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Sonogashira reaction on pyridinium *N*-heteroarylaminides

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Dedicated to Professor Carmen Nájera on the occasion of her 60th birthday

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ABSTRACT

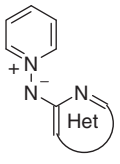
The reactivity of *N*-(5-iodopyridin-2-yl)aminide in a copper-free Sonogashira cross-coupling process is reported. The reaction proceeds on using $PdCl_2(PPh_3)_2$ and DABCO as the base under microwave irradiation in acetonitrile or water as solvents. The process can also be carried out by traditional heating in acetonitrile on using $Pd(AcO)_2$/DABCO with Cs_2CO_3.

The Sonogashira cross-coupling reaction of terminal acetylenes with aryl/alkenyl halides or triflates has proved to be a powerful method for the creation of C(sp^2)–C(sp) bonds.[1] This methodology has growing applications in diverse areas of chemistry, such as in heterocyclic systems,[2] natural product[3] synthesis and material sciences, allowing access to organic semiconductors[4] and to macrocycles for nanostructures.[5]

For several years, part of our research programme has been devoted to the study of pyridinium heteroaryl-stabilized aminides **1** (Fig. 1), compounds that have proven to be useful intermediates in heterocyclic synthesis due to their particular structure, in which a positively charged pyridinium ring is linked to a negatively charged 2-aminoheteroaryl moiety.[6] The heteroaryl ring of *N*-azinyl pyridinium aminides **1** (Fig. 1) is activated towards electrophiles and, as a result, mono- and di-halogenation process can be accomplished easily and in a selective manner at the 5- and 3-positions of the azine ring.[6b] On the other hand, a regioselective N-exoalkylation of heteroaryl-stabilized aminides **1**, followed by reduction of the N–N bond, allows the preparation of 2-alkylaminoazines[6c,d] and *N*-(2-pyridyl)-substituted polyamines.[6e,f]

In previous communications we reported the success of the Suzuki cross-coupling reaction on mono- and dibrominated aminides **2** and **3** (Fig. 1) under standard conditions, which resulted in the regioselective synthesis of 3,5-disubstituted 2-aminopyridines and 2-aminopyrazines **4** and **5**.[7] In this Letter, we report the preliminary results obtained in the Sonogashira cross-coupling reaction of halogenated aminides with terminal alkynes.

Taking into account the good results obtained with the brominated aminides **2** and **3** in the Suzuki reaction, *N*-(5-bromopyridin-2-yl)pyridinium aminide **2a** was initially used as a model



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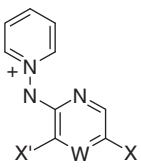
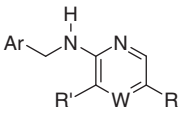


1a W = CH, X = X' = H; **1b** W = N, X = X' = H
2a W = CH, X' = H, X = Br; **2b** W = N, X' = H, X = Br
3a W = CH, X = X' = Br; **3b** W = N, X = X' = Br



4 W = CH
5 W = N

Figure 1.

