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Graphical Abstract

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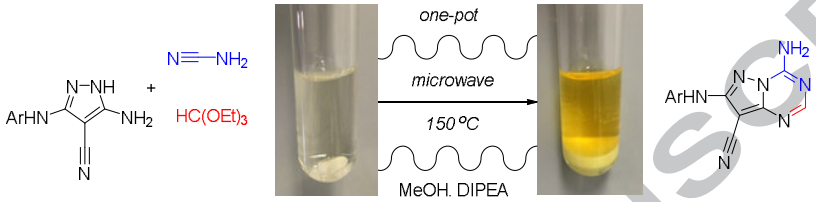

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A one-pot, three-component aminotriazine annulation onto 5-aminopyrazole-4-carbonitriles under microwave irradiation[§]

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ABSTRACT

A one-pot, three-component, microwave-assisted reaction of 5-aminopyrazole-4-carbonitriles, triethyl orthoformate and cyanamide afforded novel 7-arylamino-substituted 4-aminopyrazolo[1,5-*a*][1,3,5]triazine-8-carbonitriles. The reaction proceeded in a chemo- and regioselective manner resulting in the successful amino-1,3,5-triazine annulation onto 5-aminopyrazole-4-carbonitriles to give 4-aminopyrazolo[1,5-*a*][1,3,5]triazine-8-carbonitriles. The operational simplicity of the method and high purity of the products, which can be isolated via simple filtration, make this approach attractive for the preparation of a library of compounds for drug discovery processes.

[§] Part 27 in the series 'Fused heterocyclic systems with an *s*-triazine ring', for part 26 see Ref. 1

The development of methods for the synthesis of pyrazolo[1,5-*a*][1,3,5]triazines started more than half a century ago[2,3] and has been particularly active recently.[4] The main stimulus behind these investigations has been the identification of many biologically active compounds constructed on the basis of this heterocyclic system. The pyrazolo[1,5-*a*][1,3,5]triazine scaffold has become a very promising, from a medicinal chemistry perspective, 1,3,5-triazine-based purine isostere.[5] Amino substituents are common motifs in many interesting bioactive pyrazolo[1,5-*a*][1,3,5]triazines. Representative examples include the casein kinase II (CK2) inhibitor **1** (Figure 1), which also demonstrated good anticancer properties.[6] A cyano group at C-8 of **1** was also important for enzyme inhibition as changing it to a similar in size ethyl group led to an almost four-order decrease in the inhibitory activity. The phosphodiesterase (PDE10) inhibitor **2**, active in subnanomolar concentrations, demonstrated potential for the development of a new type of antipsychotic.[7] Pexacerfont (**3**) is a potent antagonist of corticotrophin releasing factor (CRF_1)[8] undergoing clinical trials as a therapeutic agent for the treatment of anxiety-related alcohol craving and stress-induced food craving.[9] Being strong cannabinoid receptor antagonists, compounds **4a,b** have been proposed for the treatment of obesity.[10] Additionally, **4a** showed synergistic activity with levodopa in Parkinson's disease therapy.[11]

Recently, we developed a method for the synthesis of 4-amino-substituted pyrazolo[1,5-*a*][1,3,5]triazin-2-amines, among which, 4-arylamino-substituted compounds demonstrated promising biological activity.[1] Herein, we report a one-pot, three-component synthesis of pyrazolo[1,5-*a*][1,3,5]triazines possessing an arylamino group located on C-7 of the heterocyclic system.

Previously, we successfully achieved the aminotriazine annulation onto 3-amino-substituted 1,2,4-triazole-5-amines *via* the microwave-assisted reaction with triethyl orthoformate and cyanamide.[12] Starting from 5-amino-3-arylaminopyrazole-4-carbonitriles **5**, we propose a similar approach for the synthesis of 4-amino-7-arylaminopyrazolo[1,5-*a*][1,3,5]triazine-8-carbonitriles **6** (Scheme 1, Pathway A). However, replacement of the N-4 atom in the triazole ring with a carbon atom bearing a cyano group might complicate the reaction due to the potental reactivity of the nitrile. 5-Aminopyrazole-4-carbonitriles have been known for a long time as useful building blocks for the synthesis of various heterocyclic compounds.[13] Their reactions with triethyl orthoformate or its analogues, followed by treatment of the resulting intermediate with amines have been used for the construction of pyrimidine rings in the synthesis of bioactive pyrazolo[4,3-*d*]pyrimidines.[14] Therefore, in the case of participation of the cyano group on the pyrazole ring in our three-component reaction, we might expect at least one alternative transformation or side reaction, *viz.* the formation of pyrazolo[4,3-*d*]pyrimidines **7**, which might further undergo the Dimroth rearrangement to give products **8** (Scheme 1, Pathway B).

