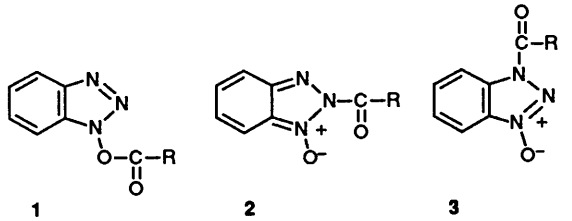
A Mechanistic Study of the Rearrangement of 1-Benzoyloxybenzotriazoles to 3-Benzoylbenzotriazole 1-Oxides

Alan R. Katritzky,*[a] N. Malhotra,[a] Wei-Qiang Fan[a] and Ernst Anders[b]
[a] *Department of Chemistry, University of Florida, Gainesville FL 32611-2046, USA*
[b] *Institut für Organische Chemie der Universität, Erlangen-Nuernberg, Henkestrasse 42, D-8520 Erlangen, Germany*

Crossover experiments demonstrate that the title rearrangement processes are intermolecular.

1-Hydroxybenzotriazole acyl derivatives are of considerable importance in peptide chemistry.[1] Konig and Gieger[2] found that racemization was suppressed by the addition of 1-hydroxybenzotriazole to dicyclohexylcarbodiimide-mediated peptide couplings. These workers proposed that the active species in such couplings, which were found to display ν C=O near 1820 cm^{-1} in solution, were the *O*-acyl derivatives **1**. However, they reported that most such protected aminoacyl derivatives **1** on isolation in the crystalline state showed ν C=O near 1730 cm^{-1} and postulated that isomerization to **2** and/or **3** had occurred.[2]



1 **2** **3**

a R = Me
b R = $MeSCH_2CH(NHCPh_3)$
c R = Ph
d R = $CH_3CH{=}CH{-}CH{=}CH$
e R = $CH_3CH{=}CH$
f R = $Ph_3CNH{-}CH$(Alanine)
g R = H

Horiki[3] isolated, in crystalline form, two of the isomeric acetates of 1-hydroxybenzotriazole, to which he assigned structures **1a** and **3a**, on spectroscopic evidence. He found that these two compounds existed in a mobile equilibrium in solution. The equilibrium constant **1a**:**3a** was found to depend on the solvent polarity, varying from 0.4 in 80% aqueous acetone to 2.4 in 20% aqueous acetone. Thus the more polar *N*-acetyl compound **3a** is favoured by the higher solvent polarity. The equilibrium position was also shown to be affected by other polar substituents in the molecule. In agreement with an earlier postulate by Huisgen,[4] Horiki[3] suggested that the interconversion **1a** to **3a** was probably intramolecular, but he pointed out that no proof was available for this.

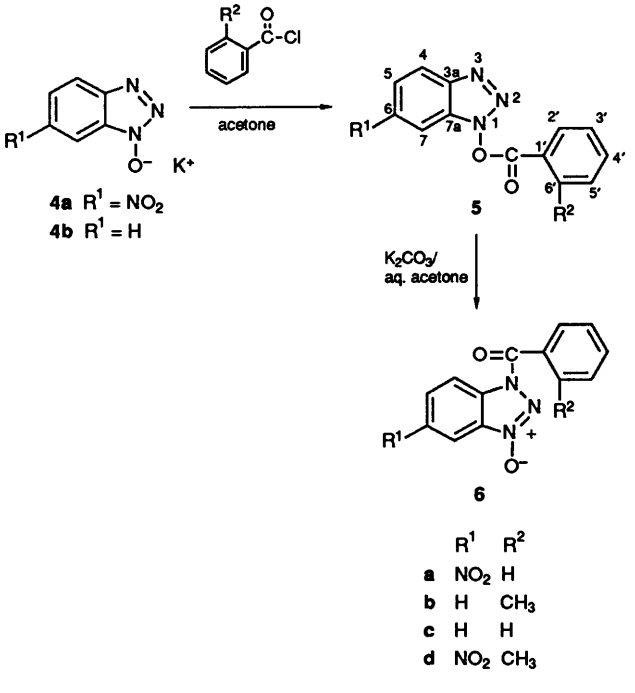
Further work[5,6] showed that the presence of base catalyses the interconversion of **1** to **3**. In DMF (dimethyl formamide) solution the pure ester **1f** slowly rearranges (2–4 days) to an equilibrium mixture **1f** ⇌ **3f** in which the amide form **3f** predominates slightly. The base, *N*-methylmorpholine, accelerated the progress towards equilibrium.[5]