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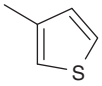
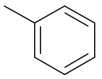
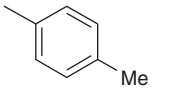
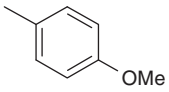
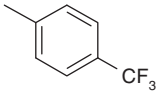
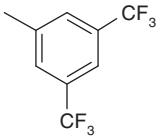
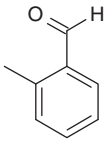
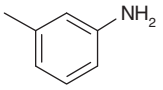
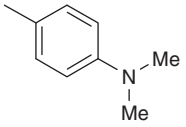
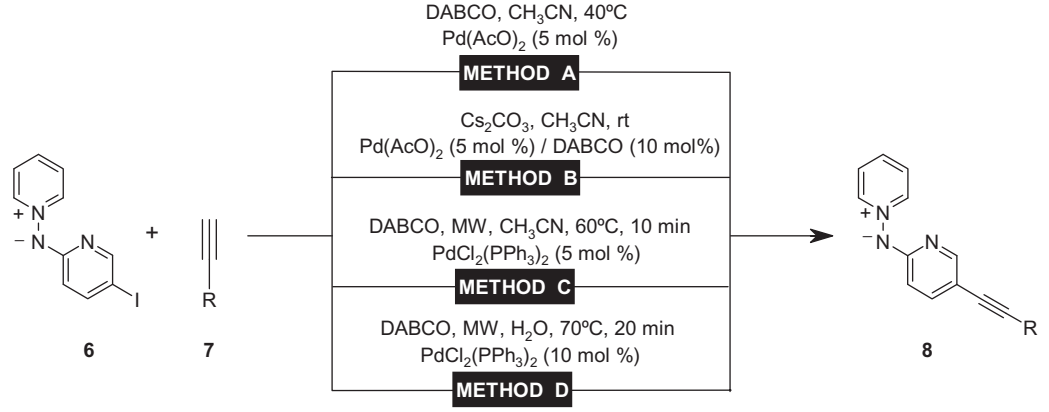
Table 1
Comparative yields for the synthesis of compounds **8a–k**

Entry	R	Method[a]	Reaction time	Product	Yield[b] (%)
1	–Si(Me)$_3$	C	10 min	**8a**	46
2	–Si(^{i}Pr)$_3$	A	24 h	**8b**	48
		B	48 h		30
		C	10 min		36
3		A	24 h	**8c**	27
		C	10 min		75
		D	20 min		34
4		A	24 h	**8d**	45
		B	24 h		66
		C	10 min		69
		D	20 min		77
5		A	24 h	**8e**	25
		B	48 h		19
		C	10 min		68
		D	20 min		74
6		A	48 h	**8f**	25
		B	48 h		51
		C	10 min		49
		D	15 min		57
7		A	24 h	**8g**	30
		C	10 min		60
		D	20 min		50
8		A	48 h	**8h**	15
		C	10 min		40
		D	20 min		19
9		A	48 h	**8i**	9
		C	15 min		47
		D	20 min		83
10		A	48 h	**8j**	21
		C	10 min		57
11		C	10 min	**8k**	30
		D	20 min		42

[a] Methods: (A) *N*-(5′-iodopyridin-2′-yl)pyridinium aminide (0.24 mmol), acetylene (0.48 mmol), DABCO (1.43 mmol) and Pd(AcO)$_2$ (5 mol %) in dry acetonitrile at 40 °C. (B) *N*-(5′-iodopyridin-2′-yl)pyridinium aminide (0.24 mmol), acetylene (0.48 mmol), caesium carbonate (1.43 mmol), DABCO (10 mol %) and Pd(AcO)$_2$ (5 mol %) in dry acetonitrile at room temperature. (C) *N*-(5′-iodopyridin-2′-yl)pyridinium aminide (0.07 mmol), acetylene (0.14 mmol), DABCO (0.42 mmol) and PdCl$_2$(PPh$_3$)$_2$ (5 mol %) in acetonitrile at 60 °C using MW. (D) *N*-(5′-iodopyridin-2′-yl)pyridinium aminide (0.07 mmol), acetylene (0.28 mmol), DABCO (0.42 mmol) and PdCl$_2$(PPh$_3$)$_2$ (10 mol %) in water at 70 °C using MW.

[b] Yields described for isolated pure product.



Scheme 1.

compound to carry out the palladium-catalyzed cross-coupling reaction with triisopropylsilylacetylene (TIP-SA) or 4-ethynylanisole as alkynylation agents. Initially, a classical catalytic system [CuI/$Pd_2Cl_2(PPh_3)_2$ and Et_3N as base in DMF or Et_3N as solvents] that proved useful with bromoquinolizinium salts[8] was tested over a range of temperatures from 80 °C to room temperature. However, this system did not give the desired product and the starting material was recovered. Negative results were also obtained when similar conditions to those suitable for the Suzuki coupling on **2a** were employed [CuI/$Pd(Ph_3P)_4$/K_2CO_3 in toluene/ethanol at different temperatures][7] and the same results were found when these conditions were applied to the more electron-deficient aminide **2b**.

