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Regiochemistry of addition of aminoheterocycles to α-cyanocinnamonitriles: formation of aza-bridged bi- and tricycles

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Abstract—The additions of various five-membered ring aminoheterocycles to α-cyanocinnamonitriles were studied. Regiochemistry of product formation can in most cases be controlled by choosing the appropriate electrophile. An α-cyanocinnamonitrile with an additional β-leaving group normally provides products arising from initial attack of the ring amino group, while exo attack predominates in the case of the parent α-cyanocinnamonitrile. Aminopyrazole and aminoindazole provide only exo products with either electrophile. Product assignments were made via X-ray and 2D NMR methods; these assignments serve as a benchmark to several literature references and to future investigations of conjugate additions of these nucleophiles.

Both 2- and 4-aminopyrimidines, and 2-aminopyridines are favored structures in drug design, possessing a hydrogen bond acceptor–donor 'hinge' required for activity against the ATP domains of kinase targets. The drive for newer, patentable structures with different inhibitory profiles led us to attempt to derive heterocycles, based on the aminopyrimidine structure, that are highly amenable to analog synthesis. We sought entry into aza-bridged 6,5-ring systems of the type shown in Figure 1, specifically those with an easily manipulable functional group adjacent to the exocyclic amino group, such as a cyano moiety. Syntheses of these heterocycles in the literature are few, and often specific to a single compound.[1] Additionally, products usually feature additional exocyclic amino or hydroxyl groups, additional fused rings, or both.

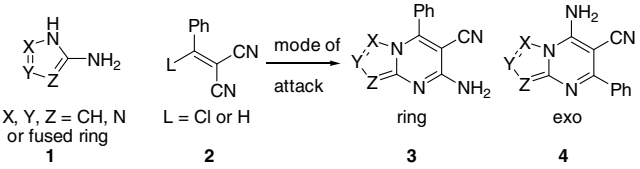

Figure 1.

Alpha-cyano acrylonitriles with a β-alkoxy,[2] β-thioalkoxy,[3] or β-chloro[4] leaving group have been employed in the syntheses of only a few heterocycles. Simple additions of amidines, guanidines, or their equivalents are rare.[2b,5] We reasoned that addition of aminoheterocycles to an appropriately substituted cinnamonitrile should provide the desired aza-bridged compounds. Alternately, an α-cyanocinnamonitrile without a β-leaving group could also give the target heterocycles due to expected autoxidation of initial products.

Heterocycles with endo- or ring-NH, and exo-amino groups can potentially add in either of two regiochemical senses, resulting from first-step conjugate addition of either group, followed by attack on the *syn*-cyano group to close the pyrimidine ring. A few examples exist in the literature of additions of these or related heterocycles to β-substituted-α-cyano acrylonitriles or acrylates, either with[1a–d,6] or without[1e–j,7] an additional β-leaving group, to form bicyclic products (Fig. 1). Conditions reported are almost uniformly weakly basic (pyridine or EtOH/amine), however, the reported regiochemical results for

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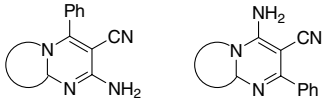
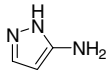
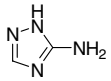
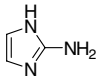
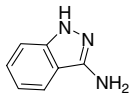
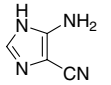
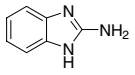
both sets of examples are mixed, with products resulting from initial conjugate addition of both exo-amino and ring-NH groups. Oddly, mention is rarely, if ever, made of the possibility, or presence, of a regioisomeric product. Moreover, structural assignments are unclear in many cases. NMR spectra for a pair of regioisomers are often very similar (see below), and previous work has typically either reported spectra as being 'consistent' with a proposed structure, or has assigned structures based on prior literature assignments, which were themselves not unambiguously determined. More compelling structural determinations, such as 2D NMR experiments or X-ray crystal structures, are lacking. Thus, in addition to synthesizing target molecules, we required reliable, definitive identification of regioisomeric products.