The existence of both structural types **1** and **3** has been unequivocally demonstrated by X-ray evidence.[2,5,6] Barlos[7] showed in 1985 that 3-(N^{α}-tritylmethionyl)benzotriazole 1-oxide crystallized in the structure **3b** of its name. Earlier the *O*-acyl structure **1c** had been proved for 1-benzoyloxybenzotriazole.[8] Rinehart and co-workers[9] found that the potassium salt of 1-hydroxybenzotriazole and sorbyl chloride gave mainly 1-(sorbyloxy)benzotriazole **1d**. While **1d** was stable in pure acetone, it underwent base-catalysed rearrangement in aqueous acetone to 3-sorbylbenzotriazole 1-oxide **3d**. Structure **3d** was also proved by X-ray analysis.

The particular role of the isomeric *O*- and *N*-acylated derivatives of 1-hydroxybenzotriazole in determining the rates of acyl transfer, and of racemization, has been the subject of considerable discussion.[8,10,11] In view of residual uncertainty regarding the structures and their interconversion, we have further studied some of these compounds and in particular we have used the cross-over technique to ascertain the mechanism of their interconversion.[9]

Results and Discussion

Preparation of the O-Acylated Compounds **5a–d**.—1-Benzoyloxy-6-nitrobenzotriazole **5a**, 1-(*o*-toluoyloxy)benzotriazole **5b**, 1-benzoyloxybenzotriazole **5c** and 1-(*o*-toluoyloxy)-6-nitrobenzotriazole **5d** were prepared by treating suspensions of the potassium salt of 1-hydroxy-6-nitrobenzotriazole or 1-hydroxybenzotriazole **4** in anhydrous acetone, with benzoyl chloride or with *o*-toluoyl chloride, respectively (Table 1, Scheme 1). The previously reported compounds **5a** and **5c** had m.p.s in agreement with literature values. Novel compounds **5b** and **5d** gave satisfactory elemental analysis (Table 1) and spectral data (Tables 2 and 3).



4a $R^1 = NO_2$
4b $R^1 = H$

5

6

	R^1	R^2
a	NO_2	H
b	H	CH_3
c	H	H
d	NO_2	CH_3

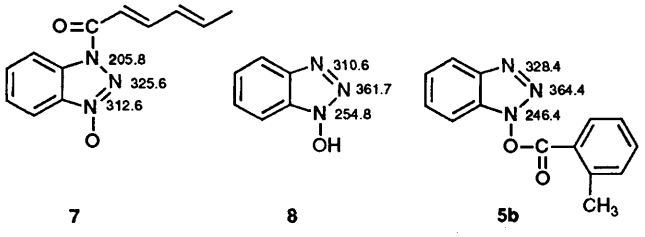
5a + **5b** $\xrightarrow{K_2CO_3/\text{aq. acetone}}$ **6a–d**

Scheme 1

Table 1 Preparation and characterization of 1-benzoyloxybenzotriazoles **5a–d** and 3-benzoylbenzotriazole 1-oxides **6a–d**

Compound	Yield (%)	M.p. (*T*/°C) Found	Lit.	ν_{max}/cm^{-1}	Crystal form	Recryst. solvent	Found (%) C	H	N	Analysis molecular formula	Calculated (%) C	H	N
5a	89	157–159	155–157[8]	1797.9	White microcrystals	C_6H_6	—	—	—	—	—	—	—
5b	88	80–82	—	1795.4	White needles	EtOH	66.9	4.4	16.0	$C_{14}H_{11}N_3O_2$	66.40	4.38	16.59
5c	78	74–76	77–8[8]	1777.4	Yellow needles	$CHCl_3$	—	—	—	—	—	—	—
5d	82	111–113	—	1795.6	Yellow microcrystals	$CHCl_3$	56.2	3.25	18.35	$C_{14}H_{10}N_4O_4$	56.38	3.38	18.78
6a	64	215–216	—	1681.3	Brown needles	Acetone	54.85	2.75	19.85	$C_{13}H_8N_4O_4$	54.94	2.84	19.71
6b	73	188–189	—	1699.9	White prisms	Acetone	66.55	4.3	16.8	$C_{14}H_{11}N_3O_2$	66.40	4.38	16.59
6c	52	177–178	—	1709.9	Cream prisms	Acetone	65.5	3.7	17.7	$C_{13}H_9N_3O_2$	65.27	3.79	17.56
6d	43	250–252	—	1706.6	Orange needles	Acetone	56.6	3.3	19.05	$C_{14}H_{10}N_4O_4$	56.38	3.38	18.78

While the *O*-acyl structures assigned to **5a–d** are compatible with their ^{1}H and ^{13}C NMR spectra, such spectra do not conclusively exclude structures **6a–d**, which would show similar chemical shifts. Firm evidence for structure **5b** was obtained from the ^{15}N NMR spectrum, which showed signals at δ 246.4 (N-1), 364.4 (N-2) and 328.4 (N-3). In a careful ^{15}N NMR study[9] associated with an X-ray crystallographic analysis of **7**, chemical shifts were assigned as shown for structures **7** and **8**. By comparison the synthesized compound **5b** is confirmed to be 1-(*o*-toluoyloxy)benzotriazole **5b** rather than its isomer 3-(*o*-toluoxy)benzotriazole 1-oxide **6b**. The ^{15}N chemical shifts are shown in Scheme 2. The structures of **5a**, **5c** and **5d** follow by analogy and are confirmed by the IR spectroscopic evidence, see below.



7 **8** **5b**

Scheme 2

Rearrangements of Compounds **5a–d** *to* **6a–d**.—Compound **5b**, when refluxed in acetone, containing catalytic amounts of K_2CO_3 and water, gave the N-3-acyl isomer **6b**. Compound **6b** showed the carbonyl absorption band at ν 1699.9 cm^{-1} in its IR spectrum, compared to ν 1798.4 cm^{-1} observed for **5b**. Similarly, compounds **5a**, **5c** and **5d** underwent rearrangement under the same conditions to give compounds **6a**, **6c** and **6d** respectively. In all cases the changes in the ν C=O frequency are consistent with changes from structure **5** to structure **6**.

Spectral Characterization of Compounds **5a–d** *and* **6a–d**.—The structures of all the 1-benzoyloxybenzotriazoles **5a–d** and their corresponding rearrangement products the 3-benzoylbenzotriazole 1-oxides **6a–d** are supported by their elementary analysis (Table 1) and NMR spectral data (Tables 2 and 3). Examination of the ^{1}H NMR spectra of **5a–d** and **6a–d** shows that all the benzotriazole ring protons and acyl aromatic and methyl protons can be individually assigned by consideration of their coupling constants. The chemical shifts and coupling constants of 1-benzoyloxybenzotriazoles **5a–d** are all very similar to those of 3-benzoylbenzotriazole 1-oxide **6a–d**. In the 6-nitro series **5a**, **5d**, **6a**, and **6d**, the 5-H proton of the benzotriazole ring clearly shows as a doublet coupled with 4-H (*J* 7.2–9.3) and with 7-H (*J* 1.5–1.9). A typical singlet is observed at δ 2.17–2.66 for the methyl group attached to a phenyl ring. ^{13}C NMR spectra of both **5** and **6** show the absorption peaks for the carbonyl carbons in the remarkably narrow range of δ 162.2–162.8. The carbon atoms directly attached to the nitro groups in the 6-nitro series (**a** and **d**) appear downfield at δ 147.5–148.0. Upfield quaternary carbon peaks are observed for the benzotriazolyl C-3a (δ 118.8–120.4) and C-7a (δ 107.9–109.4) carbons. Methyl carbons are recorded at δ 21.2–21.8. Other assignments of the ^{13}C NMR spectra are shown in Table 3.

Crossover Experiment.—An equimolar solution of compounds **5a** and **5b** was treated under the conditions used for the rearrangements above. The acetone was removed and the solid residue was taken into chloroform and dried (Na_2SO_4). The solvent was distilled off to give a mixture, which could not be separated by column chromatography due to the very close R_f values of the components. However TLC demonstrated the complete conversion of the starting materials. The ^{13}C NMR spectrum of the mixture showed the presence of four compounds. Most of the signals could be assigned to the compounds **6a–6d**, but a few overlapped. All the four carbonyl carbon signals at δ 162.5, 162.3, 162.6 and 162.0 (intensity ratio 2.3:1.0:1.7:1.5) respectively and two methyl carbon signals at δ 21.7 and 21.6 (intensity ratio 1.0:1.4) could be seen. When a mixture of **6a** and **6b** was treated under the same conditions, it remained unchanged. No **6c** or **6d** could be detected. This eliminated the possibility of an intramolecular rearrangement followed by intermolecular scrambling. Thus, the presence of four components in the reaction mixture can only be possible if the compounds **5a** and **5b** isomerize *via* an intermolecular pathway.

Conclusion

The formation of four products **6a–d** from the crossover rearrangement of **5a** and **5b** proves that rearrangement of 1-benzoyloxybenzotriazole to 3-benzoylbenzotriazole 1-oxide is *via* an intermolecular pathway.

Experimental

M.p.s were determined on a Kofler hot-stage microscope and are uncorrected. All the ^{1}H and ^{13}C NMR spectra were recorded on a Varian VXR-300 spectrometer with TMS [$(CH_3)_4Si$] as internal standard. The IR spectra were recorded on Perkin-Elmer 1640 FTIR spectrophotometer in Nujol. Acetone was dried by standing overnight over anhydrous potassium

Table 2 ^{1}H NMR spectroscopic data for compounds **5a–d** ($CDCl_3$) and **6a–d** ([$^2H_6$]DMSO)

Benzotriazole ring protons

	Unsubstituted series (**b** and **c**)							6-Nitro series (**a** and **d**)						
	4-H (d)		5-H (m)	6-H (t)		7-H (d)			4-H (d)		5-H (dd)			7-H (s)	
Compd.	δ	J/Hz	δ	δ	J/Hz	δ	J/Hz	Compd.	δ	J/Hz	δ	J_{H5-H4}/Hz	J_{H5-H7}/Hz	δ	J/Hz
5b	8.10	8.4	7.50	7.60	7.8	8.35	7.8	**5a**	8.31	7.2	8.35	7.2	1.9	8.47	1.9
5c	8.76	7.2	8.60	8.24	—[a]	8.79	7.2	**5d**	8.26	8.1	8.37	8.1	1.8	8.47	1.8
6b	8.16	8.4	7.69	7.66	—[a]	8.32	7.5	**6a**	8.31	9.0[b] 2.1	8.27	9.0	1.8	8.48	1.8
6c	8.18	8.4	7.88	7.66	—[a]	7.90	—[a]	**6d**[c]	7.95	9.3	7.86	9.3	1.5	8.80	1.5

Acyl aromatic and CH_3 protons

	Unsubstituted series (**a** and **c**)						6-Methyl series (**b** and **d**)						
	2′,6′-H (d)		3′,5′-H (t)		4′-H (t)			2′-H (d)		3′,5′-H (t)		4′-H (t)		
Compd.	δ	J/Hz	δ	J/Hz	δ	J/Hz	Compd.	δ	J/Hz	δ	J/Hz	δ	J/Hz	CH_3 (s) δ
5a	8.28	7.5	7.65	7.5	7.83	7.5	**5b**	7.53	6.6[b] 0.9	7.41	—[a]	7.46	—[a]	2.66
5c	8.10	7.8	8.00	7.8	7.94	—[a]	**5d**	8.31	10.8	7.46	8.1	7.66	8.1	2.68
6a	8.30	—[a]	7.64	8.1	7.83	8.1	**6b**	7.92	8.4	7.49	8.1	7.52	8.1	2.58
6c	8.24	8.4	7.60	—[a]	7.50	—[a]	**6d**[c]	7.83	9.3	7.09	7.5	7.30	7.5	2.17

[a] Multiplet. [b] Double doublet. [c] Signals due to the other isomer were also present.

Table 3 ^{13}C NMR spectroscopic data for compounds **5a–d** ($CDCl_3$) and **6a–d** ([$^2H_6$]-DMSO)

Compd.	C-3a	C-4	C-5	C-6	C-7	C-7a	C-1′	C-2′	C-3′	C-4′	C-5′	C-6′	C=O	CH_3
5a	128.3	119.8	121.7	147.7	105.9	145.4	124.0	130.9	129.4	136.0	129.4	130.9	162.4	—
5b	128.8	120.4	124.7	128.4	108.3	143.5	142.9	132.3	128.7	134.6	128.7	131.3	162.6	21.7
5c	128.6	120.4	124.7	128.7	108.3	143.4	124.6	130.6	129.1	135.4	129.1	130.6	162.7	—
5d	128.4	119.7	121.7	147.6	105.9	145.4	143.5	132.5	122.5	135.2	126.1	131.5	162.1	21.8
6a	128.5	118.8	121.3	148.0	108.1	146.0	144.7	132.8	124.5	135.8	129.2	130.7	162.7	—
6b	129.1	119.8	123.2	128.4	109.3	142.8	142.0	132.2	126.6	134.9	125.2	131.2	162.6	21.1
6c	128.8	119.9	124.3	128.5	109.4	142.8	125.3	132.8	129.5	135.8	129.2	130.6	162.8	—
6d	128.2	119.9	121.2	147.5	107.9	144.7	142.4	132.5	123.1	134.9	126.5	131.5	162.2	21.2

carbonate followed by distillation over phosphorus pentoxide.

Preparation of **5a–d**.—*General procedure.* Compounds **5a**, **5b**, **5c** and **5d** were prepared by refluxing equimolar amounts of the potassium salt of 1-hydroxy-6-nitrobenzotriazole **4a** (1.96 g, 9 mmol) or 1-hydroxybenzotriazole **4b** (1.55 g, 9 mmol) and benzoyl chloride (1.26 g, 9 mmol) or *o*-toluoyl chloride (1.39 g, 9 mmol) in dry acetone (100 cm^3) for 4 h. The solvent was removed under reduced pressure and the residue taken up into water. The product was extracted with chloroform, dried (Na_2SO_4) and the solvent distilled off. The products were recrystallized (spectroscopic data is given in Tables 1, 2 and 3).

Preparation of **6a–d**.—*General procedure.* A solution of the appropriate ester **5a–d** (3.95 mmol) in acetone (50 cm^3) containing potassium carbonate (0.15 g, 1.08 mmol) and water (0.5 cm^3) was heated under reflux for 4 h and then filtered. The acetone was evaporated under reduced pressure to give a residue which was recrystallized from acetone (spectroscopic data is given in Tables 1, 2 and 3).

Crossover Experiment.—The crossover experiment was performed by refluxing equimolar amounts of compounds **5a** and **5b** (3.95 mmol) in acetone (50 cm^3) containing potassium carbonate (0.15 g, 1.08 mmol) and water (0.5 cm^3) for 4 h. After the completion of the reaction (TLC), the solvent was distilled off and the residue taken into water. It was extracted with chloroform, dried (Na_2SO_4) and the solvent distilled off to give the product mixture which was analysed by NMR spectroscopy.

References

1 W. Konig and R. Gieger, in *Chemistry and Biology of Peptides*, J. Meienhofer, ed., Ann Arbor Sci. Publ., Ann Arbor, MI, 1972, p. 343.
2 W. Konig and R. Gieger, *Chem. Ber.*, 1970, **103**, 788.
3 K. Horiki, *Tetrahedron Lett.*, 1977, 1897.
4 R. Huisgen and V. Weberndorfer, *Chem. Ber.*, 1967, **100**, 71.
5 K. Barlos, D. Papaioannou and D. Theodoropoulos, *Int. J. Peptide Protein Res.*, 1984, **23**, 300.
6 K. Barlos, D. Papaioannou and C. Sanida, *Leibigs Ann. Chem.*, 1984, 1308.
7 K. Barlos, D. Papaioannou and S. Votiotis, *J. Org. Chem.*, 1985, **50**, 696.
8 D. G. McCarthy, A. F. Hegarty and B. J. Hathaway, *J. Chem. Soc., Perkin Trans. 2*, 1977, 224.
9 S. Nagarajan, S. R. Wilson and K. L. Rinehart, Jr., *J. Org. Chem.*, 1985, **50**, 2174.
10 J. S. Davies and A. K. Mohammed, *J. Chem. Soc., Perkin Trans. 1*, 1981, 2982.
11 K. Horiki, *Tetrahedron Lett.*, 1977, 1901.

Paper 1/02353E
Received 20*th May* 1991
Accepted 5*th June* 1991