PERKIN 1 COMMUNICATION

Cyclic guanidines. Part 6.[1] Synthesis of benzimidazoles by intramolecular vicarious nucleophilic substitution of hydrogen

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***m*-Nitrophenylguanidines, which carry a vicarious leaving group, cyclize under basic conditions yielding nitrobenzimidazoles. Preliminary observations of the regioselectivity of the ring closure reaction are reported.**

The principle of vicarious nucleophilic substitution of hydrogen (VNS) was first described by Golinski and Makosza.[2] This type of reaction has been used for the amination of nitroarenes[3] and also examples with O-alkyl as a vicarious leaving group are known.[4] Occasionally intramolecular VNS has been applied in the preparation of heterocycles.[5] Among the less frequently employed procedures for preparing benzimidazoles are those which start from *N*-substituted *N′*-arylamidines or -guanidines.[6] The intramolecular attack of the nitrogen atom on the aromatic moiety is accompanied by loss of the *N*-substituent. Although related to the VNS reaction, these processes are not clearly defined nucleophilic reactions since the arenes are not activated by suitable functional groups.

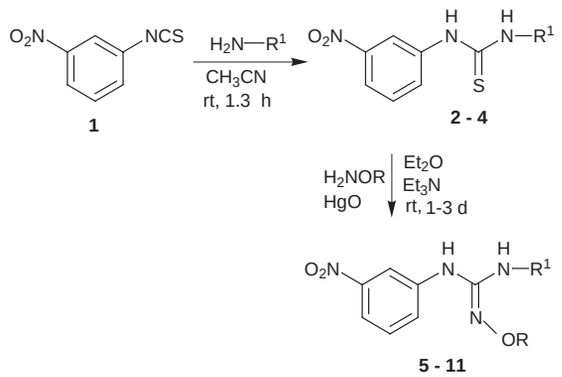
Previously we described the preparation of benzimidazoles by ring closure of (3-nitrophenyl)guanidines.[7] This base induced redox process suffers from the concomitant formation of azoxy compounds which limits the yield to ≤60%. In order to transform this reaction to a VNS reaction, we tried to introduce a potential vicarious leaving group into the starting guanidine. By this means we should be able to circumvent the formation of azoxy side products and raise the theoretical yields to 100%. As a matter of fact, in none of the described cyclization reactions have azoxy compounds been detected as by-products.

The preparation of the adducts for the VNS is depicted in Scheme 1. The addition of an amine to **1** proceeds almost quantitatively. For the synthesis of **5**–**11** from **2**–**4** the procedure of Moynihan[8] was followed which is performed under nitrogen.

When the guanidines **5**–**11** are treated with 1 to 3.8 equivalents of KO^{t}Bu in DMSO[9] or DMF,[10] cyclization occurs resulting in the formation of **12**–**17** as yellow to orange coloured substances (Scheme 2). In some instances side products of type **18**–**20** could be identified, the structures of which correspond to **15**–**17** with the NO_2-group being replaced by OR. Analogous ethers corresponding to **12**–**14** were not observed. However, **18**–**20** are not formed by direct interconversion from **15**–**17** since treatment of **15** with methoxide under cyclization conditions did not yield any **18**. Therefore, **18**–**20** must result from the reaction of some intermediate species with *in situ* generated alkoxide.

Various observations about the regioselectivity of the ring closure reaction can be made. The nucleophile attacking the nitroaromatic moiety is always represented by the guanidino-N bearing the alkoxy-group and never by the guanidino-N carrying the alkyl (or arylalkyl) group. The ratio of the *ortho* cyclization products **12**–**14** to *para* products **15**–**17** seems to depend on several parameters, for example, the nature (size) of R, reaction temperature and solvent. Clearly OMe as a vicarious leaving group seems to favour the *ortho* cyclization irrespective of the nature of R^1, solvent and temperature. Also when R^1 is Pr^i (**8**–**10**) then the *ortho* cyclization is predominantly triggered.