We began by adding various aminoheterocycles to both β-Cl-α-cyanocinnamonitrile (**2a**)[8] and α-cyanocinnamonitrile (**2b**). Results are shown in Table 1. Reactions with **2a** were refluxed for 24 h, though reactions usually were complete in 2–4 h; initial addition products were evident immediately by LC–MS, but further heating was necessary to drive all intermediates to the final closed forms. Reactions with **2b** were also refluxed for 24 h, though again they were sometimes completed much sooner, and occasionally products could only be obtained by stopping reactions after a short time due to decomposition; yields in these cases were maximized by carefully following reactions by LC–MS. Reported yields are from chromatographic separation, though products could often be obtained in sufficient yield by trituration from the reaction mixtures with ether. All reactions were performed a minimum of two times.[9]

Table 1.



3 initial ring attack **4** initial exo attack

Amino-heterocycle	Reaction conditions	Products resulting from reaction with	
		L=Cl (**2a**)	L=H (**2b**)
 **1a**	EtOH/TEA	**4a**, 68%, **5**, 21%	**4a**, 75%
	EtOH/NaOEt	**4a**, 80%, **5**, 7%	**4a**, 47%
	Pyr/NaOAc	**4a**, 70%	**4a**, 57%
 **1b**	EtOH/TEA	**3b**, 71%	**4b**, 54%[b]
	EtOH/NaOEt	**3b**, 78%	**4b**, 40%[b]
	Pyr/NaOAc	**3b**, 51%	**4b**, 65%
 **1c**[a]	EtOH/TEA	**3c**, 69%	**4c**, 12%[c]
	EtOH/NaOEt	**4c**, 81%	**4c**, 60%
 **1d**	EtOH/TEA	**6**, 82%, **4d**, 14%	**4d**, 77%
	EtOH/NaOEt	**6**, 80%, **4d**, 14%	**4d**, 40%
 **1e**	EtOH/TEA	**3e**, 82%	**4e**, 44%[b,c]
	EtOH/NaOEt	**3e**, 77%	—
 **1f**	EtOH/TEA	**3f**, 89%	**4f**, 58%[b]
	EtOH/NaOEt	**3f**, 75%	**4f**, 8%[c]

[a] 1/2 H_2SO_4 salt. Reactions run with 2 equiv of base.
[b] Isolated product subsequently reacted with 1 equiv DDQ in DCM/water for 10 min. Yield is for two steps.
[c] Refluxed for 1 h.

As Table 1 shows, in almost all cases one of the anticipated products predominated, usually in good to excellent yield. As expected, yields were almost uniformly lower when **2b** was employed. The most electron-poor rings did not autoxidize under the normal reaction conditions (open air reflux), requiring subsequent treatment with DDQ to aromatize the newly formed ring in near-quantitative yield from the initial product. The main observation from Table 1 is that exclusively exo-derived products were formed from reactions with **2b**, while the outcome of reactions with **2a** seemed to depend on the nature of the heterocycle. In most cases products were derived from initial ring attack, however the aminopyrazole and aminoindazole **1a** and **1d** afforded exo products.

Surprisingly, a minor product in almost all reactions with 3-aminopyrazole **1a** was compound **5**, presumably derived from initial attack of the position 1 nitrogen of the pyrazole ring. We expected that reactions using the corresponding indazole **1d** would generate more of the analogous product, since the fused benzene ring should bias localization of the acidic NH to position 1. In the event, product ratios were almost completely reversed, with excellent yields of **6** and only small amounts of the exo-derived product **4d**. Thus, ring attack of both **1a** and **1d** takes place via N1 rather than N2, and subsequent ring closure is accompanied by opening of the original ring, likely via the exo-imine tautomers of the initial intermediates (Fig. 2). We also sometimes saw variable amounts of a cyanoimine analogous to **5** in reactions of **1b** with **2a**.