The starting 5-amino-3-arylaminopyrazole-4-carbonitriles (**5**) were prepared using a known method,[15] exploiting the reaction of 3,3-bis(methylsulfanyl)-2-cyanoacrylonitrile (**9**)[16] with various anilines, followed by treatment of the resulting products **10** with hydrazine thus affording 5-amino-3-arylaminopyrazole-4-carbonitriles **5** (Scheme 2).

An attempt to carry out the reaction of **5a** with triethyl orthoformate and cyanamide under microwave irradiation (150 °C, 25 min) led to the formation of a mixture of several products. The main component (75%) of this mixture was the desired product **6a**, which could be isolated chromatographically. We were unable to improve the reaction outcome on manipulating the reaction time and temperature. Adding a base [diisopropylethylamine (DIPEA)] to the reaction mixture also did not increase the yield of **6a**, but allowed isolation of this compound exclusively by simple filtration.

The scope of this method was explored by the preparation of a library of 7-arylamino-substituted 4-aminopyrazolo[1,5-*a*][1,3,5]triazine-8-carbonitriles **6** (Table 1).[17] Compounds **6** were obtained in pure form under similar conditions. Electron-withdrawing and electron-donating substituents on the arylamino moiety were equally well tolerated and the yields for all compounds within the series were comparable.

The cyano group on the pyrazole ring remained intact as confirmed by a band at 2209-2228 cm^{-1} in the IR spectra

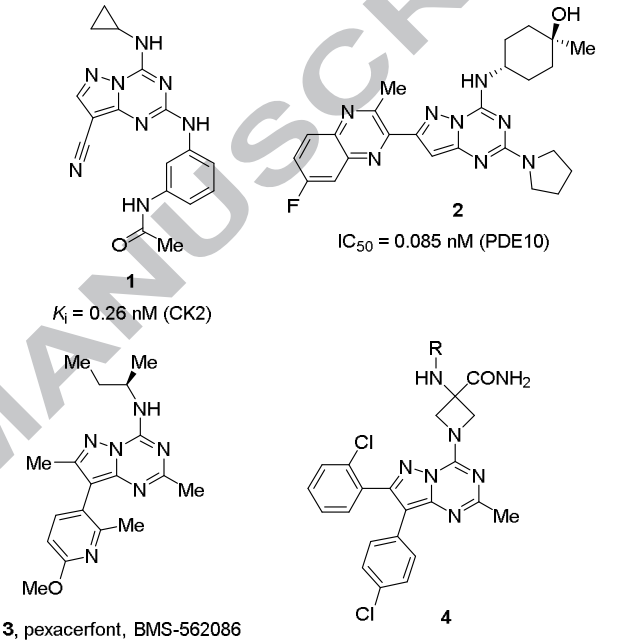
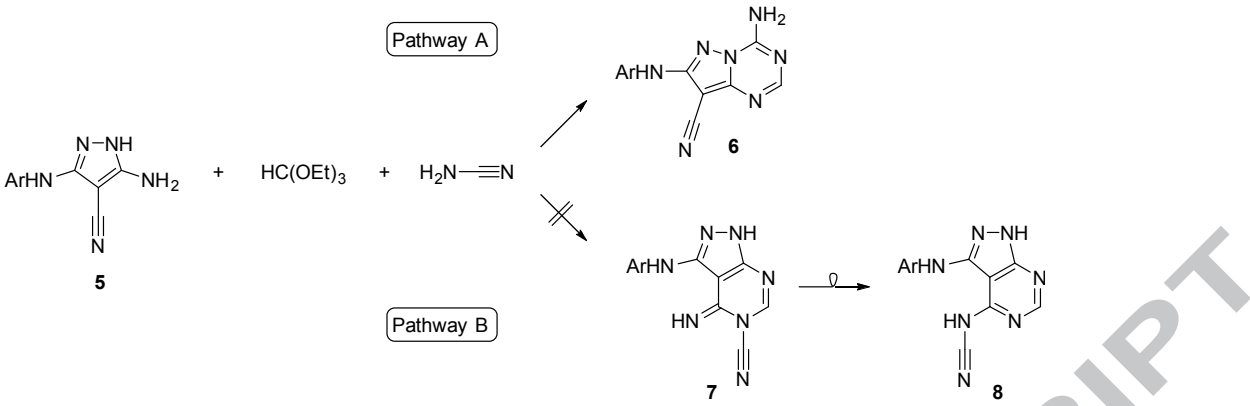


