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Ambident Reactivity of Nitro Heteroaromatic Anions

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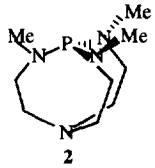
Abstract: Two classes of nitro heteroaromatic compounds such as quinoxalines **7a,b** and benzothia/selenadiazoles **7c,d** with ethyl isocyanoacetate in the presence of 1,8-diazabicyclo[5,4,0]undec-7-ene gave the corresponding pyrimidine *N*-oxides **8a-d**, whilst, in contrast, use of proazaphosphatrane **2** or iminophosphorane **4** as a base under similar conditions gave the corresponding pyrroles **9a-d**. Copyright © 1996 Elsevier Science Ltd

Compounds containing a pyrrole ring such as the isoindoles are important intermediates for the preparation of highly conjugated porphyrins and conducting polypyrroles with low band-gaps. Recently, we have reported that these annulated pyrroles are readily prepared by the reaction of polycyclic aromatic nitro compounds with ethyl isocyanoacetate in the presence of DBU.[1,2] However, this method has two serious drawbacks. First, simple nitroaromatics such as 1-nitronaphthalene gave the corresponding pyrroles in quite poor yields.[2] Second, when this method was extended to the nitro heteroarenes, the corresponding pyrroles were not obtained and pyrimidine *N*-oxides were the sole products in some cases.[3]

Recently, the yields of pyrroles prepared from nitro alkenes with ethyl isocyanoacetate were greatly improved[4] by using a much stronger non-nucleophilic base such as proazaphosphatrane[5] or iminophosphorane[6] than DBU. Therefore, we applied these bases to the preparation of annulated pyrroles. Thus, the yields of pyrroles derived from 1-nitronaphthalene **1** and 6-nitroquinoline **5** were greatly improved (Table 1). Moreover, *m*-dinitrobenzene could be converted into the corresponding nitroisoindole by use of the base **4**.

Table 1. Effect of bases on the yield of the reaction of 1-nitronaphthalene **1** and 6-nitroquinoline **5**

Run	Substrate	Base	Conditions[a]	Product /%[b]
1	**1**	DBU	RT, 24h	**3**/2
2	**1**	DBU	60°C, 48h	**3**/12
3	**1**	**2**	RT, 24h	**3**/21
4	**1**	**4**	RT, 24h	**3**/22
5	**5**	DBU	66°C, 7days	**6**/trace
6	**5**	**4**	RT, 24h	**6**/44



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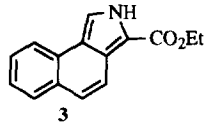

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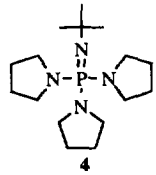

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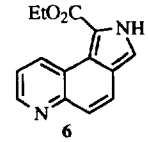

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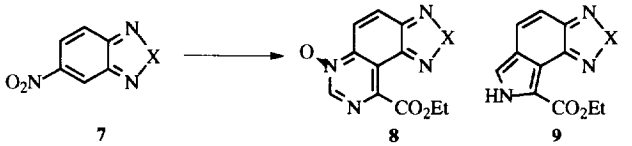
[a] Solvent: THF. [b] Yields refer to pure isolated product.

Other non-ionic bases such as 1,5-diazabicyclo[4.3.0]non-5-ene (DBN), 1,1,3,3-tetramethylguanidine or 1,8-bis(dimethylamino)naphthalene and ionic bases were not effective.

The most drastic change was observed in the reaction of two classes of compounds, that is, quinoxaline derivatives and benzothia/selenadiazole derivatives. The results are shown in Scheme 1 and Table 2.



7 8 9

a X = $CH_3C{=}CCH_3$ c X = S

b X = PhC=CPh d X = Se

Scheme 1

As we described in a previous paper[3], nitroquinoxalines **7a,b** reacted with ethyl isocyanoacetate in the presence of DBU to give the corresponding pyrimidine *N*-oxide **8a,b** in 15 and 32% yield as the sole product, respectively. In contrast, when the reaction of **7a,b** with ethyl isocyanoacetate was conducted using the phosphazene base **4**, the corresponding pyrrole **9a,b**[7] was obtained without any contamination by a pyrimidine *N*-oxide.