One of the most important modifications of the initial Sonogashira reaction conditions involved the use of an alternative to CuI, not only due to its presence as a potential contaminant that is difficult to remove but also because it enhances the formation of the undesired homocoupling by-products of the terminal alkyne.[1e,f] In contrast, 1,4-diazabicyclo[2.2.2]octane (DABCO), an unhindered and nucleophilic base, proved to be a highly efficient and inexpensive ligand for the Pd-catalyzed cross-coupling reaction.[9,10] Li et al., reported the use of catalytic amounts of DABCO as a ligand in combination with palladium acetate and K_2CO_3 or Cs_2CO_3 as the base in the copper-free Sonogashira cross-coupling reaction.[9] The same authors also used DABCO as a base, in large excess, for the coupling of aryl iodides to phenylacetylene on finding that the use of CuI had an adverse effect.[10a] Recently, DABCO was found to act as catalyst in metal/solvent- and phosphane-free Sonogashira coupling of iodoarenes.[10b]

The use of DABCO as base (3 equiv) in the coupling between **2a** and TIPSA in acetonitrile at 50 °C, with $Pd(OAc)_2$ as a catalyst, gave only traces of **8b** in the reaction mixture. The best result (36% yield) was obtained on using 8 equiv of base.

The heteroaryl ring of *N*-azinyl pyridinium aminides **2** (Fig. 1) is deactivated (electron rich) for the cross-coupling alkynylation due to the electron-releasing effect of the exocyclic nitrogen. Given this knowledge, and bearing in mind that Sonogashira coupling takes place more efficiently with iodinated than brominated heteroarenes, we decided to assess the cross-coupling of *N*-(5-iodopyridin-2-yl)pyridinium aminide **6**[6a] and phenylacetylene. The best results (45% yield) were obtained on using a 1:2:6 ratio of aminide/phenylacetylene/DABCO in dry acetonitrile as the solvent at 40 °C and $Pd(AcO)_2$ (5 mol %) as the catalyst. Medium-to-low yields of the coupled aminides **8** (<50%) were obtained after 24 h (or 48 h) on applying these conditions (method A)[11a] to other terminal acetylenes (see Table 1). The use of DABCO as a ligand (10 mol %) with $Pd(AcO)_2$ (5 mol %) and Cs_2CO_3 (6 equiv) as the base at room temperature afforded better results for compounds **8d** and **8f**, but had a negative effect on the reaction yields of alkynyl aminides **8b** and **8e** (see Table 1, method B).[11b]

The ability of microwaves (MW) to shorten reaction times and to increase product purities and reaction yields has been well documented and this technique can often make otherwise unsuccessful processes possible.[12] This procedure can also be applied to Sonogashira cross-coupling reactions, for which polar solvents and microwave activation have often been employed.[13] Bearing in mind the advantages of MW-assisted organic synthesis outlined above, we envisaged that the use of this technique could improve the coupling on the iodinated aminide **6**. Several tests were performed to find the best temperature and reaction time in the cross-coupling with *p*-methoxyphenylacetylene on employing the catalyst, base and solvent used in method A and also with the same ratio of reactants. The nature of the palladium source is known to have an influence on certain Pd-mediated processes and, as a result, the catalyst $PdCl_2(PPh_3)_2$, which is widely used in Sonogashira cross-couplings,[13] was assessed.

