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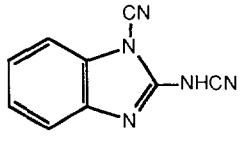
1-Aza-1',3'-Diaza-3,3'-Sigmatropic Rearrangements — A Convenient Synthesis of Benzimidazole Derivatives

M. Teresa V. L. Carvalho, Ana M. Lobo*, Paula S. Branco, and Sundaresan Prabhakar*

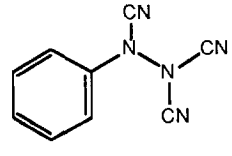
Secção de Química Orgânica Aplicada, Departamento de Química, and SINTOR-UNINOVA,
campus Faculdade de Ciências e Tecnologia, Universidade Nova de Lisboa,
2825 Monte de Caparica, Portugal

Abstract: 1-Aryl-2-acyl-2-cyanohydrazines undergo smooth thermal rearrangements to provide 2-aminoacylbenzimidazoles in excellent yields. A short synthesis of the highly mutagenic dietary amine, IQ, is reported. © 1997 Elsevier Science Ltd.

Reports of hetero-Cope rearrangements[1] involving the cleavage of N-N bonds of simple open chain aryl hydrazine derivatives where the two nitrogen atoms are retained in the final products are scarce. Pellizzari[2] had described one such reaction, where phenylhydrazine is converted to the benzimidazole (**1**) when treated with BrCN in ethanol.



1

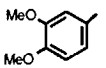
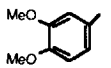


2

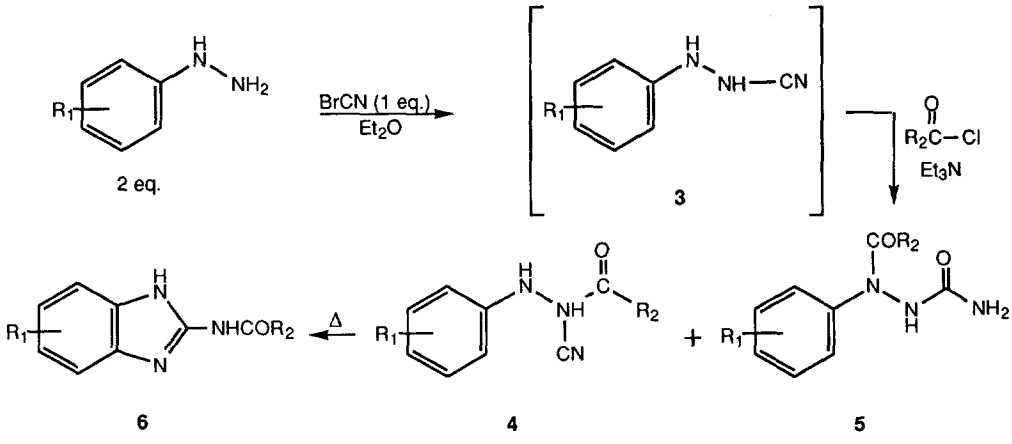
Subsequent elegant mechanistic study of Bird[3] established that the reaction proceeds through an intermediate, the tricyano compound **2**, which suffers a 3,3-sigmatropic rearrangement to give the product. The limitation inherent in the method, namely the length of time involved (typically 10-14 days for 50-60% yield) and the failure of some substances (e.g., 5-quinolyl hydrazine) to form imidazoles, prompted us to develop an expeditious and an alternative route to the title compounds (Scheme).

Accordingly, arylhydrazine[4] (2 eq.) was treated with BrCN (1 eq.) in dry Et_2O at 0°C. After the reaction was complete (tlc control), the mixture was filtered rapidly under N_2 atmosphere to remove the precipitate ($ArNH_3^+ Br^-$). The filtrate containing the unstable 1-aryl-2-cyanohydrazine[5] **3** on acylation with the appropriate acid chloride (R_2COCl ; 1 eq.) and Et_3N (1 eq.) furnished the requisite starting material, 1-aryl-2-acyl-2-cyanohydrazine[6] **4**, accompanied by small amounts of the urea[7] **5** which was easily removed by column chromatography. The compounds thus prepared are collected in the Table, which shows that a wide variety of hydrazine derivatives could be prepared, except when a strongly electron withdrawing group is present in the *p*-position (entry **i**). On heating a solution of **4a** in diphenylether (0.02 M) to 190°C a clean reaction ensued, and the product **6a** (78% yield), isolated by evaporation of the solvent *in vacuo* and purified by crystallisation, was found to be identical with an authentic sample of 2-aminoacetylbenzimidazole[8] (m.p. ; m.m.p ; t.l.c ;

