Hydroxylation of Nitroarenes with Alkyl Hydroperoxide Anions via Vicarious Nucleophilic Substitution of Hydrogen

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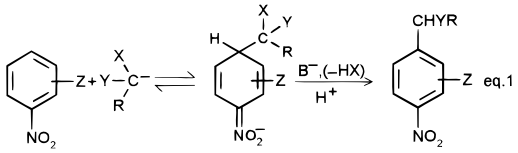
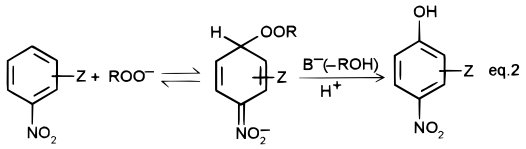
Carbo- and heterocyclic nitroarenes react with anions of *tert*-butyl and cumyl hydroperoxides in the presence of strong bases to form substituted *o*- and *p*-nitrophenols. The reaction usually proceeds in high yields and is of practical value as a method of synthesis and manufacturing of nitrophenols. Orientation of the hydroxylation can be controlled to a substantial extent by selection of the proper conditions. Basic mechanistic features of this process were clarified.

Introduction

Vicarious Nucleophilic Substitution of hydrogen (VNS) allows the direct introduction of substituents onto electrophilic aromatic rings.[1] A variety of carbo- and heterocyclic nitroarenes, as well as some electrophilic heterocycles lacking a nitro group, undergo this process with carbanions that contain a leaving group X at the carbanionic center. The reaction proceeds according to the addition−elimination scheme shown in eq 1.[2]



The amination of a nitroarene with hydroxylamine[3] apparently proceeds by a similar mechanism, although a hydride shift has been proposed for the transformation of the σ^H adduct into products.[4] Recently, more efficient amination processes were described and use such amination agents as aminotriazoles,[5] *O*-methyl hydroxylamine,[6a] and *N*,*N*,*N*-trimethylhydrazinium iodide.[6b] No mechanistic proposals has been made for these processes, but they seem to follow a general VNS mechanism, namely nucleophilic addition followed by base-induced β-elimination. This mechanism was shown to operate in the amination of nitroarenes with sulfenamides.[7] Since anions of alkyl hydroperoxides (ROOH) can be considered to be nucleophiles that bear a leaving group (RO) at the anionic center, like α-halocarbanions and anions of sulfenamides, etc., they can be expected to undergo the VNS reaction with nitroarenes to produce nitrophenols as shown in eq 2.



Although alkyl hydroperoxides are rather strong OH-acids, the corresponding anions exhibit relatively high nucleophilicity, due to the so-called α-effect.[8] The nucleophilic reactivity of anions of alkyl hydroperoxides is exemplified in their well-documented reactions with alkylating agents which give unsymmetrical dialkyl peroxides.[9] More relevant to the subject of this paper are reactions of these anions with electrophilic alkenes. The formation of oxiranes by the nucleophilic addition of alkyl hydroperoxide anions, followed by intramolecular S_N2 type substitution of an RO group,[10] resembles the reactions of α-halo carbanions in related cyclopropanation reactions. Moreover, it was reported that the anion of *tert*-butyl hydroperoxide reacts with nitroalkenes to yield nitroketones.[11] This reaction appears to be analogous to the aliphatic VNS process described recently by us.[12] There were also reports on the reactions of alkyl hydroperoxide anions with polynitroarenes. Formation of the corresponding σ-adducts was confirmed by spectroscopy,[13] and the kinetic study of nucleophilic aromatic substitution (S_NAr) of halogen in halonitroarenes by hydroperoxide anion demonstrates its high reactivity.[14]

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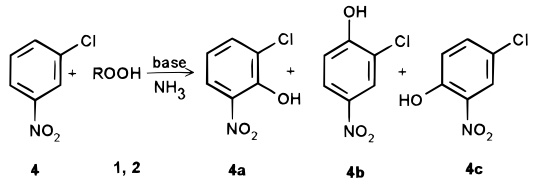
Finally, the second step of the VNS reaction of nitroarenes with anions of alkyl hydroperoxides, namely β-elimination of the alcohol from the σ-adduct, is feasible since it is analogous to the base-catalyzed decomposition of secondary alkyl peroxides by an E2 elimination pathway, which yields ketones and alcohols.[15] Indeed, the VNS hydroxylation of nitroarenes with alkyl hydroperoxide anions does occur satisfactorily as reported in our preliminary communication.[16] Similar observations were made by a German group.[17] This paper presents a full account of our studies on the nucleophilic hydroxylation of nitroarenes with alkyl hydroperoxide anions.

Results and Discussion

Reaction Conditions. Because of their availability and stability, *tert*-butyl hydroperoxide t-BuOOH **1**, cumene hydroperoxide $PhMe_2COOH$ **2**, and triphenylmethyl hydroperoxide Ph_3COOH **3** were selected as reagents for the hydroxylations of nitroarenes. Preliminary studies indicated that powdered KOH or NaOH or t-BuOK in liquid NH_3 assured the best yields of nitrophenols. The choice of alkyl hydroperoxide and the base was often a crucial determinant of the course of the reaction, as exemplified for 3-chloronitrobenzene **4** (Table 1). In the presence of an insoluble base such as NaOH or KOH, the hydroxylation occurs regioselectively at position 4 giving *p*-nitrophenol derivative **4b** in high yield. On the other hand, in the presence of t-BuOK mixtures of *o*- and *p*-nitrochlorophenols **4a**−**c** were produced, the ortho hydroxylation being favored when **2** and t-BuOK were in high concentration. This effect on the orientation can be attributed to the faster elimination of more acidic phenyldimethyl carbinol than *tert*-butyl alcohol and will be discussed later. Although the VNS hydroxylation can also be performed in DMF, the use of this solvent is limited, by a more complicated workup procedure. The reaction also proceeds in THF; however, this solvent is less convenient and the previously reported preference for *ortho* substitution in the VNS reactions of chlorocarbanions in THF[18] was not observed in the current hydroxylation.

Hydroxylation of Nitrobenzene and Its Monosubstituted Derivatives. Hydroxylation of nitrobenzene **5** and a range of its 3-substituted analogues (**4**, **6**−**14**) with cumene hydroperoxide **2** (Tables 1 and 2) occurs selectively at the position *para* to the nitro group when carried out in the presence of KOH in NH_3. Nitrobenzene itself shows moderate electrophilic activity, thus its reaction is slow. Nevertheless, the yield of *p*-nitrophenol **5b** was high, based on on consumed substrate **5**. Similar low reactivity was observed for less electrophilic 3-substituted nitrobenzenes **6** and **7**, deactivated by electron-donating methyl and methoxy groups. More electrophilic nitrobenzene derivatives, substituted in the *meta*-position with electron-withdrawing groups, such as halogens, CF_3, SO_2CH_3, COPh, CN, and NO_2, easily underwent the VNS hydroxylation giving corresponding *p*-nitrophenols regioselectively and in high yields. Interestingly, for the efficient conversion of 3-nitrobenzophenone **14** a longer reaction time was required. Lower susceptibility of ketone **14** to the VNS hydroxylation is apparently due to a competing, reversible addition of the alkyl hydroperoxide anion to the carbonyl group. The reaction of 3-nitrobenzaldehyde **15** and methyl 3-nitrobenzoate **16** with the anion of **2** did not result in VNS hydroxylation, but rather an addition to the carbonyl group. Thus, under the applied reaction conditions, aldehyde **15** was slowly oxidized to 3-nitrobenzoic acid **17**.[19] The same carboxylic acid **17** was obtained from methyl ester **16**, apparently due to transesterification with the alkyl hydroperoxide anion, followed by base-induced decomposition of the peroxy ester. A similar reaction of methyl 3-nitrobenzoate **16** was observed in the VNS amination where an attack of the sulfenamide anion on the ester group gave primarily the acylated sulfenamide.[7]

Table 1

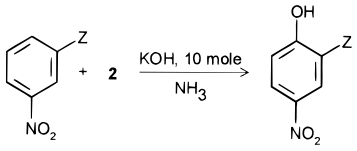


4 **1, 2** **4a** **4b** **4c**

ROOH	base (mol)	time (min)	yield, %	ratio (**4a**:**4b**:**4c**)[a]
1	NaOH (10)	60	73	0:100:0
2	KOH (10)	60	80	0:100:0
1	t-BuOK (2.5)	15	87	3:94:3
1	t-BuOK (5)	15	80	14:76:10
2	t-BuOK (5)	15	76	25:59:16
1[c]	t-BuOK (2.5)	40	41(82)[b]	2:95:3
1[d]	t-BuOK (2.5)	15	66	1:99:0

[a] Ratio **4b**:(**4a** + **4c**) based on isolated products; **4a**:**4c** from ^{1}H NMR. [b] Calculated on consumed **4**. [c] Reaction in THF at −25 °C. [d] Reaction in DMF at −25 °C.

Table 2



Z	substrate no.	product no.	yield, %
H	**5**	**5b**[a]	31(86)[b]
Me	**6**	**6b**[a]	18(78)[b]
OMe	**7**	**7b**[a]	24(73)[b]
F	**8**	**8b**	76
Cl	**4**	**4b**	84
Br	**9**	**9b**	82
CF_3	**10**	**10b**	86
SO_2Me	**11**	**11b**	85
CN	**12**	**12b**	87
NO_2	**13**	**13b**	90
COPh	**14**	**14b**[a]	74
CHO	**15**	**17**	28(54)[b]
CO_2Me	**16**	**17**[c]	90

[a] Reaction time: 3 h. [b] Calculated on consumed substrate. [c] The same result was obtained with t-BuOK.

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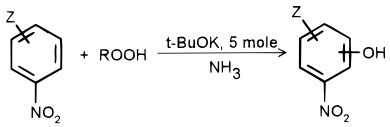
Table 3

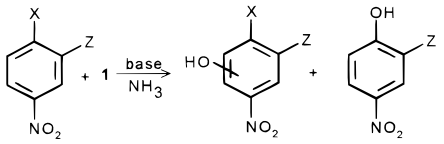


Z	substr	ROOH	position of OH	product no.	yield, %
4-Cl	**18**	**2**[a,b]	4	**5b**[c]	36(72)[d]
4-Cl	**18**	**1**[e]	2	**18a**	27(34)[d]
			4	**5b**[c]	27(34)[d]
4-Cl	**18**	**2**	2	**18a**	73
			4	**5b**[c]	7
4-Br	**19**	**2**	2	**19a**	80
			4	**5b**[c]	3
4-I	**20**	**2**	2	**20a**	62
			4	**5b**[c]	traces
4-F	**21**	**2**	4	**5b**[c]	74
4-OMe	**22**	**2**[b]	2	**22a**	4(17)[d]
			4	**5b**[c]	5(21)[d]
4-CF_3	**23**	**1**[e]	2	**23a**	80
4-SO_2Ph	**24**	**1**	2	**24a**	33
			4	**5b**[c]	38
4-CN	**25**	**2**[e]	2	**25a**	41
			1	**25b**[c]	7
2-Cl	**26**	**2**[f]	4	**26a**	37
			2	**5a**[c]	37
2-F	**27**	**2**	2	**5a**[c]	51
2-OMe	**28**	**2**[b]	4	**28a**	8(47)[d]
2-CF_3	**29**	**1**[e]	4	**29a**	88
			6	**29b**	1

[a] KOH was used instead of t-BuOK. [b] Reaction time: 1 h. [c] S_NAr of halogen, OMe, SO_2Ph, or NO_2 group. [d] Calculated on consumed substrate. [e] 2.5 equiv of t-BuOK was used. [f] In the presence of NaOH only S_NAr was observed.

The conditions for selective *para*-hydroxylation of 3-substituted nitrobenzene derivatives appeared unsuitable in the reactions of *para*- and *ortho*-substituted nitrobenzenes with **1** and **2** where the competitive S_NAr process could play a substantial role (Table 3). For example, the reaction of 4-chloronitrobenzene **18** with **2** and KOH gave 4-nitrophenol **5b** as the sole product, formed by substitution of the halogen, followed by a spontaneous decomposition of the unstable nitroaryl cumyl peroxide.[13,20] The desired VNS hydroxylation of 4-halonitrobenzenes **18**, **19**, and **20** (hal = Cl, Br, I) was achieved when **2** was used in the presence of an excess of t-BuOK in high concentration. However, with 4-fluoronitrobenzene **21**, which is very reactive in the S_NAr of halogen process, substitution of fluorine took place. The reaction of *p*-methoxynitrobenzene **22** yielded small amounts of *ortho*-hydroxylated product **22a** and 4-nitrophenol **5b** formed apparently by S_NAr of the methoxy group. Thus **22**, similar to **21**, showed preference for the S_NAr reaction, although due to the electron-donating character of the MeO group its overall reactivity was low. Surprisingly, nitrobenzene derivatives substituted at the *para* position with electron-withdrawing groups, in spite of the expected enhanced electrophilic character of the ring, reacted in diverse ways. Thus, 4-(trifluoromethyl)nitrobenzene **23** smoothly gave the expected *o*-hydroxy derivative **23a**, while in the reaction of nitrosulfone **24** substitution of the phenylsulfonyl group competed to a significant extent with the VNS process. Hydroxylation of 4-cyanonitrobenzene **25** furnished the expected phenol **25a** in a moderate yield, along with a small amount of 4-cyanophenol **25b**, which resulted from the substitution of the nitro group. In the reactions of a few *ortho*-substituted nitrobenzenes **26**−**29** similar diversity was observed (Table 3), namely competing and dominating formation of *o*-nitrophenol **5a** via S_NAr of the halogen in *o*-chloro- and *o*-fluoronitrobenzenes **26** and **27**, but low reactivity of *o*-nitroanisole **28** and high yield of the VNS hydroxylation of *o*-(trifluoromethyl)nitrobenzene **29**.

Table 4



3-Z	4-X	substr no.	base (mol)	position of OH	product no.	yield, %
NO_2	F	**30**[a]	t-BuOK(5)	4	**13b**[b]	63
NO_2	Cl	**31**	t-BuOK(2.5)	6	**31a**	83
NO_2	Cl	**31**	NaOH(10)	6	**31a**	79
				4	**13b**[b]	1
CN	Cl	**32**	t-BuOK(2.5)	6	**32a**	62
CN	Cl	**32**	NaOH(10)	4	**12b**[b]	50
CF_3	Cl	**33**	t-BuOK(2.5)	6	**33a**	86
Cl	Cl	**34**	t-BuOK(2.5)	2	**34a**	57
				6	**34b**	12
				4	**4b**[b]	13

[a] **2** used instead of **1**. [b] S_NAr of halogen.

Disubstituted Nitrobenzene Derivatives (Table 4). Most interesting is the comparison of the reaction of 2,4-dinitrofluorobenzene (Sanger's reagent **30**) and its chloro analogue **31** with anions of **1** and **2**. In the case of **30** the only result was substitution of the very labile fluorine, whereas in 2,4-dinitrochlorobenzene **31** the selective VNS process at position 6 dominated even when NaOH was used as the base. In 4-chloro-3-cyano- and 4-chloro-3-trifluoromethyl derivatives of nitrobenzene **32** and **33**, the VNS hydroxylation gave practical results only when it was carried out in the presence of t-BuOK. Interestingly, in 3,4-dichloronitrobenzene **34** the substitution of hydrogen at the more crowded position 2 was the major process, although replacement of the chlorine also occurred to some extent. These results, when compared to those obtained with 4-chloronitrobenzene **18** (Table 3), show that introduction of an additional electron-withdrawing group at the *meta*-position strongly promotes the VNS reaction over chlorine substitution.

Nitronaphthalenes (Table 5). A bicyclic aromatic ring system provides additional stabilization of the anionic *σ*-adducts; hence, nitronaphthalene derivatives readily enter into the VNS reaction with α-chloro carbanions[1,21] and sulfenamides.[7] Good reactivity of nitronaphthalenes in the VNS reaction was also observed in the hydroxylation of 1-nitronaphthalene **35**. The reaction proceeded efficiently giving the expected 2- and 4-hydroxy derivatives in high yields. It should be stressed that the orientation of the hydroxylation is dependent on the kind of base used; thus, 2- or 4-hydroxy-1-nitronaphthalenes can be obtained in high yield and selectivity. These results are of significant practical importance and will be discussed together with mechanistic questions. A similar but weaker effect of conditions

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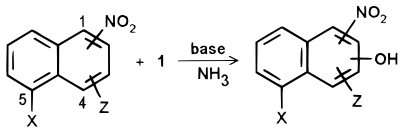
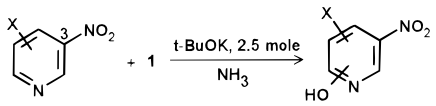
Table 5



position of NO_2,Z,X	substr	base[a]	position of OH	product no.	yield, %
1-NO_2	**35**	t-BuOK	2	**35a**	81
			4	**35b**	4
1-NO_2	**35**	NaOH	2	**35a**	traces
			4	**35b**	88
1,5-diNO_2	**36**	t-BuOK	2	**36a**	81
			4	**36b**	5
1,5-diNO_2	**36**	NaOH	2	**36a**	22
			4	**36b**	61
1-NO_2-5-Br	**37**	t-BuOK	2	**37a**	85
			4	**37b**	traces
1-NO_2-5-Br	**37**	NaOH	2	**37a**	32
			4	**37b**	44
1-NO_2-4-OMe	**38**	t-BuOK	2	**38a**	63
			4	**38b**	2
1-NO_2-4-Cl	**39**	t-BuOK	2	**39a**	85
			4	**35b**	traces
2-NO_2	**40**	t-BuOK	1	**40a**	84

[a] t-BuOK, 2.5 mol; NaOH, 10 mol.

Table 6

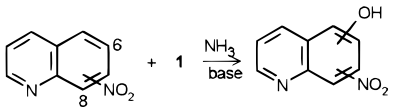


X	substr no.	position of OH	product no.	yield, %
4-OEt	**41**	6	**41a**	78
6-OMe	**42**	2	**42a**	75
6-Cl	**43**	2	**43a**	64

on the orientation was observed in the reaction of 1,5-dinitronaphthalene **36** and 1-nitro-5-bromonaphthalene **37**. The hydroxylation can be directed to the *ortho*-position under properly selected conditions, whereas the selective substitution of *para*-hydrogen was somewhat impeded, apparently by steric hindrance by substituents in position 5. The high reactivity of nitronaphthalenes was also evidenced in the reactions of 4-methoxy- and 4-chloro-1-nitronaphthalenes **38** and **39** where the substitution of hydrogen at position 2 was the dominant process. Finally, 2-nitronaphthalene **40** reacted exclusively at position 1 as already observed in other VNS reactions.[1,21]

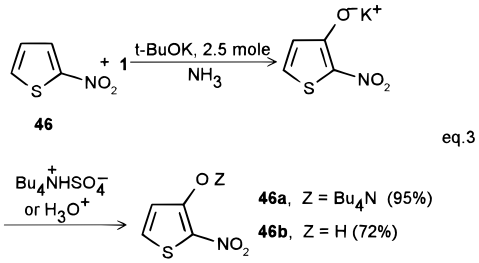
Aromatic Heterocycles. Nitro derivatives of pyridine, quinoline, and other aromatic heterocycles react readily with carbanions in the VNS process.[1,22] These heteroaromatic compounds were also highly reactive toward alkyl hydroperoxide anions. For example, hydroxylation of 4-ethoxy-3-nitropyridine **41** occured efficiently at position 6 whereas 6-substituted 3-nitropyridines **42** and **43** reacted exclusively at position 2 (Table 6). All hydroxynitropyridines were isolated in their pyridone forms. It should be stressed that in 3-nitro-6-chloropyridine **43**, VNS of hydrogen was the exclusive process and that S_NAr substitution of the very labile halogen was not observed.

Table 7

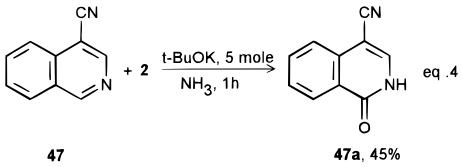


position of NO_2	substr no.	base (mol)	position of OH	product no.	yield, %
8	**44**	t-BuOK (2.5)	7	**44a**	67
	44	NaOH (10)	5	**44b**	79
6	**45**	t-BuOH (2.5)	5	**45a**	86

As expected, nitroquinolines reacted similarly to nitronaphthalenes. Hydroxylation of 8-nitroquinoline **44** could be directed by the reaction conditions to give selectively the 7- or 5-hydroxy derivative, and 6-nitroquinoline **45** reacted solely at position 5 (Table 7). In the reaction of 2-nitrothiophene **46** (eq 3), hydroxylation at position 3 proceded almost quantitatively; however,



the product 2-nitro-3-hydroxythiophene **46b** decomposed upon attempted purification. It was finally isolated as a stable, crystalline tetrabutylammonium salt **46a** using an ion-pair extraction procedure. Some efforts were also made to perform the hydroxylation of electrophilic heteroarenes lacking a nitro group but previously shown to react with carbanions along the VNS pathway.[23] For example, acridine did not react with alkyl hydroperoxide anions, while 4-cyanoisoquinoline **47**[24] entered the VNS hydroxylation, albeit producing a moderate yield (eq 4).



The reported results indicate that cumene hydroperoxide **2** is in some cases a more efficient hydroxylation agent than **1** because higher acidity assures faster elimination of phenyldimethyl carbinol than *tert*-butyl alcohol from the respective σ^H adducts. This effect appears to be more important than the somewhat larger steric demands of **2** than **1**. We expected that the elimination should be particularly facile for the σ^H adducts of the anion $\mathbf{3}^-$ to nitroarenes because of the high acidity of Ph_3COH. Examples presented in Table 8 show however that the bulkiness of $\mathbf{3}^-$ hinders its reactions (both VNS and S_NAr) in positions *ortho* to the NO_2 group.

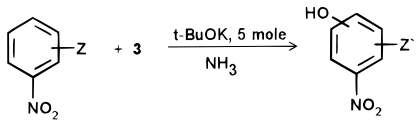
Mechanism and Orientation. In our previous papers it was shown that the VNS reaction proceeds via nucleophilic addition of α-halo carbanions to nitroaromatic rings followed by a base-induced *β*-elimination of

(22) Makosza, M. *Synthesis* **1991**, 103. Makosza, M.; Kwast, E. *Tetrahedron* **1995**, *51*, 8339.

(23) Makosza, M.; Goliński, J.; Rykowski, A. *Tetrahedron Lett.* **1983**, 3277.

(24) Owczarczyk, Z. Ph.D. Thesis, IChO-PAN, 1988.

Table 8



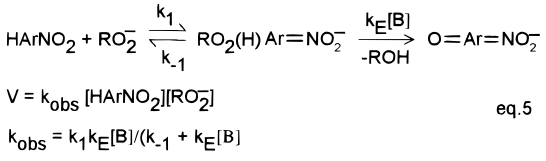
Z	substr no.	position of OH	Z′	product no.	yield, %
4-Cl	**18**	4[c]	H	**5b**	24(7)[a,b]
		2	4-Cl	**18a**	19(73)[a,b]
2-Cl	**26**	4	2-Cl	**26a**	58(37)[a,b]
		2[c]	H	**5a**	3(37)[a,b]
2,3-Cl_2	**48**	4	2,3-Cl_2	**48b**	66(28)[a]
		6	2,3-Cl_2	**48a**	4(19)[a]
		2[c]	3-Cl	**4b**	9(18)[a]

[a] Results when **2** was used. [b] Data from Table 3. [c] S_NAr of Cl.

HX from the σ^H adducts.[1,2] This general mechanistic picture was formulated on the basis of the effect of strength and base concentration on the reaction rate, estimated via intramolecular competition between VNS of hydrogen and S_NAr of halogen in *p*-fluoronitrobenzene and some other halonitroarenes. An excess of strong base assured domination of the former process whereas, when carbanions were in low concentration without the presence of an additional base, substitution of fluorine was the main process.[1,2] In our preliminary communication an analogous β-elimination mechanism was suggested for the VNS hydroxylation on the basis of similar competitive experiments.[16]

Here mechanistic features of this reaction will be discussed on the basis of the competition between S_NAr of halogen and VNS of hydrogen, the kinetic isotope effect in this reaction, and its orientation pattern.

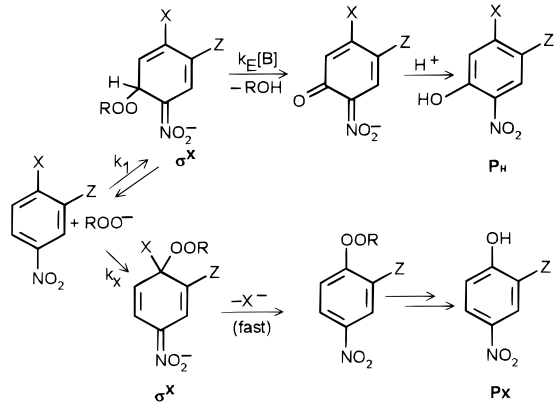
The overall rate of the hydroxylation can be described by eq 5. According to this equation the rate-limiting step



may vary depending on the value of the partitioning factor $k_{-1}/k_E[B]$. When $k_{-1}/k_E[B] \gg 1$, eq 5 can be simplified to $k_{obs} = (k_1/k_{-1})k_E[B]$. Here, equilibrium of the σ^H-adduct formation is established and the subsequent elimination is the rate-limiting step; hence, the overall reaction rate depends linearly on the base concentration. This situation is likely to occur for moderately electrophilic nitroarenes which form short-lived, easily dissociating σ^H-adducts, and/or for a slow elimination step caused by low strength and concentration of base and by steric hindrance. On the other hand, when $k_{-1}/k_E[B] \ll 1$, eq 5 is reduced to $k_{obs} = k_1$. Here the elimination step is a fast and kinetically less important process. This situation is expected for stable, slowly dissociating σ-adducts as well as for fast elimination driven by a high concentration of a strong base.

Between these two border cases there is a range of intermediate situations, namely $k_{-1}/k_E[B] \approx 1$. In these cases the influence of the base concentration on the overall reaction rate will be nonlinear and smaller than for the case $k_{-1}/k_E[B] \gg 1$, and the rate-limiting step cannot be clearly defined and may vary depending on the reaction conditions.

Table 9



X	Z	substr no.	ROOH	base (mol)	P_H[a] (**18a** or **31a**) % yield	P_X[a] (**5b** or **13b**) % yield
Cl	H	**18**	**2**	NaOH (10)	0	36(50)[b]
Cl	H	**18**		**2**$^-$ K^+ (2.5)	0	50(53)[b]
Cl	H	**18**	**1**	t-BuOK (2.5)	27	27(79)[b]
Cl	H	**18**	**1**	t-BuOK (5)	47	16(88)[b]
Cl	H	**18**	**2**	t-BuOK (5)	73	7
Cl	NO_2	**31**	**1**	t-BuOK (2.5)	83	0
Cl	NO_2	**31**		**1**$^-$ K^+ (1)	50	20(78)
Cl	NO_2	**31**	**1**	NaOH (10)	79	1
F	H	**21**	**2**	t-BuOK (5)	0	74
F	NO_2	**30**	**2**	t-BuOK (5)	0	63

[a] Yields of isolated products. [b] Conversion.

Although we have not undertaken kinetic examination of the VNS hydroxylation, we believe that reliable mechanistic conclusions can be drawn from the results and observations made in the synthetic studies and semiquantitative competitive experiments discussed in terms of these kinetic considerations.

Competition of VNS versus S_NAr of Halogen (Table 9). Effect of a base on the rate of VNS can be estimated from its competition with S_NAr of halogen because under given conditions of temperature, solvent, and counterion, the rate of the latter process should not be affected by the base concentration.[25] Thus the intramolecular competition between S_NAr of halogen and VNS of hydrogen can serve as a simple probe to evaluate an effect of base on the overall rate of the latter process. The ratio of products from VNS of hydrogen (P_H) and substitution of halogen (P_X) will depend on the strength and concentration of a base, provided that the elimination is a kinetically important step in the VNS reaction, namely $P_H/P_X = k_1k_E[B]/k_{-1}k_x$. As the relation of the elimination rate $k_E[B]$ to k_{-1} is growing, the influence of the base on this competition will decrease until the constant value of $P_H/P_X = k_1/k_x$. Results obtained with 4-chloronitrobenzene **18** (Table 9) fit satisfactorily the mechanistic concept of the VNS hydroxylation. When the reaction was carried out in the presence of NaOH, exclusive substitution of chlorine took place. A similar result was obtained when the reaction was performed with an excess of potassium salt of **2**, when t-BuOK was absent. Apparently a weak base sodium salt of **2** operating in these two experiments (NaOH is practically insoluble in the reaction medium) was responsible for the

(25) Miller, J. Aromatic Nucleophilic Substitution, Elsevier, 1968. Terrier, F. Nucleophilic Aromatic Displacement, Verlag Chemie, Weinheim, 1991.

slow rate of elimination and consequently overall VNS reaction, and thus S_NAr of Cl dominated.

On the other hand, when the reaction was carried out with an excess of t-BuOK the VNS process was favored. These results indicate that the VNS reaction rate is efficiently accelerated by base; thus, it proceeds via a base-induced elimination from the σ^H adduct, and the elimination is the rate-limiting step at least in the range of base concentrations used in these experiments. Moreover, the greater extent of hydrogen substitution of **18** observed in the experiments with **2** can be explained as an effect of faster elimination of phenyldimethylcarbinol which is more acidic than *tert*-butyl alcohol eliminated in the reaction with **1**. This suggests an E2 character to the elimination because its rate depends on the kind and concentration of base and the kind of leaving group.

Results of these competitive experiments also indicate that the addition to the chloronitrobenzene ring at positions occupied by hydrogen proceeds faster than at those occupied by chlorine ($k_1 > k_{Cl}$). Surprisingly, with 1-chloro-2,4-dinitrobenzene **31**, the VNS hydroxylation almost completely dominated chlorine substitution, regardless of the reaction conditions. Hydrogen substitution was the primary process even when the potassium salt of hydroperoxide **1**, a much weaker base, was used without an excess, so the elimination was a slow process. This is perhaps due to the high stability of the σ^H-adduct derived from the highly electrophilic dinitroarene which is formed faster than the σ^X-adduct and dissociates more slowly than the subsequent β-elimination.

In the VNS reaction of α-chlorocarbanions, 4-fluoronitrobenzene was the suitable model compound in which VNS and S_NAr processes occurred simultaneously, and the competition between these reactions was governed by the concentration of base, whereas in 4-chloronitrobenzene the S_NAr of chlorine was hardly observed.[1,2] This indicates that addition of carbanions to nitroaromatic rings occurs faster at positions bearing hydrogen than at those bearing fluorine.[2] Even in 2,4-dinitrofluorobenzene **30**, VNS of hydrogen with α-chloro carbanions proceeds faster than S_NAr of fluorine.[26] On the other hand, attempts at VNS hydroxylations of 4-fluoronitrobenzene **21** and 2,4-dinitrofluorobenzene **30** with **1** and **2** resulted exclusively in S_NAr of fluorine, even under conditions strongly favoring the elimination step, namely when hydroperoxide **2** and t-BuOK were in high concentration. Thus one can conclude that alkyl hydroperoxide anions add to nitroarenes in positions occupied with hydrogen faster than in positions occupied with Cl, Br and I, but not F. The tendency of O-nucleophiles to add to nitroaromatic rings at positions bearing F is known.[27]

Finally, a comment on the course of the S_NAr reaction of halogen with alkyl hydroperoxide anions, which is not a simple process (Scheme 1) is warranted. Nitroaryl alkyl peroxides initially formed in this reaction are known to be unstable and to decompose rapidly, probably via a homolytic pathway.[13,20] The formation of substantial amounts of 2-*tert*-butoxy-4-nitrophenol **49** is a strong piece of evidence supporting the homolytic dissociation pathway of the initial S_NAr product. Since formation of **49** is suppressed when excess t-BuOK is present in the reaction mixture (Table 3), one can suppose that the intermediate nitrophenoxide radical is converted into the nitrophenoxide anion via electron transfer from t-BuO^- anion, rather than during hydrogen abstraction from the solvent.

Scheme 1

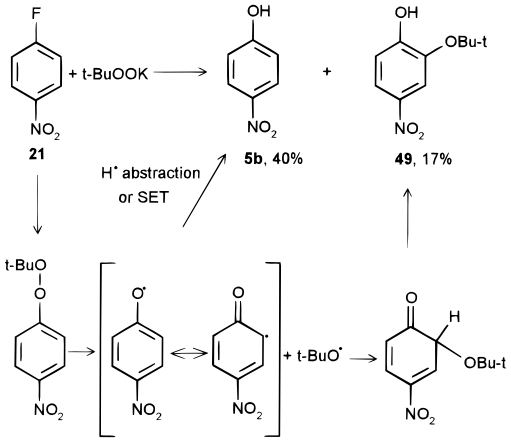
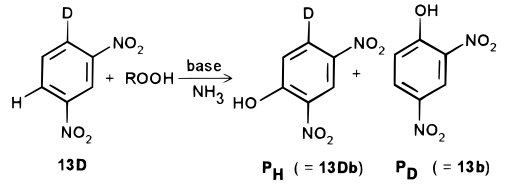


Table 10



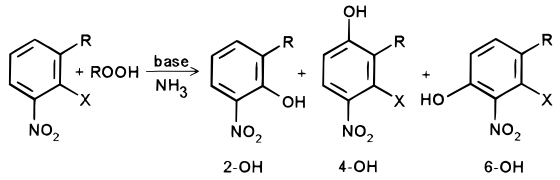
ROOH	base (mol)	yield, %	P_H/P_D (KIE)
1	NaOH (10)	77	7.0 ± 0.3
2	NaOH (10)	75	7.1 ± 0.4
	1$^-$ K^+ (2.5)	83	6.0 ± 0.2
1	t-BuOK (2.5)	76	0.98 ± 0.01
2	t-BuOK (2.5)	74	0.96 ± 0.02

Kinetic Isotopic Effect (Table 10). The kinetic isotope effect in the VNS hydroxylation was studied using 1-deutero-2,4-dinitrobenzene **13D** as a model compound in which competition between substitution of 1-D and 5-H was observed. The value of the kinetic isotope effect, KIE, was measured as the ratio of the H vs D substitution products (P_H/P_D) and was estimated via mass spectrometry. The deuterated dinitrobenzene **13D** was prepared via diazotization of 2,4-dinitroaniline in D_2SO_4 followed by reduction of the diazonium salt with deuterohypophosphoric acid.[2] Its isotopic purity was 96.4% as established by MS measurements. In separate experiments when **13D** was treated with t-BuOK in NH_3 and also when it was subjected to hydroxylation with 0.5 equiv of **1**, it was shown that loss of the label in the recovered substrate was negligible and within the experimental error: 2.1% and 2.5%, respectively. The value of KIE in the VNS hydroxylation of **13D** was greatly affected by the reaction conditions (Table 10). These results fit well the general mechanistic scheme of the VNS process.

For the hydroxylation carried out in the presence of NaOH with both of the alkyl peroxides **1** and **2** a significant value of KIE ≈ 7 was observed. A similar value of KIE ≃ 6 was observed when t-BuOOK, generated by treatment of **1** with an equimolar amount of t-BuOK, was used in the reaction. Obviously under these conditions the rate constant of the elimination with a weak base has a small value; hence, it was a slow process

(26) Makosza, M.; Stalewski, J. *Lieb. Ann. Chem.* **1991**, 605.
(27) Bordwell, F. G.; Hughes, D. L. *J. Am. Chem. Soc.* **1986**, *108*, 5991.

Table 11



X	R	substr no.	ROOH	base (mol)	yield, %	ratio[a] 2-OH	4-OH	6-OH
						8a	**8b**	**8c**
H	F	**8**	**2**	KOH (10)	76	0	100	0
H	F	**8**	**1**	t-BuOK (2.5)	83	8	92	0
H	F	**8**	**2**	t-BuOK (5)	72	63	37	0
						12a	**12b**	**12c**
H	CN	**12**	**2**	KOH (10)	87	0	100	0
H	CN	**12**	**1**	t-BuOK (2.5)	86	3	86	11
H	CN	**12**	**1**	t-BuOK (5)	84	5	77	18
H	CN	**12**	**2**	t-BuOK (5)	77	13	44	43
							29a	**29b**
CF_3	H	**29**	**1**	t-BuOK (2.5)	89	–	99	1
CF_3	H	**29**	**2**	t-BuOK (5)	72	–	64	36

[a] Ratio: **12b**(**12a**+**12c**) based on isolated products, **12a**:**12c** from ^{1}H NMR.

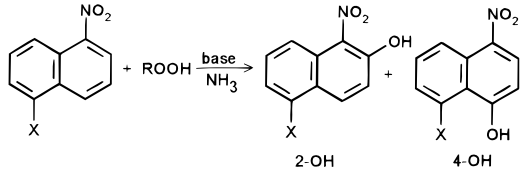
determining the overall reaction rate. On the other hand, when the reaction of **1** and **2** were each carried out in the presence of an excess of t-BuOK, there was no difference in the rate of substitution of H and D, so the value of KIE was ~1. These results suggest that the elimination effected by a weak base, namely, the alkyl hydroperoxide anion, is the rate-determining step. The significant value of KIE agrees with the supposition that the elimination is of E2 character. On the other hand, disappearance of KIE when the reaction is carried out with an excess of t-BuOK, a strong, soluble base, can be rationalized by a high rate of elimination with the strong base and its high concentration which assures that $k_{-1}/k_{E(H,D)}[B] \ll 1$. Thus the observed ratio of products P_H and P_D reflects the ratio of σ^H and σ^D adducts initially formed (no equilibration can occur because of the rapid consumption of each of them). Alternatively, a situation when the rate constants k_E for the elimination of ROD and ROH induced by a strong base become similar because of an early, unsymmetrical transition state, thus the value $k_{E(H)}/k_{E(D)} \approx 1$ hence $P_H \approx P_D$, cannot be excluded. Since the secondary KIE for the nucleophilic addition has a small value, it can be neglected in these semiquantitative experiments. This change of the KIE value depending on the reaction conditions, namely strength and concentration of base, is compatible with the conclusion from the competition between replacement of chlorine and hydrogen in the structurally related and similarly electrophilic 1-chloro-2,4-dinitrobenzene **31**.

Orientation of the VNS Hydroxylation (Tables 11−13). As already mentioned, the orientation of the VHS hydroxylation is strongly affected by the reaction conditions. A general trend emerged: in the reactions performed with NaOH or KOH a highly selective *para*-hydroxylation usually occurred while when excess t-BuOK was used, a competing *ortho*-substitution process took place and, for certain nitroarenes, prevailed. A reasonable explanation for this phenomenon can also be associated with the change of the value of the partitioning factor $k_{-1}/k_E[B]$, depending on the reaction conditions. Kinetic analysis of the competition between *ortho* and *para* hydrogen substitution (P_o/P_p) is rather complicated. However, for the border values of $k_{-1}/k_E[B]$ the ratios of (P_o/P_p) can be estimated from simple transformations of eq 5. Assuming the fast elimination step at both the *ortho* and *para* positions $k_{-1}/k_E[B] \ll 1$, the ratio of the products will be determined by the kinetic preferences in the addition step, namely the rate of formation of isomeric σ-adducts, $P_o/P_p \approx k_1^{ortho}/k_1^{para}$. In contrast, when the elimination is the slow, rate-limiting step $k_{-1}/k_E[B] \gg 1$, the value $P_o/P_p = (k_1k_E/k_{-1})^{ortho}/(k_1k_E/k_{-1})^{para}$ will depend on the relative stability of the isomeric σ^H-adducts as well as the corresponding rate constants of the elimination. In this respect the effect of t-BuOK concentration on the orientation of hydroxylation in 3-chloronitrobenzene **4** (Table 1), 3-fluoronitrobenzene **8**, and 3-cyanonitrobenzene **12** (Table 11) is informative. Following this reasoning, the substantial extent and even domination of the *ortho*-hydroxylation under the fast elimination conditions observed for 3-fluoro- and 3-cyanonitrobenzene **8** and **12** (Table 11) and especially for nitronaphthalenes (Table 12) indicates that for these nitroarenes formation of σ^H-adducts at the *ortho* positions proceeds faster than at the *para* position $k_1^{ortho} > k_1^{para}$.

Obviously, the exact values of k_1^{ortho}/k_1^{para} can not be extracted from these results, as it is not certain whether the border case of the fast elimination is already operating. On the other hand, *para*-hydroxylation generally observed under the slow elimination conditions suggests higher stability of the *para* σ-adducts; $(k_1/k_{-1})^{para} > (k_1/k_{-1})^{ortho}$ hence $k_{-1}^{para} \ll k_{-1}^{ortho}$. Faster elimination from the less sterically hindered *para* σ-adduct $k_E^{para} > k_E^{ortho}$ should also be considered; however, it is difficult to separate these two effects. Some kinetic data available for substituted 1,3-dinitrobenzenes indicate that anionic σ-adducts at positions *ortho* to the nitro groups are formed faster and also decompose faster than isomeric *para* adducts.[28] It appears that this is the case for the majority of nitroarenes.

The *ortho*:*para* hydroxylation ratio depends also on the temperature of the process. For example, in the reaction of 1-nitronaphthalene **35**, the extent of *para* hydroxylation increases with the increase of temperature (Table 13). This effect can be due to faster equilibration of the σ-adducts, hence the tendency toward thermodynamic control at higher temperatures.

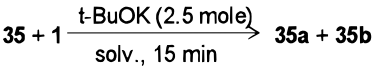
Table 12



X	substr no. "**i**"	ROOH	base (mol)	yield, % 2-OH (**ia**)	yield, % 4-OH (**ib**)
H	**35**	**1**	NaOH (10)	traces	88
H	**35**	**2**	NaOH (10)	5	81
H	**35**	**1**	t-BuOK (2.5)	81	4
H	**35**	**2**	t-BuOK (2.5)	79	4
NO_2	**36**	**1**	NaOH (10)	22	61
NO_2	**36**	**2**	NaOH (10)	64	30
NO_2	**36**	**1**	t-BuOK (2.5)	81	5
NO_2	**36**	**2**	t-BuOK (2.5)	81	4
Br	**37**	**1**	NaOH (10)[a]	32	44
Br	**37**	**2**	NaOH (10)[a]	61	19
Br	**37**	**1**	t-BuOK (2.5)	85	traces

[a] Reaction time: 3 h.

Table 13



solv	temp, °C	yield, % **35a**	yield, % **35b**
NH_3	−65	86	1
NH_3	−33	81	4
DMF	−25	76	7
DMF	0	61	22
DMF	25	50	40

Conclusions

Hydroxylation of nitroarenes with *tert*-butyl and cumene hydroperoxides **1** and **2** by vicarious nucleophilic substitution is a general process of wide scope. Available data suggests that it proceeds via nucleophilic addition of the alkyl hydroperoxide anion to nitroarenes followed by base-induced β-elimination of the alcohol. It appears that the elimination proceeds according to an E2 type mechanism and that there is a full range of relations between the rates of the addition and elimination processes.

Experimental Section

General. *tert*-Butyl hydroperoxide **1** (80% in *t*-Bu_2O_2) and triphenylmethyl hydroperoxide **3** (*pure* grade) were purchased from Aldrich. Cumene hydroperoxide **2** (90%, technical grade) was used without purification. Commercially available starting nitroarenes were purified when necessary. The following substrates were prepared: 3-nitrophenyl methyl sulfone **11**,[29] 4-nitrophenyl phenyl sulfone **24**,[30] 1-bromo-5-nitronaphthalene **37**,[31] 1-methoxy-4-nitronaphthalene **38**,[32] 1-chloro-4-nitronaphthalene **39**,[33] and 4-cyanoisoquinoline **47**.[34] Solvents: gaseous NH_3 was dried by passing through KOH pellets tube prior to its condensation; DMF (puriss. p.a.) was kept over molecular sieves (4A); THF was distilled over sodium−benzophenone. TLC: silica gel $60F_{254}$ (Merck). Flash chromatography: silica gel 60 (230−400 mesh, Merck) and hexane−ethyl acetate or chloroform or chloroform−methanol. Melting points (mp) are not corrected, literature mp are quoted from *Beilstein's Handbuch der Organischen Chemie* (unless otherwise stated). NMR: in acetone-d_6 unless otherwise stated, chemical shifts δ in ppm in relation to internal standard TMS. Satisfactory elemental analyses (C, H, N) were obtained for all products.

Reactions of Alkyl Hydroperoxides with Nitroarenes in Liquid Ammonia. General Procedure. To a stirred solution of *t*-BuOK (2.5 or 5.0 equiv) or suspension of powdered NaOH (10 equiv) or KOH (10 equiv) in liquid NH_3 (ca. 10 mL) was added dropwise a solution of nitroarene (3 mmol) and alkyl hydroperoxide (3.3 mmol) in dry THF (3 mL). The reaction was conducted under reflux at ca. -33 °C over 15 min for *t*-BuOK, or 1 h for NaOH or KOH (unless otherwise stated, see tables for details). Then solid NH_4Cl was added, ammonia evaporated, and the reaction mixture treated with 1 N HCl (20 mL) and extracted with CH_2Cl_2 (3 × 15 mL). Combined organic extracts were washed with 0.5 N NaOH (3 × 10 mL), alkaline solution of nitrophenolates was acidified with 6 N HCl and extracted with CH_2Cl_2 (3 × 15 mL), and the organic phase was dried (Na_2SO_4) and evaporated. In most cases the residue was subjected to flash chromatography to give pure products. Certain products were purified by recrystallization; **41a**, **42a**, **44a** from ethanol; **43a**, **44b**, **45a** from aqueous acetone; **47a** from acetone−heptane.

Reactions in THF or DMF of Nitroarenes 4 and 35. A solution of nitroarene (3 mmol) and hydroperoxide **1** (0.300 g, 3.3 mmol) in THF or DMF (3 mL) was added dropwise to t-BuOK (0.840 g, 7.5 mmol) in THF or DMF (10 mL). The resulting mixture was stirred for 15 min at the temperature given in the Tables 1 and 13, and then the reaction mixture was diluted with 1 N HCl (40 mL) and the products were isolated following the General Procedure.

Reactions of Potassium Salts of Hydroperoxides 1 or 2 and Nitroarenes 13D, 18, 21, and 31. To a cold (ca. −50 °C) solution of t-BuOK (3 or 7.5 mmol) in liquid NH_3 (10 mL) was added an equimolar amount of hydroperoxide **1** or **2**. The reaction mixture was allowed to warm up to the reflux temperature, and then a solution of nitroarene (3 mmol) in THF (3 mL) was added and the mixture stirred over 1 h. Products were isolated according to the General Procedure.

Ammonium Salt 46a. Hydroxylation of 2-nitrothiophene **46** (3 mmol) with hydroperoxide **1** and t-BuOK in liquid NH_3 was performed as given in General Procedure. After the ammonia was evaporated, the residue was diluted with water (20 mL) and treated with tetrabutylammonium hydrogen sulfate (1.02 g, 3 mmol), and the mixture was shaken vigorously over a few min and then extracted with CH_2Cl_2 (3 × 15 mL). Combined organic solutions were dried (Na_2SO_4) and evaporated to give the crude salt **46a** which was recrystallized from hexane−ethyl acetate.

4a: mp 70−71 °C (water) (lit. mp 70−71 °C). ^{1}H NMR δ 7.13 (dd, 1H, J = 8.6, 8.2), 7.86 (dd, 1H, J = 8.2, 1.6), 8.13 (dd, 1H, J = 8.6, 1.6).

4b: mp 111−112 °C (water) (lit. mp 111 °C). ^{1}H NMR δ 7.23 (d, 1H, J = 9.0), 8.12 (dd, 1H, J = 9.0, 2.8), 8.26 (d, 1H, J = 2.8).

4c: mp 87−89 °C (water) (lit. mp 70−71 °C). ^{1}H NMR δ 7.25 (d, 1H, J = 9.0), 7.70 (dd, 1H, J = 9.0, 2.7), 8.10 (d, 1H, J = 2.7).

5a: mp 43−44 °C (hexane) (lit. mp 45 °C). Compared with an authentic sample (TLC).

5b: mp 112−114 °C (water) (lit. mp 45 °C). Compared with an authentic sample (TLC).

6b: mp 92−94 °C (water) (lit. mp 95 °C). ^{1}H NMR δ 2.30 (s, 3H), 7.01 (d, 1H, J = 8.8), 7.99 (dd, 1H, J = 8.8, 2.9), 8.06 (d, 1H, J = 2.9).

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7b: mp 101−103 °C (water) (lit. mp 103−104 °C). ^{1}H NMR δ 4.00 (s, 3H), 7.02 (d, 1H, J = 8.6), 7.80 (d, 1H, J = 2.6), 7.85 (dd, 1H, J = 8.6, 2.6).

8a: mp 90−92 °C (hexane) (lit. mp 91−92 °C). ^{1}H NMR (DMSO-d_6) δ 7.01 (td, 1H, J = 8.4, 5.0), 7.60 (ddd, 1H, J = 10.6, 8.4, 1.6), 7.74 (dt, 1H, J = 8.4, 1.6).

8b: mp 118−120 °C (water). ^{1}H NMR (DMSO-d_6) δ 7.14 (t, 1H, J = 8.9), 8.01 (ddd, 1H, J = 8.9, 2.7, 1.2), 8.10 (dt, 1H, J = 11.1, 2.7).

9b: mp 112−114 °C (water) (lit. mp 113−114 °C). ^{1}H NMR δ 7.21 (d, 1H, J = 9.0), 8.15 (dd, 1H, J = 9.0, 2.7), 8.40 (d, 1H, J = 2.7).

10b: mp 135−136 °C (benzene−hexane) (lit.[35] mp 134−135 °C). ^{1}H NMR δ 7.32 (d, 1H, J = 9.1), 8.37 (dd, 1H, J = 9.1, 2.8), 8.42 (d, 1H, J = 2.8).

11b: mp 167−169 °C (water). ^{1}H NMR δ 3.33 (s, 3H), 7.34 (d, 1H, J = 9.1), 8.41 (dd, 1H, J = 9.1, 2.9), 8.66 (d, 1H, J = 2.9).

12a: mp 130−132 °C (ethanol) (lit. mp 132−133 °C). ^{1}H NMR δ 7.31 (dd, 1H, J = 8.6, 7.7), 8.15 (dd, 1H, J = 7.7, 1.7), 8.47 (dd, 1H, J = 8.6, 1.7). IR: 2240.

12b: mp 193−194 °C (ethanol) (lit. mp 194 °C). ^{1}H NMR δ 7.32 (d, 1H, J = 9.2), 8.39 (dd, 1H, J = 9.2, 2.8), 8.57 (d, 1H, J = 2.8). IR: 2240.

12c: mp 140−142 °C (ethanol) (lit. mp 143−145 °C). ^{1}H NMR δ 7.41 (d, 1H, J = 8.7), 8.04 (dd, 1H, J = 8.7, 2.1), 8.56 (d, 1H, J = 2.1). IR: 2230.

13b: mp 112−114 °C (ethanol) (lit. mp 113−114 °C). ^{1}H NMR δ 7.23 (d, 1H, J = 9.3), 8.33 (dd, 1H, J = 9.3, 2.8), 8.85 (d, 1H, J = 2.8).

14b: mp 120−122 °C (ethanol) (lit. mp 119−121 °C). ^{1}H NMR δ 7.29 (d, 1H, J = 8.7), 7.60−7.90 (m, 5H), 8.45 (dd, 1H, J = 8.7, 2.8), 8.52 (d, 1H, J = 2.8). IR: 1630.

17: mp 140−142 °C (water), identical with an authentic sample.

18a: mp 37−39 °C (water) (lit. mp 39 °C). ^{1}H NMR δ 7.13 (dd, 1H, J = 9.1, 2.3), 7.27 (d, 1H, J = 2.3), 8.14 (d, 1H, J = 9.1).

19a: mp 40−42 °C (hexane) (lit. mp 42 °C). ^{1}H NMR δ 7.28 (dd, 1H, J = 9.0, 2.1), 7.44 (d, 1H, J = 2.1), 8.05 (d, 1H, J = 9.0).

20a: mp 94−96° (hexane) (lit. mp 96 °C). ^{1}H NMR δ 7.48 (dd, 1H, J = 8.8, 1.8), 7.65 (d, 1H, J = 1.8), 7.85 (d, 1H, J = 8.8).

22a: mp 93−95° (ethanol) (lit. mp 96 °C). ^{1}H NMR δ 3.96 (s, 3H), 6.66 (m, 1H, J = 9.9, 2.6), 6.66 (m, 1H, J = 2.6), 8.08 (m, 1H, J = 9.9);

23a: oil. ^{1}H NMR δ 7.25 (dd, 1H, J = 8.9, 1.9), 7.47 (d, 1H, J = 1.9), 8.25 (d, 1H, J = 8.9).

24a: mp 141−143 °C (ethanol). ^{1}H NMR δ 7.60 (dd, 1H, J = 8.7, 2.0), 7.65−7.77 (m, 4H), 8.04−8.08 (m, 2H), 8.27 (d, 1H, J = 8.7).

25a: mp 119−121 °C (ethanol) (lit. mp 121 °C). ^{1}H NMR δ 7.47 (dd, 1H, J = 8.6, 1.7), 7.66 (d, 1H, J = 1.7), 8.24 (d, 1H, J = 8.6). IR: 2240.

25b: mp 109−112 °C (hexane) (lit. mp 113 °C). ^{1}H NMR (AA′XX′ system) δ 6.98−7.01 (m, 2H), 7.59−7.62 (m, 2H). IR: 2220.

26a: mp 120−122 °C (water) (lit. mp 121−122 °C). ^{1}H NMR δ 6.99 (dd, 1H, J = 9.0, 2.6), 7.08 (d, 1H, J = 2.6), 8.01 (d, 1H, J = 9.0).

28a: mp 142−144 °C (ethanol) (lit. mp 144 °C). ^{1}H NMR δ 3.93 (s, 3H), 6.54 (dd, 1H, J = 9.0, 2.4), 6.68 (d, 1H, J = 2.4), 7.88 (d, 1H, J = 9.0).

29a: mp 77−79 °C (benzene−hexane) (lit. mp 78,5−79 °C). ^{1}H NMR δ 7.29 (dd, 1H, J = 8.9, 2.6), 7.35 (d, 1H, J = 2.6), 8.08 (d, 1H, J = 8.9).

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29b: mp 69−72 °C (hexane) (lit.[36] mp 71−73 °C). ^{1}H NMR δ 7.38 (dm, 1H, J = ∼8), 7.50 (dm, 1H, J = ∼8), 7.66 (tm, 1H, J = ∼8).

31a: mp 90−91 °C (water) (lit. mp 92 °C). ^{1}H NMR δ 7.54 (s, 1H), 8.84 (s, 1H).

32a: mp 125−127 °C (ethanol−water). ^{1}H NMR δ 7.56 (s, 1H), 8.71 (s, 1H). IR: 2230.

33a: mp 53−54 °C (benzene−hexane). ^{1}H NMR δ 7.53 (s, 1H), 8.46 (s, 1H).

34a: mp 66−67 °C (ethanol−water). ^{1}H NMR δ 7.35 (d, 1H, J = 9.3), 8.16 (d, 1H, J = 9.3).

34b: mp 67.5−68 °C (ethanol−water) (lit.[37] mp 68 °C). ^{1}H NMR δ 7.48 (s, 1H), 8.29 (s, 1H).

35a: mp 102−104 °C (ethanol) (lit. mp 103 °C) identical with an authentic sample (TLC).

35b: mp 163−164 °C (water) (lit. mp 164 °C) identical with an authentic sample (TLC).

36a: mp 190 °C, dec (ethanol−water) (lit. mp 187 °C, dec). ^{1}H NMR δ 7.66 (d, 1H, J = 9.6), 7.84 (dd, 1H, J = 8.6, 7.7), 8.03 (ddd, 1H, J = 8.6, 1.0, 0.9), 8.17 (dd, 1H, J = 7.7, 1.0), 8.46 (dd, 1H, J = 9.6, 0.9).

36b: mp 233 °C, dec (ethanol−water) (lit. mp 235 °C, dec). ^{1}H NMR δ 7.19 (d, 1H, J = 8.7), 7.82 (dd, 1H, J = 7.5, 1.1), 7.90 (dd, 1H, J = 8.8, 7.5), 8.49 (d, 1H, J = 8.7), 8.82 (dd, 1H, J = 8.8, 1.1);

37a: mp 126−127 °C (ethanol−water). ^{1}H NMR δ 7.56 (d, 1H, J = 9.4), 7.57 (dd, 1H, J = 8.6, 7.5), 7.75 (ddd, 1H, J = 8.6, 1.0, 0.9), 7.83 (dd, 1H, J = 7.5, 1.0), 8.33 (dd, 1H, J = 9.4, 0.9).

37b: mp 201−203 °C, dec (ethanol−water). ^{1}H NMR δ 7.15 (d, 1H, J = 8.7), 7.57 (dd, 1H, J = 8.6, 7.5), 7.96 (dd, 1H, J = 7.5, 1.1), 8.26 (d, 1H, J = 8.7), 8.57 (dd, 1H, J = 8.6, 1.1).

38a: mp 121−123 °C (ethanol). ^{1}H NMR δ 4.20 (s, 3H), 6.75 (s, 1H), 7.52−7.57 (m, 1H), 7.77−7.81 (m, 1H), 8.26−8.29 (m, 1H), 8.87−8.89 (m, 1H).

39a: mp 127−128 °C (ethanol). ^{1}H NMR δ 7.59 (s, 1H), 7.65 (ddd, 1H, J = 8.5, 6.9, 1.2), 7.78 (ddd, 1H, J = 8.5, 6.9, 1.1), 7.88 (ddd, 1H, J = 8.5, 1.1, 0.7), 8.27 (ddd, 1H, J = 8.5, 1.2, 0.7).

40a: mp 128−129 °C (ethanol) (lit. mp 128 °C) identical with an authentic sample (TLC).

41a: mp 207−209 °C (ethanol). ^{1}H NMR (DMSO-d_6) δ 1.40 (t, 3H, J = 7.0), 4.13 (q, 2H, J = 7.0), 5.80 (s, 1H), 8.38 (s, 1H). IR: 1660.

42a: mp 177−179 °C (ethanol) (lit.[38] mp 172−173 °C). ^{1}H NMR (DMSO-d_6) δ 3.92 (s, 3H), 6.26 (d, 1H, J = 9.0), 8.36 (d, 1H, J = 9.0). IR: 1680.

43a: mp 189−191 °C, dec (acetone). ^{1}H NMR (DMSO-d_6) δ 7.09 (d, 1H, J = 8.4), 8.44 (d, 1H, J = 8.4). IR: 1670.

44a: mp 250−251 °C, dec (ethanol) (lit. mp 255 °C, dec). ^{1}H NMR δ 7.47 (dd, 1H, J = 8.3, 4.4), 7.50 (d, 1H, J = 9.1), 8.02 (d, 1H, J = 9.1), 8.37 (dd, 1H, J = 8.3, 1.7), 8.85 (dd, 1H, J = 4.4, 1.7).

44b: mp 261−263 °C, dec (acetone−water) (lit.[39] mp 261 °C, dec). ^{1}H NMR (DMSO-d_6) δ 6.88 (d, 1H, J = 8.8), 7.67 (dd, 1H, J = 8.5, 4.5), 8.26 (d, 1H, J = 8.8), 8.71 (dd, 1H, J = 8.5, 1.8), 9.01 (dd, 1H, J = 4.5, 1.8).

45a: mp > 255 °C, dec (acetone−water) (lit.[40] mp > 250 °C, dec). ^{1}H NMR (DMSO-d_6) δ 7.47 (dd, 1H, J = 9.5, 0.7), 7.69 (dd, 1H, J = 8.4, 4.4), 8.25 (d, 1H, J = 9.5), 8.84 (ddd, 1H, J = 8.4, 1.7, 0.7), 9.06 (dd, 1H, J = 4.4, 1.7).

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46a: mp 121−123 °C (hexane−ethyl acetate). ^{1}H NMR δ 0.94−1.90 (m, 28H), 3.41−3.49 (m, 8H), 6.09 (d, 1H, J = 6.2), 7.19 (d, 1H, J = 6.2).

46b: dec without melting. ^{1}H NMR δ 6.90 (d, 1H, J = 5.9), 7.87 (d, 1H, J = 5.9).

47a: mp 259−261 °C (acetone−heptane) (lit.[41] mp 257 °C). ^{1}H NMR δ 7.66−7.70 (m, 1H), 7.79−7.82 (m, 1H), 7.91−7.95 (m, 1H), 8.09 (s, 1H), 8.33−8.36 (m, 1H). IR: 2220, 1690.

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48a: mp 74−75 °C (hexane) (lit. mp 76 °C). ^{1}H NMR δ 7.19 (d, 1H, J = 9.1), 7.60 (d, 1H, J = 9.1).

48b: mp 152−154 °C (heptane−diethyl ether) (lit.[42] 154 °C).

49: oil. ^{1}H NMR δ 1.45 (s, 9H), 7.07 (d, 1H, J = 8.8), 7.90 (dd, 1H, J = 8.8, 2.7), 7.92 (d, 1H, J = 2.7).

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