Preliminary results obtained on raising the temperature from 40 to 80 °C showed that the best yields of **8f** were obtained at 60 °C. In contrast, changes in the reaction time from 10 to 20 min did not improve reaction yields. The catalyst $PdCl_2(PPh_3)_2$ was better than $Pd(OAc)_2$ and led to an increase in the yield by 10%. Under our optimal conditions (5% $PdCl_2(PPh_3)_2$, 6 equiv. DABCO) the Sonogashira cross-coupling was performed with the iodinated aminide **6** and various acetylenes under microwave irradiation at 60 °C in acetonitrile with a reaction time of 10 min (see Table 1, method C).[14] The yields of alkynyl aminides **8** were higher (with the exception of **8b**) than those obtained on using method A but yields were still only moderate. It is necessary to point out that unreacted starting material was recovered in all the experiments—with the amount recovered depending on the particular reaction. Eventual complexation of palladium by some of the final acetylenic reaction products[1f] and the high electron density in the pyridine ring of iodinated aminide **6** may explain why the conversion was not fully achieved.

Water has been recognized as an attractive medium for organic reactions[15] not only from environmental and economic points of view but also because other solvents do not have to be dried and products can be easily isolated. In recent years many protocols for Sonogashira coupling reactions in neat water[16] or in aqueous/organic[17] solvents have been reported. The study of the alkynylation of aminide **6** was completed by using water as the solvent instead of acetonitrile (Scheme 1). A screening of temperatures in the range 60–100 °C and reaction times of 10–25 min was performed in the coupling between *p*-methoxyphenylacetylene and aminide **6**. It was found that after 15 min at 70 °C compound **8f** was obtained in 57% yield. On extending the method to other acetylenes the reaction time was increased to 20 min. Slightly better yields of aminides **8** were obtained on using method D[18] rather than method C—with the exception of **8c**, **8g** and **8h**, where more by-products were detected in the reaction mixture.

The problems associated with the industrial use of Pd-processes concern the cost and the tedious recovery of the metal and this has encouraged the use of copper-based catalysts as an alternative.[19] Chen et al., reported a palladium-free copper-catalyzed cross-coupling reaction of aryl iodides and terminal acetylenes under microwave irradiation in neat water.[19a] We attempted to apply similar conditions for the coupling between aminide **6** (1 equiv) and phenylacetylene (1.5 equiv) in the presence of TBAB (1 equiv), CuI (10 mol %), PPh_3 (10 mol %) in a MW-assisted process at 120 °C for 20 min in neat water. However, **8d** was not observed in the reaction mixture and only 2-phenylethynylpyridine was identified. The same result was obtained on increasing the amount of base or the reaction time. This result is consistent with the greater preference of the copper acetylide intermediate for the electron-deficient 2-position of the pyridinium ring over the 'electron-rich' pyridine heterocycle.

In conclusion, we had developed a general method for the palladium-catalyzed, copper-free cross-coupling reactions of the non-activated *N*-(5-iodopyridin-2-yl)pyridinium aminide and terminal acetylenes under microwave irradiation, using acetonitrile or water as solvents and DABCO as the base. Efforts to improve the yields of the alkynylated products and to expand the scope of the Sonogashira-type reactions to other aminides are now in progress in our laboratory.

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RD06/0016/0016) for financial support and the Universidad de Alcalá (UAH) for a studentship (M.C.).