Table 2. Conversion of nitro compounds to pyrimidines or pyrroles

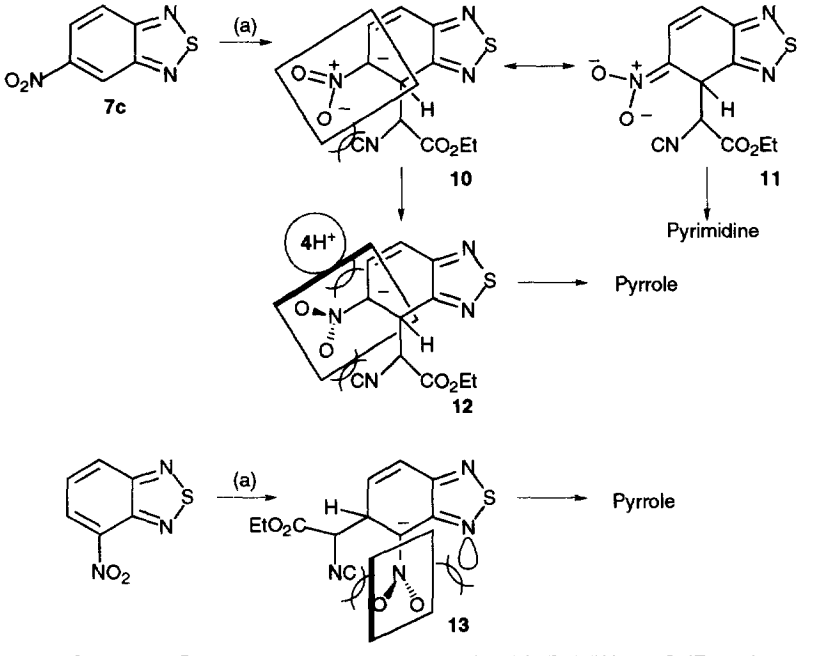
Run	Substrate	base	Conditions[a]	Yield/%	
				Pyrimidine **8**	Pyrrole **9**
1	**7a**	DBU	RT, 48h	15[b]	0
2	**7a**	**4**	RT, 24h	0	38[b]
3	**7b**	DBU	RT, 48h	32[b]	0
4	**7b**	**4**	RT, 24h	0	39[b]
5	**7c**	DBU	RT, 5h	21[b]	0
6	**7c**	**4**	RT, 40h	3[c]	46
7	**7d**	DBU	RT, 5h	28[b]	0
8	**7d**	**4**	RT, 24h	3[c]	30

[a] Solvent: THF. [b] Yields refer to pure isolated product. [c] Determined by NMR.

Similarly, 5-nitrobenzothiadiazole **7c** and 5-nitrobenzoselenadiazole **7d** with ethyl isocyanoacetate in the presence of DBU gave the corresponding pyrimidine *N*-oxide **8c,d**, whilst we were able to obtain the benzothia/selenadiazole annulated pyrroles **9c,d**[7] with a small amount of pyrimidine *N*-oxide **8c,d** by the use of the base **4**. Thus, this is a unique synthetic method to obtain such pyrroles **9a-d**.

In a previous paper[3], we proposed a mechanism for the formation of pyrroles and pyrimidines (Scheme 2). The initial attack of ethyl isocyanoacetate anion occurred at the β-position of the nitro groups to form an

anionic intermediate. When the nitro group was coplanar with an aromatic ring, this intermediate could be represented by two resonance structures **10** and **11** owing to the ambident character of the nitro group. In the case of 5-nitrobenzothiadiazole **7c**, the subsequent cyclization took place on the intermediate **11**, and the product was the annulated pyrimidine *N*-oxide **8c**. On the other hand, the annulated pyrrole results from 4-nitrobenzothiadiazole which cyclized by way of an intermediate **13**. When 5-nitrobenzothiadiazole **7c** reacted with ethyl isocyanoacetate in the presence of the base **4**, the corresponding anionic intermediate was twisted because of the bulkiness of the counter cation **4**H$^+$. Thus, the corresponding pyrrole was obtained in this case.



Scheme 2. *Reagents and Conditions* : (a)$CNCH_2CO_2Et$. DBU or **4**, THF, rt, 5h,

The present pyrrole synthesis using phosphazene base **2** or **4** provides an attractive method for the preparation of isoindoles from aromatic nitro compounds, by which the problems incurred in the method using DBU are solved.

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7 Satisfactory spectroscopic and analytical data were obtained for all new compounds. Selected physical and spectroscopic data for **9a**: mp 191 °C; δ_H ($CDCl_3$) 1.56 (t, 3H, *J* 7.18), 2.73 (s, 3H), 2.81 (s, 3H), 4.55 (q, 2H, *J* 7.12), 7.50 (d, 1H, *J* 8.85), 7.54 (d, 1H, *J* 3.05), 7.76 (d, 1H, *J* 9.16) and 10.38 (brs, 1H); δ_C ($CDCl_3$) 14.68 (CH_2CH_3), 22.61, 22.96, 61.09 (CH_2CH_3), 116.03, 116.39, 122.18, 123.54, 124.12, 125.69, 137.92, 142.06, 150.33, 150.70 and 161.49; ν_{max}(KBr)/cm^{-1} 3240, 1644, 1416, 1388, 1348, 1334, 1266 and 1204; λ_{max}($CHCl_3$)/nm 377, 364, 327, 318 and 278; *m/z* 269 (M^+, 69%), 223 (M^+-EtOH, 100) and 197 (76) (Found; C, 66.5, H, 5.5, N, 15.8. $C_{15}H_{15}N_3O_2$ requires C, 66.90, H, 5.61, N, 15.60%). For **9d**: mp 176 °C; δ_H ($CDCl_3$) 1.48 (t, 3H, *J* 7.17), 4.52 (q, 2H, *J* 7.12), 7.35 (d, 1H, *J* 3.35), 7.36 (d, 1H, *J* 9.48), 7.53 (d, 1H, *J* 9.48) and 10.04 (brs, 1H); *m/z* 297 [M^+ (^{82}Se), 17%], 296 [M^+ (^{81}Se), 13], 295 [M^+ (^{80}Se), 85], 294 [M^+ (^{79}Se), 6], 293 [M^+ (^{78}Se), 43], 292 [M^+ (^{77}Se), 16], 291 [M^+ (^{76}Se), 17], 249 (M^+-EtOH, 100), 169 (47) and 143 (34) (Found; C, 45.0, H, 3.2, N, 14.2. $C_{11}H_9N_3O_2Se$ requires C, 44.91, H, 3.08, N, 14.28%).

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