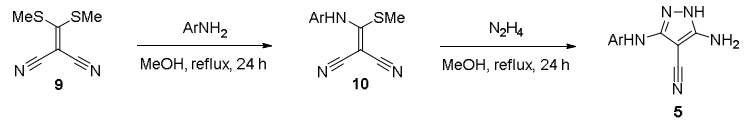
Figure 1. Some biologically active amino-substituted pyrazolo[1,5-*a*][1,3,5]triazines **1-4**.

(stretching vibrations) and resonances at 112.8-113.2 ppm in the ^{13}C NMR spectra, therefore supporting the cyclization according to Pathway A (Scheme 1) and the formation of compounds **6**.

The low-field shifted singlet (8.14-8.19 ppm) and two broad signals at 8.33-8.48 ppm and 8.94-8.98 ppm in the ^1H NMR spectra of compounds **6** were attributed to the ring proton (H-2) and the primary amino group protons at C-4 of the newly constructed aminotriazine ring. The lone pair of electrons of an amino group nitrogen on a 1,3,5-triazine ring possesses a high degree of delocalization resulting in the substantial *p*-character of the orbital and locking the amino group and its substituents in the plane of the heterocyclic ring.[18] This phenomenon was manifested in hindered rotation around the C-N bond of the amino group and consequent splitting of the ^1H NMR signals of this group in spectra of unsymmetrically substituted 1,3,5-triazines. In the case of compounds **6**, intramolecular hydrogen bonding with a nitrogen atom of the pyrazole ring could also contribute to the magnetic inequivalence of the two protons of the amino group at C-4 and therefore splitting of their signals in the ^1H NMR spectra.



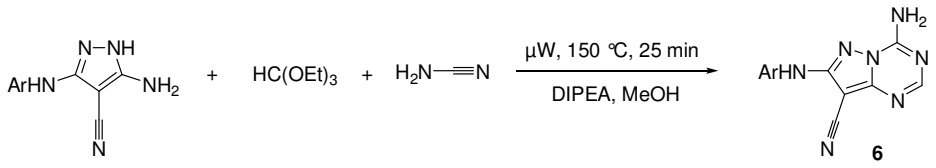
Scheme 1. Three-component reaction of 5-amino-3-arylaminopyrazole-4-carbonitriles **5** with triethyl orthoformate and cyanamide.

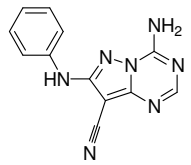
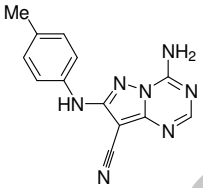
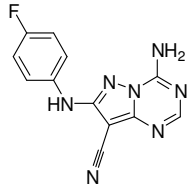
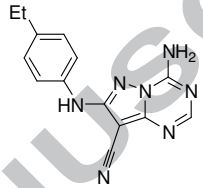
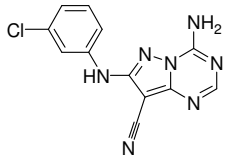
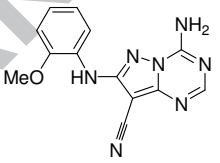
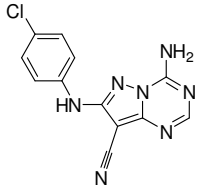
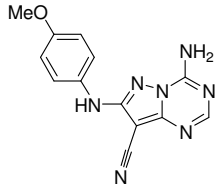
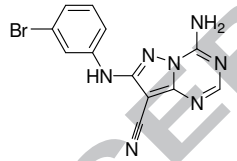
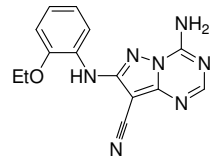
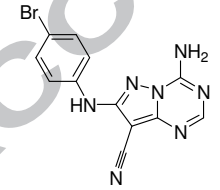
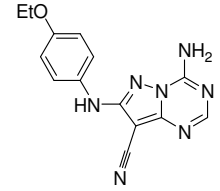
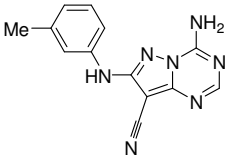
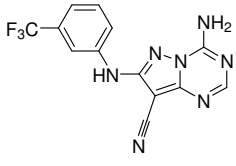