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11. (a) *Method A*: The acetylene **7** (0.48 mmol) was added to a solution of *N*-(5′-iodopyridin-2′-yl)pyridinium aminide **6** (0.07 g, 0.24 mmol) and DABCO (0.16 g, 1.43 mmol) in dry acetonitrile (5 mL) and the reaction mixture was vigorously stirred for 45 min at room temperature to give a purple solution. $Pd(AcO)_2$ (5 mol %) was then added. The mixture was stirred at 40 °C until starting material was no longer detected by TLC. The inorganic salts were filtered off through Celite. The filtrate was evaporated in vacuo and the product was purified by chromatography on silica gel, using ethanol as eluent, and crystallized from a suitable solvent and characterized.; (b) *Method B*: A round-bottomed flask was charged with *N*-(5′-iodopyridin-2′-yl)pyridinium aminide **6** (0.07 g, 0.24 mmol), caesium carbonate (0.47 g, 1.43 mmol) and DABCO (10 mol %). The mixture was flushed with argon for 10 min. Dry acetonitrile (5 mL), the corresponding acetylene **7** (0.48 mmol) and $Pd(AcO)_2$ (5 mol %) were added. The mixture was stirred at room temperature until starting material was no longer detected by TLC. The inorganic salts were filtered off through Celite. The filtrate was evaporated in vacuo and the product was purified by chromatography on silica gel, using ethanol as eluent, and crystallized from a suitable solvent and characterized.*N-[5-(Phenylethynyl)pyridin-2-yl]pyridinium aminide* (**8d**): orange solid (method A 45%, method B 66%, ethyl acetate/hexane), mp 46–48 °C; IR (KBr) ν_{max} (cm^{-1}): 2924, 2852, 2204, 1587, 1459, 1380, 1131, 815, 755, 690; ^1H NMR (300 MHz, CD_3OD): δ 8.75 (2H, dd, J = 6.9 and 1.3 Hz, *H*2(6)), 8.13 (1H, tt, J = 7.7 and 1.3 Hz, *H*4), 7.87 (3H, m, *H*3(5) and *H*6′), 7.45 (3H, m, *H*2″(6″) and *H*4′), 7.34 (3H, m, *H*3″(5″) and *H*4″), 6.50 (1H, dd, J = 8.9 and 1.0 Hz, *H*3′); ^{13}C NMR (75 MHz, CD_3OD): δ 164.9 (*C*2′), 150.9 (*C*6′), 145.2 (*C*2(6)), 140.3 (*C*4′), 138.9 (*C*4), 132.0 (*C*2″(6″)), 129.4 (*C*3″(5″)), 128.7 (*C*3(5) and *C*4″), 125.4 (*C*1″), 111.5 (*C*3′), 107.2 (*C*5′), 89.9 (C_α≡), 89.0 (C_β≡). MS (EI, *m*/*z*): 271 (74, M^+), 270 (100), 165 (68), 164 (75), 139 (25), 138 (36), 135 (37), 114 (21), 79 (38), 52 (31); HRMS (ESI-TOF, CH_3OH): calcd for $C_{18}H_{14}N_3$: $[M+H]^+$ 272.1188, found 272.1188. Anal. Calcd for $C_{18}H_{13}N_3$: C, 79.68; H, 4.83; N, 15.49. Found: C, 79.36; H, 5.09; N, 15.62.
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14. *Method C*: *N*-(5′-iodopyridin-2′-yl)pyridinium aminide **6** (0.02 g, 0.07 mmol), DABCO (0.05 g, 0.42 mmol), $PdCl_2(PPh_3)_2$ (5 mol %), acetonitrile (1 mL) and the corresponding acetylene **7** (0.14 mmol) were placed in a standard CEM 10 mL pressurized reaction vial. The reaction mixture was then magnetically stirred and irradiated in the microwave system at 60 °C for 10 min. The solvent was removed under vacuum and the product was purified by chromatography on silica gel, using ethanol as eluent. The products were finally crystallized from a suitable solvent and characterized.
