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Amide Anions as Unexpected Activating Groups in Nucleophilic Heteroaromatic Substitution

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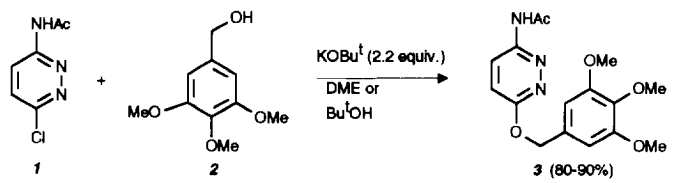
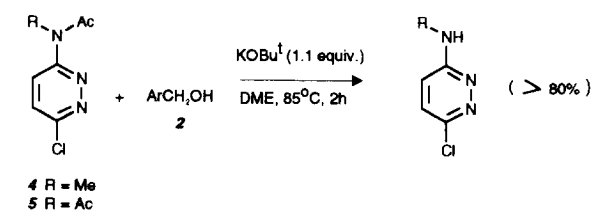
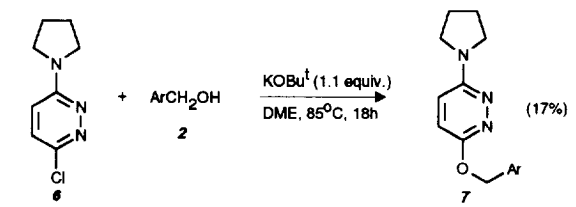
Abstract: Nucleophilic displacement of halide by alkoxide in pyridazines, phthalazines, a thiazole and a thiadiazole is unexpectedly activated by acetamido anion substituents compared to neutral amido and amino substituents.

During the synthesis of some pyridazinyl ethers, we made an intriguing observation on the relative reactivities of 3-chloropyridazines towards 3,4,5-trimethoxybenzyl alcohol ***2***. 3-Amino-6-chloropyridazine[1] reacted slowly with the alkoxide anion from ***2*** in a complex, low-yielding reaction, but its *N*-acetyl derivative ***1***[2] reacted cleanly and rapidly to give the desired ether ***3***. In 1,2-dimethoxyethane (DME) or t-butanol in the presence of 2.2 equivalents of potassium t-butoxide, ***1*** and ***2*** gave ***3*** in 80-90% yield in about 1 hour.





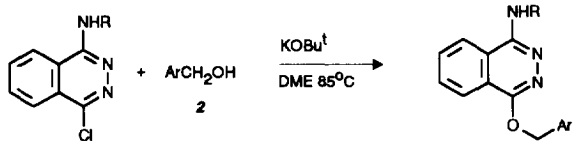


However, in the absence of the acetamido *N*-H (and hence, in these basic conditions, of the derived anion) there was little or no reaction. The acetamido anion was, of course, expected to be much less activating than the neutral substituent in nucleophilic displacement of chlorine by alkoxide.

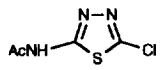
When the anions of ***1*** and ***2*** were each preformed with sodium hydride in DME before mixing, the ether ***3*** was again formed rapidly and cleanly in the same high yield. However, when the *N*-methylacetamide ***4***[3] or the bis-acetyl derivative ***5*** were subjected to the same conditions, the chlorine was not displaced; the only reaction observed, in high yield (>80%), was *N*-deacetylation. The methylacetamide ***4*** was taken as a model for the *neutral N*-H compound ***1***. The latter did not deacetylate under the same conditions; presumably it was all converted into the acetamido anion which resisted further nucleophilic attack. Deacetylation of the bis-acetyl derivative ***5*** by the alkoxide from ***2*** must be fast, as would be expected, converting the alkoxide into its acetate and leaving little or no alkoxide to displace chlorine from the anion of ***1*** formed by deacetylation, and indeed the ether ***3*** was not formed.

If nucleophilic displacement of chlorine had occurred from the neutral form of acetamide ***1***, then similar displacement in the bis-acetyl derivative ***5***, with two electron - withdrawing acetyl groups, would surely have been faster, but no displacement of chlorine from ***5*** was observed. Furthermore, when 3-chloro-6-pyrrolidinopyridazine ***6***[4] was subjected to exactly the same conditions, the reaction was markedly slower and more complex. After 18 hours at reflux, both the alcohol ***2*** and the pyridazine ***6*** were recovered, together with baseline products and only a low yield (17%) of the ether ***7***. Here there is no possibility of anion formation, but there is also no amide function. The *N*-pivaloyl derivative analogous to ***1*** underwent the same rapid and clean reaction with alcohol ***2*** (1.5equiv.) and sodium hydride (2.5 equiv.) in DME to give the analogous product ***3*** (Bu^tCO for Ac) (87%).