Ar = Ph (**5a**), 4-ClC$_6$H$_4$ (**5d**), 3-MeC$_6$H$_4$ (**5g**), 2-MeOC$_6$H$_4$ (**5j**), 4-EtOC$_6$H$_4$ (**5m**), 4-FC$_6$H$_4$ (**5b**), 3-BrC$_6$H$_4$ (**5e**), 4-MeC$_6$H$_4$ (**5h**), 4-MeOC$_6$H$_4$ (**5k**), 3-F$_3$CC$_6$H$_4$ (**5n**) 3-ClC$_6$H$_4$ (**5c**), 4-BrC$_6$H$_4$ (**5f**), 4-EtC$_6$H$_4$ (**5i**), 2-EtOC$_6$H$_4$ (**5l**),

Scheme 2. Synthesis of 5-amino-3-arylaminopyrazole-4-carbonitriles (**5**).

Table 1. Synthesis of 7-arylamino-substituted 4-aminopyrazolo[1,5-*a*][1,3,5]triazine-8-carbonitriles **6**.



Product	Structure	Yield (%)	Mp (ºC)	Product	Structure	Yield (%)	Mp (ºC)
6a		49	295-296[a]	**6h**		44	307-309[c]
6b		51	296-298[b]	**6i**		51	277-279[c]
6c		55	323-325[c]	**6j**		43	276-278[a]
6d		57	318-320[d]	**6k**		59	254-256[e]
6e		47	325-326[b]	**6l**		57	290-292[a]
6f		54	325-327[a]	**6m**		58	254-256[e]
6g		48	307-308[a]	**6n**		43	336-338[a]

Recrystallization solvents: [a] MeCN, [b] DMF and H_2O, [c] EtOH, [d] methoxyethanol, [e] pentanol.

In summary, we have successfully developed a one-pot, multicomponent, microwave-assisted synthesis of hitherto unknown 7-arylamino-substituted 4-aminopyrazolo[1,5-*a*][1,3,5]triazine-8-carbonitriles **6**. The developed approach utilizes selective annulations of the aminotriazine ring onto 5-amino-3-arylaminopyrazole-4-carbonitriles **5**. The good synthetic accessibility of pyrazoles **5** makes this method a very convenient

tool for the preparation of libraries of molecules for biological investigations.

Acknowledgements

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.XX.XXX. These data include experimental details, copies of ^{1}H and ^{13}C NMR spectra of the prepared compounds and photographs of products and the corresponding reaction mixtures prior to and after applying microwave irradiation.

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17. *General method for the synthesis of 7-arylamino-substituted 4-aminopyrazolo[1,5-a][1,3,5]triazine-8-carbonitriles* ***6***. A mixture of 5-amino-3-arylaminopyrazole-4-carbonitrile **5** (1 mmol), cyanamide (50.4 mg, 1.2 mmol), triethyl orthoformate (0.3 mL, 1.8 mmol) and DIPEA (87 µL) in MeOH (2 mL) was irradiated in a 10 mL seamless pressure vial using a CEM Discover microwave synthesizer operating at maximum microwave power (up to 150 W) at 150 °C for 25 min. After cooling, the precipitated product **6** was filtered, washed with cold MeOH and recrystallised from a suitable solvent.
Experimental data for some representative compounds:
4-Amino-8-cyano-7-phenylaminopyrazolo[1,5-a][1,3,5]triazine ***(6a)****:* mp 295-296 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 6.96 (1H, t, ^{3}J = 7.3 Hz, H-4′), 7.29 (2H, t, ^{3}J = 8.0 Hz, H-3′ and H-5′), 7.88 (2H, d, ^{3}J = 7.7 Hz, H-2′ and H-6′), 8.17 (1H, s, H-2), 8.42 (1H, br s, NH), 8.94 (1H, br s, NH), 9.44 (1H, s, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 68.4 (C-8), 113.1 (C≡N), 118.1 (C-2′ and C-6′), 121.2 (C-4′), 128.7 (C-3′ and C-5′), 140.6 (C-1′), 149.8 (C-8a), 152.9 (C-4), 154.8 (C-7), 157.1 (C-2); IR (ATR): ν 3388 (N-H), 3284 (N-H), 3048 (C-H), 2215 (C≡N), 1684, 1590, 1555, 1512, 1466 cm^{-1}. Anal. Calcd. for $C_{12}H_9N_7$: C, 57.37; H, 3.61; N, 39.02. Found: C, 57.25; H, 3.64; N, 38.88.
4-Amino-8-cyano-7-(4-fluorophenylamino)-pyrazolo[1,5-a][1,3,5]triazine ***(6b)****:* mp 296-298 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.10 (2H, dd, ^{3}J = 8.9 Hz, $^{3}J_{HF}$ = 8.9 Hz, H-3′ and H-5′), 7.91 (2H, dd, ^{3}J = 9.2 Hz, $^{4}J_{HF}$ = 4.8 Hz, H-2′ and H-6′), 8.16 (1H, s, H-2), 8.45 (1H, br s, NH), 8.94 (1H, br s, NH), 9.50 (1H, s, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 68.2 (C-8), 113.0 (C≡N), 115.0 (d, $^{2}J_{CF}$ = 21.9 Hz C-3′ and C-5′), 119.7 (d, $^{3}J_{CF}$ = 7.5 Hz C-2′ and C-6′), 137.0 (d, $^{4}J_{CF}$ = 2.1 Hz C-1′), 149.8 (C-8a), 152.9 (C-4), 154.8 (C-7), 157.0 (d, $^{1}J_{CF}$ = 237.8 Hz C-4′), 157.2 (C-2); IR (ATR): ν 3381 (N-H), 3288 (N-H), 3063 (C-H), 2219 (C≡N), 1683, 1595, 1561, 1502, 1462 cm^{-1}. Anal. Calcd. for $C_{12}H_8FN_7$: C, 53.53; H, 3.00; N, 36.42. Found: C, 53.38; H, 3.09; N, 36.28.
4-Amino-7-(3-chlorophenylamino)-8-cyanopyrazolo[1,5-a][1,3,5]triazine ***(6c)****:* mp 323-325 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.00 (1H, ddd, ^{4}J = 0.8 Hz, ^{4}J = 2.0 Hz, ^{3}J = 7.9 Hz, H-4′), 7.31 (1H, t, ^{3}J = 8.1 Hz, H-5′), 7.79 (1H, t, ^{4}J = 2.1 Hz, H-2′), 8.00 (1H, ddd, ^{4}J = 0.8 Hz, ^{4}J = 2.2 Hz, ^{3}J = 8.3 Hz, H-6′), 8.18 (1H, s, H-2), 8.56 (1H, br s, NH), 8.97 (1H, br s, NH), 9.64 (1H, s, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 68.7 (C-8), 112.9 (C≡N), 116.6 (C-6′), 117.2 (C-2′), 120.9 (C-4′), 130.4 (C-5′), 133.1 (C-3′), 142.0 (C-1′), 149.9 (C-8a), 153.0 (C-4), 154.4 (C-7), 157.3 (C-2); IR (ATR): ν 3360 (N-H), 3309 (N-H) 3098 (C-H), 2215 (C≡N), 1656, 1589, 1553, 1521, 1469 cm^{-1}. Anal. Calcd. for $C_{12}H_8ClN_7$: C, 50.45; H, 2.82; N, 34.32. Found: C, 50.33; H, 2.94; N, 34.19.
18. Fernandez, M. I.; Oliva, J. M.; Armesto, X. L.; Canle, L. M.; Santaballa, J. A., *Chem. Phys. Lett.* **2006**, *426*, 290-295.