The two experiments in DMF reveal a tendency towards a decrease of side products. All these observations taken together do not allow clearcut regioselectivity rules to be deduced, but they only show rough trends. Generally the *ortho* cyclization seems to be preferred, which is in accord with mechanistic ideas,[11] as well as with observations from related cyclizations.[7]

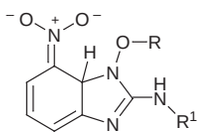


Compound	R	R^1	Total yield (%)[a]
5	Me	Bu	65
6	Et	Bu	63
7	Bn	Bu	89
8	Me	Pr^i	79
9	Et	Pr^i	80
10	Bn	Pr^i	68
11	Me	Bu	75

[a] Isolated yield.

Scheme 1

As far as the mechanism of the reaction is concerned, we believe, that cyclization is initiated by deprotonation of the –NH–OR group. In general the –*N*OR$^-$ nucleophile attacks predominantly *ortho* to the nitro group leading to an anionic σ-complex **21**. Elimination of ROH followed by reprotonation would give **12**–**14**. At present we regard the *para* cyclization as the exception.



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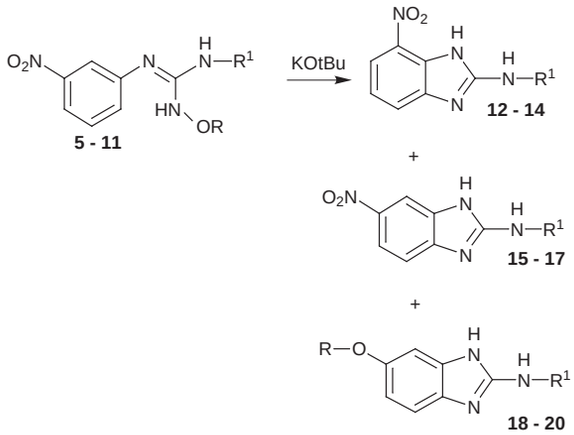
The significance of this reaction is as a route to specifically substituted benzimidazoles. The regioselectivity seems to be influenced by the nature of the vicarious leaving group OR as well as by the reaction conditions. Future experiments with this type of ring closure will allow rules for the expected regioselectivity to be established. There are many possibilities for chemically modifying the nitro group which offer the potential of preparing benzimidazoles as starting materials for multiple purposes.



Starting material	R	R^1	KO^{t}Bu (equiv.)	Solvent	Reaction temp. (°C)	Products (yield [%])[a]		
5	Me	Bu	2.5	DMSO	20	**12** (57)	**15** (1.6)	**18** (4.7)
6	Et	Bu	1.0	DMSO	70	**12** (4)	**15** (16)	—
7	Bn	Bu	1.1	DMSO	70	**12** (3.8)	**15** (16)	—
8	Me	Pr^i	3.0	DMSO	20	**13** (64)	**16** (1[b])	—
			3.0	DMF	20	**13** (65)	—	—
9	Et	Pr^i	3.0	DMSO	50	**13** (24)	**16** (24[b])	**19** (12[b])
			3.0	DMF	50	**13** (36)	**16** (9[b])	—
10	Bn	Pr^i	3.8	DMSO	20	**13** (47)	—	**19** (7[b])
11	Me	Bn	2.5	DMSO	60	**14** (42)	**17** (7.1)	**20** (13)

[a] Isolated yield, unless stated otherwise. [b] Yield calculated from mixture.

