effect (see the ESI†). A secondary kinetic isotope effect as showing $k_H/k_D \approx 1.1$ was observed, suggesting that the reaction might involve a radical process.[5a,b] When the reaction was conducted in the presence of TEMPO, a radical scavenger,[21] the benzylic C–H nitration was suppressed (see the ESI†), thus further supporting a radical process.[20]

On the basis of the above experiments and previous literatures,[19b,20,22,23] a proposed mechanism for the $AgNO_2$-mediated nitration of the quinoxaline benzylic C–H bond is described in Scheme 1. On the one hand, $AgNO_2$ may release the NO_2 radical upon treatment with[20,22a] or without $K_2S_2O_8$.[22b,c] Over the course of the reaction, the formation and gradual consumption of a brown gas, which should be assigned to NO_2 gas,[20,22] were indeed observed in the sealed tube. On the other hand, Ag(I) could be oxidized into Ag(II) species which then underwent single electron transfer from **1a** to generate a radical intermediate **B** (or **C**).[19b,23] The combination of the radical species NO_2 and **B** finally gave nitroalkane **2a.**

A possible reaction mechanism for the $AgNO_2$-mediated ketonization of the secondary benzylic C–H bond (**1q**) and direct conversion of **8a** to **9a** is proposed in Scheme 2. These two processes might involve the formation of an NO radical[24] and oxime intermediates (**14** and **15**).[16] Under the oxidative conditions, ketoxime **14** and aldoxime **15** could be further converted into ketone **2q**′ and nitrile **9a**, respectively.[16]



Scheme 1 Proposed mechanism for the nitration of **1a**.



Scheme 2 Proposed mechanism for the formation of **9a** and **2q**′.

In summary, we have developed a novel method for the $AgNO_2$-mediated direct nitration of the quinoxaline tertiary C–H bond and direct conversion of 2-methyl quinoxalines into 2-quinoxaline nitriles in the presence of $K_2S_2O_8$, which represents the first example of transition metal-involved sp^3 C–H nitrations[17,18] and silver-mediated direct conversion of the benzylic methyl group into a cyano group with the use of NO_2^- as the N-source.[14–16] Further exploration of this new approach for the synthesis of more valuable compounds is underway in our laboratory.

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