Table

#	Starting material (**4**)					Product (**6**)				
	R_1	R_2	Yield (%)	M.p. °C [a]	Time[b] (min)	R_1	R_2	Yield (%)	M.p. °C [a]	
a	H	Me	55	90-93	S_1	150	H	Me	76	318 EtOH
b	2-Me	Me	35	90-91	S_1	75	7-Me	Me	93	210-211 S_2
c	3-Me	Me	60	oil		210	4-Me 6-Me	Me Me	80	287-289 S_2
d	4-Me	Me	62	78-80	S_2	150	5-Me	Me	75	289-290 S_2
e	2-Br	Me	55	97-98	S_2	145	7-Br	Me	89	229-232 S_2
f	4-Br	Me	40	100-101	S_2	240	5-Br	Me	86	304-306 S_2
g	3-Cl	Me	35	oil		400	4-Cl 6-Cl	Me Me	41 39	229-231 S_2 300-302 S_2
h	H		60	137-138	S_2	210	H		95	229-232 S_3
i	4-NO_2	Me	0	—		—	—		—	

a) Solvents- S_1: Et_2O; S_2: EtOAc-*n*-hexane; S_3: EtOAc-MeOH-*n*-hexane. b) Temperature of reaction 190°C.



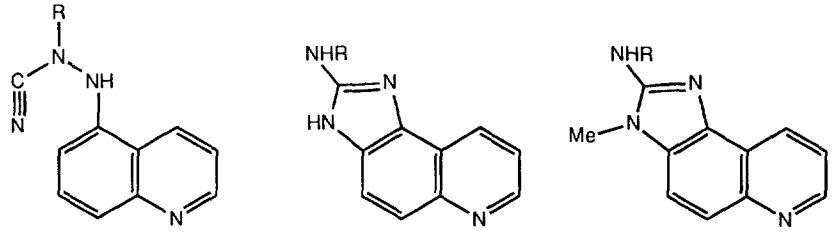
Scheme

^{1}H NMR and IR). The various benzimidazoles[9] **6** prepared in an analogous manner are collected in the Table.

The compounds **4g** and **4c** , possessing *m*-substituents, afforded on rearrangement both the regioisomers involving ring closure to the ortho and para position relative to the substituent in the ring. In the case of **4g** the two isomers could be separated by fractional crystallisation (EtOAc-*n*-hexane) and the structures assigned on the basis of their respective ^{1}H NMR spectra. However, a similar separation could not be achieved with the mixture obtained from **4c**. The ^{1}H NMR spectrum of the product, once crystallised, showed the presence of the two isomers in a *ca.* 1:1 ratio.

The heterocyclic cyanamide **7** (R = H) and its acetyl derivative **7** (R=MeCO), obtained from 5-quinolylhydrazine[10] in the usual manner, both underwent smooth thermal cyclisation to give 2-amino-3H-imidazo[4,5-f]quinoline[11] **8** (R = H ; 91%) and the corresponding acetyl derivative **8** (R=Ac ; 83%) respectively. The m.p. (278°C dec.) and the δ values of the various protons in the ^{1}H NMR spectrum of the former were in agreement with those reported for the same compound obtained by a lengthier route.[12] The compound **8** (R=H) had been previously converted into the highly mutagenic amine 2-amino-3-methyl-3H-imidazo[4,5-f]quinoline, IQ , (**9**), resulting from protein decomposition of cooked meat and broiled fish.[13]

In conclusion it is shown that the hitherto little known arylacylcyanohydrazines can be profitably employed to synthesise 2-aminoacylbenzimidazoles.



7 **8** **9 , IQ**

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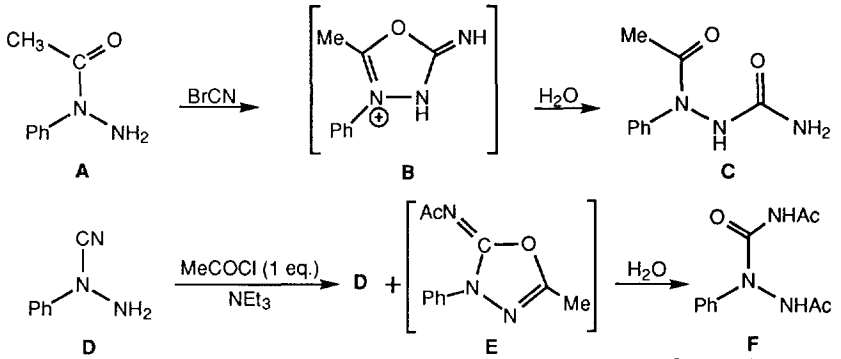
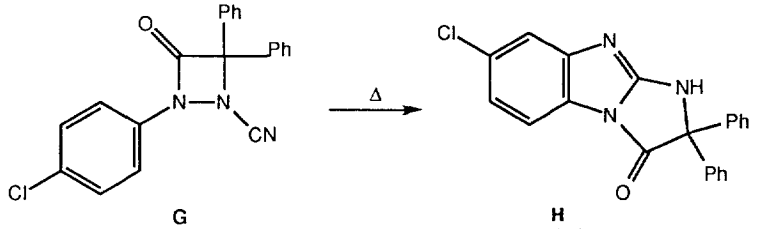
2. Pellizzari, G.; Gaiter, A. *Gazz. Chim. Ital.*, **1918**, *48*, 151-162.
3. Bird, C. W.; Wong, C. K. *Tetrahedron Lett.*, **1974**, *14*, 1251-1252.
4. Supplied by Aldrich Chem. Co (Spain).
5. For the preparation, using ClCN, the instability and reactivity of 1-phenyl-2-cyanohydrazine, see: Pellizzari, G; Tivoli, D. *Gazz. Chim. Ital.*, **1892**, *22*, 226-236; Pellizzari, G. *Gazz. Chim. Ital.*, **1910**, *41*, 54-59.
6. The predominance of the N-acylcyanamide **4** is to be attributed to the bulkiness of the acylating species ($Et_3{}^+NCOR_2$ Cl^-) which makes acylation on the nitrogen atom attached to the aryl ring difficult. The use of R_2COCl in conjunction with $NaHCO_3$ led to the formation of urea **5** in greater quantity.
7. It is likely that the formation of the ureas **5** occurs *via* the 1-aryl-1-acyl-2-cyanohydrazine generated competitively with **4**. For example 1-phenyl-1-acetylhydrazine (**A**) on cyanation (BrCN) affords exclusively the urea **C** with exceptional ease, most probably due to the intervention of the intermediate **B**. A similar neighbouring participation is also manifested in the attempted acetylation of the cyanamide **D** which gives the urea **F**, via **E** (unpublished observation from our laboratory).



On the other hand, the successful cyclisation of the diazetidin-4-one **G** to the corresponding benzimidazole **H** is to be attributed, *inter alia*, to the geometric impossibility of the carbonyl and N-CN to interact (see: Bird, C. W. *J. Chem. Soc.*, **1964**, 5284-5289).



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9. a) For a review describing other synthetic methods for 2-aminobenzimidazoles and their important applications, see: Rastogi, R.; Sharma, S. *Synthesis*, **1983**, 861-882. b) All new compounds gave satisfactory elemental analysis or accurate mass measurements. Their spectra (IR and ^1H NMR) were consistent with the assigned structures.
10. Hunig, S.; Werner, H. *Ann.*, **1959**, *628* , 46-55.
11. This result was totally unexpected in view of the general instability of arylcyanamides **4** observed in our study.
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