Scheme 2

Notes and references

1 Part 5: F. Esser, K.-H. Pook, A. Carpy and J.-M. Léger, *Synthesis*, 1994, 77.

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9 Representative experimental procedure with DMSO as solvent: **5** (2.82 g, 10.6 mmol) was dissolved in DMSO (50 ml) and KO^{t}Bu (3 g, 26.4 mmol) was added under nitrogen. The solution, which was stirred at room temperature for 9.5 h changed colour from light brown *via* dark blue to red–brown. It was poured into ice-cold water (700 ml), extracted with a 1:1 mixture of ether–ethyl acetate and with ether. The combined organic phases were washed with water, filtered and the solvent evaporated. The crude product was flash chromatographed over silica gel using ethyl acetate–cyclohexane (1:1) and ethyl acetate as eluents. Apart from unchanged **5** (0.55 g, 20%), were obtained **12** (1.42 g, 57%), mp 197–200 °C; δ_H (250 MHz, $CDCl_3$): 10.14 (1H, s, N*H*), 7.81 (1H, d, *J* 7.6, Ar*H*^{5}), 7.65 (1H, d, *J* 7.6, Ar*H*^{7}), 7.14 (1H, dd, *J* 7.6, 7.6, Ar*H*^{6}), 5.39 (1H, t, *J* 4.5, N*H*CH$_2$), 3.54 (2H, m, NHC*H*$_2$), 1.70 (2H, m, C*H*$_2$), 1.44 (2H, m, C*H*$_2$CH$_3$), 0.95 (3H, t, *J* 7.0, C*H*$_3$); MS (ion spray) *m*/*z* 235 (M + H$^+$, 100%); **15** (0.04 g, 1.6%), mp 182–183 °C; δ_H (250 MHz, $CDCl_3$–DMSO-d_6 = 3:1): 8.06 (1H, d, *J* 2.4, Ar*H*^{4}), 7.98 (1H, dd, *J* 8.9, 2.4, Ar*H*^{6}), 7.24 (1H, d, *J* 8.9, Ar*H*^{7}), 5.83 (1H, t, *J* 4.3, N*H*CH$_2$), 3.47 (2H, m, NHC*H*$_2$), 1.65 (2H, m, C*H*$_2$), 1.44 (2H, m, C*H*$_2$CH$_3$), 0.96 (3H, t, *J* 7.5, C*H*$_3$); MS (ion spray) *m*/*z* 235 (M + H$^+$, 100%) and **18** (0.11 g, 4.7%) as a highly viscous oil, δ_H (250 MHz, $CDCl_3$): 8.37 (1H, s, NH), 6.99–6.86 (2H, m, Ar*H*^{4} + Ar*H*^{7}), 6.58 (1H, dd, *J* 6.4, 2.4, Ar*H*^{6}), 5.56 (1H, s, N*H*CH$_2$), 3.86 (3H, s, OC*H*$_3$), 3.38 (2H, t, *J* 7.0, NC*H*$_2$), 1.50 (2H, m, C*H*$_2$), 1.23 (2H, m, C*H*$_2$CH$_3$), 0.78 (3H, t, *J* 7.5, CH$_2$C*H*$_3$); MS (ion spray) *m*/*z* 220 (M + H$^+$, 93%), 164 (57), 149 (100).

10 Representative experimental procedure with DMF as solvent: **8** (5.05 g, 20 mmol) was dissolved in DMF (90 ml) and KO^{t}Bu (6.72 g, 60 mmol) was added under nitrogen. The solution was stirred at room temperature for 17 h. It was poured into 1 M Na_2CO_3 solution (1 l), which was extracted with ethyl acetate (2 × 0.5 l). The combined extracts were filtered and concentrated under reduced pressure. The crude product was chromatographed over silica gel using ethyl acetate–cyclohexane (1:1) as eluent. From the main fraction **13** (2.84 g, 65% yield) was obtained as orange coloured crystals, mp 246–249 °C; δ_H (250 MHz, $CDCl_3$): 9.80 (1H, s, N*H*), 7.81 (1H, dd, *J* 8.5, 0.9, Ar*H*^{5}), 7.65 (1H, d, *J* 7.9, Ar*H*^{7}), 7.14 (1H, dd, *J* 8.5, 7.9, Ar*H*^{6}), 4.94 (1H, d, *J* 7.3, N*H*-CH), 4.15 (1H, m, NH-C*H*), 1.36 (6H, d, *J* 6.4, (C*H*$_3$)$_2$CH); MS (ion spray) *m*/*z* 221 (M + H$^+$, 100%).

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