The combination of **1c** and **2a** was the only example in which any sensitivity to reaction conditions was

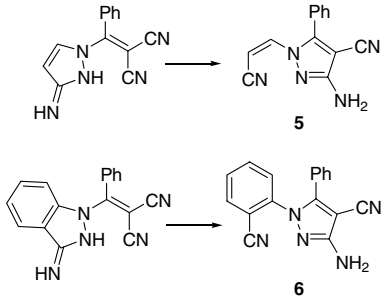


Figure 2.

observed. It is not clear to us why the more basic conditions caused a preference for the exo product. We do note that this result was reproducible, and that these two reactions were the only ones in the study in which we routinely saw evidence of opposite regioisomers as minor products.

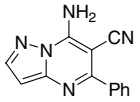
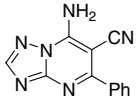
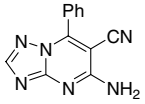
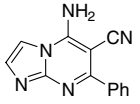
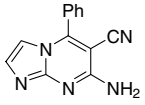
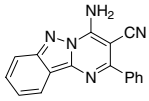
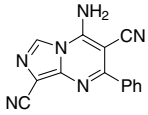
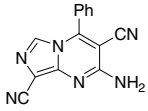
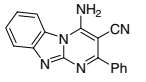
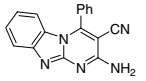
Interestingly, benzimidazole **1f** forms the ring attack-derived product **3f** upon reaction with **2a**, in spite of the severe steric compression created by the benzo and phenyl rings forced into close proximity. This structure was confirmed by a ROESY experiment (see below), but the ^{1}H spectrum alone provides evidence of this structure through the large upfield shift of the benzo protons indicating strong shielding by the phenyl ring.

Structural assignments were made primarily on the basis of X-ray and NMR structure determinations of selected products. We obtained X-ray crystal structures of compounds **3c**, **4b**, **5**, and **6**.[10] Additionally, the structures of **3e**, **3f**, **4c**, **4f**, and **6** were confirmed using various NMR techniques (COSY, ROESY, HSQC, and HMBC) to assign ^{1}H and ^{13}C resonances, and using ROESY correlations to assign structure. Thus at least one of the pairs of isomers **b**, **c**, **e**, and **f** was unambiguously assigned, as well as the unexpected products **5** and **6**. Table 2 compiles the ^{1}H NMR spectra of the isomeric products. Of note is the pattern of chemical shifts of the heterocyclic ring protons. Resonances of the compounds resulting from initial exo attack are consistently shifted farther downfield than their corresponding ring attack-derived regioisomers. The X-ray structure of **4b** also verifies the identity of the ring nitrogen involved in ring closure as N2 and not N4. The structure for **3b** was assigned by analogy to this, though we cannot rule out the isomer where initial attack takes place via N4.

We were unable to unambiguously assign structures to **4a** and **4d**, but we feel confident in assigning them as exo attack-derived products for two reasons. First, a scan of the literature shows that aminopyrazoles overwhelmingly react via the exo-amino group, not only toward Michael acceptors but a wide variety of electrophiles. The universality of exo-products from **2b** in this study also argues for **4a/4d**, as does the presence of the ring attack-derived **5** and **6**.

The results can be rationalized as follows. In the case of **2a**, heterocycle addition is irreversible, so the outcome is determined by kinetic control of the first step. With **2b**, however, initial addition gives rise to what can be seen as Michael-type intermediates, which can exchange exo- and ring-added forms via elimination and subsequent addition of a second molecule. Thus the exo preference in **2b** manifold probably reflects a thermodynamic bias toward initial exo-addition. This mechanistic framework explains the generation of the hindered **3f** as a result of kinetic control. In the cases of **1a** and **1d**, both the extreme preference for reaction at the exo amino group, and the preference within the ring attack manifold for reaction via N1 rather than N2, effectively close off the pathway toward products of type **3**. The preference for exo products from **1a** is in keeping with the literature on aminopyrazoles, which shows a strong preference for reaction at the exo amine.