N-[5-(Trimethylsilanylethynyl)pyridin-2-yl]pyridinium aminide (**8a**): orange solid (46%, ethyl acetate/hexane), mp 139–141 °C; IR (KBr) ν_{max} (cm^{-1}): 2143, 1591, 1465, 1381, 1291, 1139, 862, 841; ^1H NMR (300 MHz, CD_3OD): δ 8.72 (2H, dd, J = 6.9 and 1.3 Hz, *H*2(6)), 8.13 (1H, tt, J = 7.7 and 1.3 Hz, *H*4), 7.86 (2H, dd, J = 7.7 and 6.9 Hz, *H*3(5)), 7.77 (1H, dd, J = 2.1 and 0.9 Hz, *H*6′), 7.35 (1H, dd, J = 8.8 and 2.1 Hz, *H*4′), 6.43 (1H, dd, J = 8.8 and 0.9 Hz, *H*3′), 0.22 (9H, s, CH_3); ^{13}C NMR (75 MHz, CD_3OD): δ 165.0 (*C*2′), 151.4 (*C*6′), 145.2 (*C*2(6)), 140.5 (*C*4′), 139.0 (*C*4), 128.7 (*C*3(5)), 111.3 (*C*3′), 107.0 (*C*5′), 105.5 (C_β≡), 93.5 (C_α≡), 0.2 (CH_3). MS (EI, *m*/*z*): 267 (54, M^+), 266 (100), 125 (14); HRMS (APCI-TOF): calcd for $C_{15}H_{18}N_3Si$: $[M+H]^+$ 268.1270, found 268.1271. Anal. Calcd for $C_{15}H_{17}N_3Si{\cdot}1/2H_2O$: C, 65.18; H, 6.56; N, 15.20. Found: C, 65.39; H, 6.39; N, 15.18.
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18. *Method D*: *N*-(5′-iodopyridin-2′-yl)pyridinium aminide **6** (0.02 g, 0.07 mmol), DABCO (0.05 g, 0.42 mmol), $PdCl_2(PPh_3)_2$ (10 mol %), water (1 mL) and the corresponding acetylene **7** (0.28 mmol) were placed in a standard Biotage Initiator microwave vial. The reaction mixture was then magnetically stirred and irradiated in the microwave system at 70 °C for 20 min. The solvent was removed under vacuum and the product was purified by chromatography on silica gel, using ethanol as eluent. The products were finally crystallized from a suitable solvent and characterized.
N-[5-(3-Thiophenylethynyl)pyridin-2-yl]pyridinium aminide (**8c**): orange solid (34%, ethyl acetate/hexane), mp 130–132 °C; IR (KBr) ν_{max} (cm^{-1}): 2193, 1593, 1479, 1464, 1384, 1141, 774; ^1H NMR (300 MHz, CD_3OD): δ 8.74 (2H, dd, J = 6.9 and 1.3 Hz, *H*2(6)), 8.11 (1H, tt, J = 7.7 and 1.3 Hz, *H*4), 7.86 (2H, dd, J = 7.7 and 6.9 Hz, *H*3(5)), 7.83 (1H, dd, J = 2.3 and 0.7 Hz, *H*6′), 7.52 (1H, dd, J = 3.1 and 1.0 Hz, *H*2″), 7.43 (1H, dd, J = 8.9 and 2.3 Hz, *H*4′), 7.42 (1H, dd, J = 4.9 and 3.1 Hz, *H*5″), 7.15 (1H, dd, J = 4.9 and 1.0 Hz, *H*4″), 6.49 (1H, dd, J = 8.9 and 0.7 Hz, *H*3′); ^{13}C NMR (75 MHz, CD_3OD): δ 164.8 (*C*2′), 150.7 (*C*6′), 145.1 (*C*2(6)), 140.2 (*C*4′), 138.8 (*C*4), 130.6 (*C*4″), 128.6 (*C*3(5)), 128.3 (*C*2″), 126.5 (*C*5″), 124.2 (*C*3″), 111.5 (*C*3′), 107.5 (*C*5′), 88.2 (C_α≡), 85.0 (C_β≡). MS (EI, *m*/*z*): 277 (69, M^+), 276 (100), 171 (69), 170 (34), 145 (16), 127 (36), 79 (41), 52 (38); HRMS (ESI-TOF, CH_3OH): calcd for $C_{16}H_{12}N_3S$: $[M+H]^+$ 278.07317, found 278.07464. Anal. Calcd for $C_{16}H_{11}N_3S$: C, 69.29; H, 4.00; N, 15.15; S, 11.56. Found: C, 69.65; H, 4.17; N, 15.04; S, 11.29.
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