The above results point to a significantly enhanced reactivity of the acetamidopyridazine ***1*** in its anionic form which hardly seems compatible with normal nucleophilic aromatic substitution (S_NAr) where activation by electron withdrawing groups is predominant. The scope of this observation was therefore investigated further, with the phthalazines ***8***[5] and ***9*** and the 5-membered heterocycles ***10***[6] and ***11***.[7]



8 R = H
9 R = Ac



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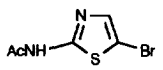

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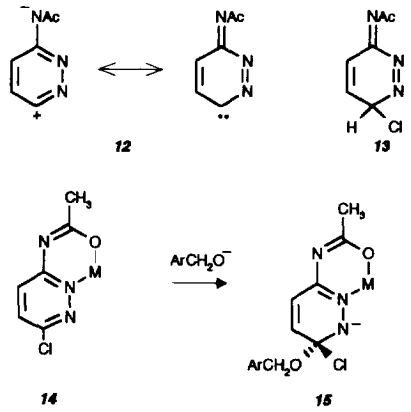
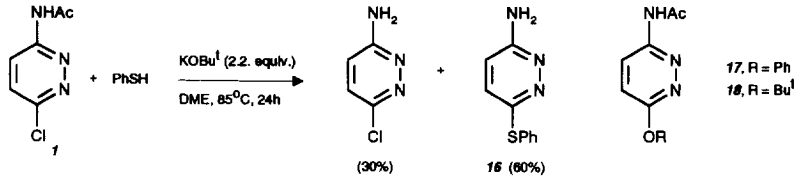
Under our standard conditions 1-amino-4-chlorophthalazine ***8*** gave very little chlorine displacement in 4 hours, whilst its N-acetyl derivative ***9*** rapidly gave the corresponding ether in quantitative yield (t.l.c.) and in an isolated yield of 87% in 1 hour. The amino compound ***8*** has also been shown to react very slowly with methanolic sodium methoxide;[8] the even slower reaction of the anion of 1-chloro-4-hydroxyphthalazine (***9***, O^- for N^-Ac)[8] is in marked contrast with the high reactivity of the amide anion of ***9*** in our reaction. Similarly 2-acetamido-5-chloro-1,3,4-thiadiazole ***10*** and 2-acetamido-5-bromothiazole ***11*** (5-halothiazoles being unexpectedly susceptible to nucleophilic displacement reactions[9]) both underwent clean displacement (t.l.c.) of halogen under the standard conditions to give the corresponding trimethoxybenzyl ethers, isolated in 52 and 46% yield respectively. When sodium hydride was used as base, the bromo compound ***11*** also gave some debrominated product; in the absence of the alcohol ***2*** this product, 2-acetamidothiazole, was isolated in 90% yield.

Reaction Mechanism In view of the apparent activation of halogen displacement by the acetamido anion, alternatives to the common two-step S_NAr mechanism were considered. A hetaryne mechanism is not possible for phthalazine ***9*** and thiadiazole ***10*** and would be of very high energy for the thiazole ***11***. It can probably be ruled out for all the substrates since mixtures of regioisomers were never observed; for example, in many conversions of ***1*** into ***3*** (in high yield), the 5-aryloxy isomer of ***3*** was not detected.



When 3-acetamido-6-chloropyridazine ***1*** was heated to reflux in DME with potassium t-butoxide (1.1 equiv.) for an extended period (18 hours) no new products were formed and ***1*** was recovered (90%); thus loss of chloride from the anion of ***1*** to give the carbenic-dipolar intermediate ***12*** is also very unlikely. As noted above, ether ***3*** was rapidly produced by interaction of the preformed anions of ***1*** and ***2***, suggesting that a proton source is not necessary, and thus intermediate formation of the allylic tautomer ***13*** of ***1*** also appears unlikely. Single electron transfer to the anion of ***1*** seems equally unlikely, and indeed *p*-dinitrobenzene had no effect upon the reaction. Thus we resort for the present to the S_NAr mechanism proceeding from the anion of ***1***, as the ion pair ***14*** with the metal ion (M=Na, K) chelated, to the tetrahedral intermediate ***15*** stabilised by dipolar attraction.

We briefly studied the reaction of chloropyridazine *1* with two other nucleophiles. With the strongly nucleophilic thiophenoxide [from thiophenol (1.1 equiv.) and potassium t-butoxide (2.2 equiv.) in DME containing a little 1,3-dimethylimidazolidin-2-one to aid solubility] some deacetylation of *1* (30%) was observed for the first time. The major product *16* (60%) was that of nucleophilic substitution and deacetylation. When thiophenol was replaced by phenol there was much less deacetylation; surprisingly the major product was not the phenoxy derivative *17* but the t-butoxy derivative *18* (57%); the unexpected



replacement of chlorine by t-butoxy had not been observed in any of the earlier reactions. When the acetamide anion was preformed from *1* and sodium hydride in DME and heated with potassium t-butoxide for 3 days the t-butoxy ether *18* was formed in high yield (82%), thus providing another illustration of the high reactivity to nucleophilic displacement of chlorine in the anion of the acetamidopyridazine *1*.

The scope and mechanism of the acetamido anion as an activating (electron - withdrawing?) group in nucleophilic aromatic substitution has still to be determined. If these remarkably clean reactions extend to a wider range of substrates and nucleophiles, they could be useful in synthesis, particularly with aminoheterocycles bearing relatively inert halogens.

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