Table 2.

Product and reaction mode			NMR shifts (DMSO, 300 MHz, δ)		
			NH_2	Bi/tricycle	Ph
	**4a**	exo	8.89	8.26, 6.62	7.81 (2), 7.54 (3)
	**4b**	exo	9.25	8.61	7.84 (2), 7.58 (3)
	**3b**	ring	7.87	8.27	7.84 (2), 7.66 (3)
	**4c**	exo	8.87	8.12, 7.63	7.82 (2), 7.55 (3)
	**3c**	ring	7.28	7.29, 7.05	7.78 (2), 7.70 (3)
	**4d**	exo	9.15	8.13, 7.77, 7.63, 7.23	7.92 (2), 7.58 (3)
	**4e**	exo	6.63	8.11	7.74 (2), 7.46 (3)
	**3e**	ring	7.97	7.69	7.83 (2), 7.71 (3)
	**4f**	exo	8.80	8.59, 7.75, 7.55, 7.39	7.88 (2), 7.57 (3)
	**3f**	ring	9.95	7.56, 7.26, 6.82, 5.90	7.79 (2), 7.76 (3)

It is important to note that the intermediate α-carbanions were not symmetric; that is, they were substituted by two different groups rather than being doubly cyano-substituted, one would have to consider the potentially complicating issues of double bond isomer interconversion, and a difference in ring closure rates stemming from the different trapping electrophiles. For example, we reacted aminopyrazole **1a** with both double-bond isomers of methyl 3-chloro-2-cyanocinnamate **7**, and in both cases the only product, **8**, resulted from closure on the ester (Fig. 3). The structure of **8** was established by X-ray crystallography of its sodium salt.

Here, it seems clear that double-bond isomerization can occur, and that ring closure on the ester is much faster than on the nitrile. Interestingly, an earlier paper reports

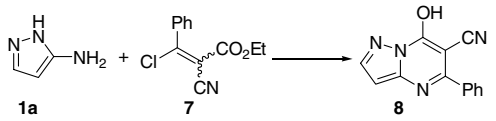


Figure 3.

that a similar pair of intermediates closes preferentially on the nitrile under acidic conditions.[7a]

Finally, we note that as expected, preliminary experiments show that substitution on the β-phenyl group or replacement of the phenyl with an alkyl group does not have an effect on regiochemical outcome. Thus in this study, through rigorous structure determination we have established the general regiochemical outcome of additions of this family of heterocyclic amines, and provided evidence of an element of product control by the nucleophiles. This mechanistic understanding should be applicable to analogous additions to other activated unsaturated systems.

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9. Genreal procedures: Reactions with **2a**: A solution of heterocyclic amine (1 mmol), **2a** (1 mmol), and base (1 mmol) in 5 mL absolute ethanol was refluxed for 24 h. Products were obtained by chromatography on silica gel, or triturated by addition of ether to the cooled reaction mixture. Reactions with **2b**: A solution of heterocyclic amine (1 mmol), **2b** (1 mmol), and base (1 mmol) in 5 mL absolute ethanol was refluxed in open air for 1–24 h, following progress by LC–MS. In cases where autoxidation occurred, products were obtained as above. Where unoxidized products were formed, chromatography was followed by taking up the pure unoxidized product in DCM (5 mL) and water (2 mL) and stirring with DDQ (1 equiv) for 10 min. The layers were then separated and the final product subjected to chromatography through a short silica gel column.
10. Crystallographic data (excluding structure factors) for the structures in this Letter have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 648309–648313 for **3c**, **5**, **4b**, **8**, and **6**, consecutively. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(0) 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk].