CHEMICAL REVIEWS

REVIEW

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The Chemistry of *N*-Hydroxyamidoximes, *N*-Aminoamidoximes, and Hydrazidines

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CONTENTS

1. INTRODUCTION

N-Hydroxyamidoximes, *N*-aminoamidoximes, and hydrazidines belong to a class of compounds with the general formula RC═NX(NHY) where X = OH or NH_2, Y = OH or NH_2, and R is a linear side chain, carbocycle residue, or heterocycle

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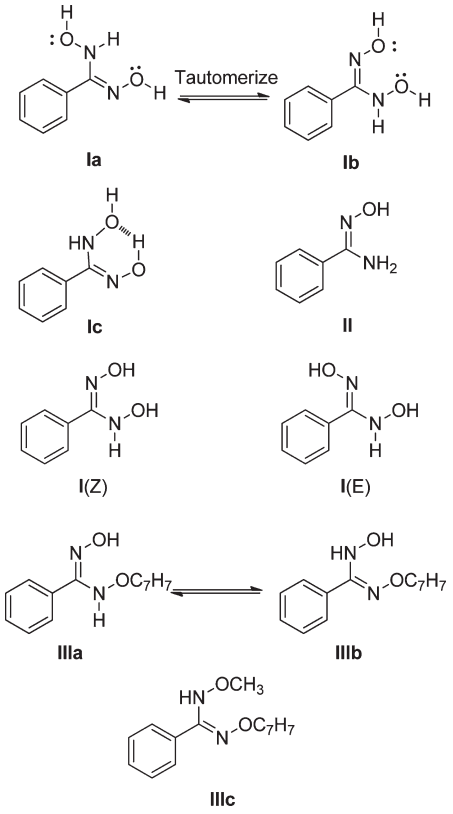


Figure 1. Tautomerization, conformation, and configuration of *N*-hydroxyamidoximes.

residue. Their structures are similar to those of amidoximes and amidrazones, but they possess very different synthetic utility and pharmacological properties. There are several reviews published on the synthetic and biological applications of amidrazones and amidoximes.[1−8] However, a comprehensive review on the preparative methods, synthetic utility, and biological applications is missing for this class of compounds thus far. We now attempt to readdress the situation by providing a detailed compilation on the chemistry of *N*-hydroxyamidoximes, *N*-aminoamidoximes, and hydrazidines in terms of the structure, preparative methods, reactivity, and biological applications.

2. STRUCTURE AND CONFIGURATION

2.1. *N*-Hydroxyamidoximes

N-Hydroxyamidoximes **I** are sometimes named as *N*,*N*′-dihydroxyimidamides or oxyamidoximes **Ia**.[1] Clement et al. studied and compared chemical shifts and coupling constants *J* (^{15}N, ^{1}H) of several amidoximes via ^{15}N NMR (DMSO). Clements states that benzamidoxime **II** exists only in the form of an oxime with no other tautomer detected. "However, it was also claimed that *N*-hydroxybenzamidoxime **I** exists in two tautomeric forms (**Ia** and **Ib**) in rapid equilibrium (Figure 1)." Clement reported two ^{15}N signals associated with an oxime type nitrogen and a hydroxylamine type nitrogen but claimed that the lack of NH coupling was due to rapid tautomerism between **Ia** and **Ib**.[9,10] Unfortunately, the two observations are incompatible since **Ia** and **Ib** are identical and therefore rapid tautomerism between them would afford only one ^{15}N NMR signal. It seems likely that the lack of N−H coupling is due to exchange with the solvent rather than a tautomeric equilibrium, and this is consistent with two ^{15}N NMR signals. Barassin et al. studied the configuration and conformation of *N*-hydroxybenzamidoxime and found that the *Z*-configuration **IZ** is favored energetically over configuration **IE**, and conformation **Ic** is the predominant form due to the stabilization by hydrogen bonding (Figure 1).[11]

2-Phenyl-4-benzyl-oxy-amidoxime (DMSO) exists in two tautomeric forms in which the **IIIa** form is more stable than **IIIb** form at room temperature. Upon methylation of the OH group, **IIIc** was reported as the more stable as shown in Figure 1.[12]

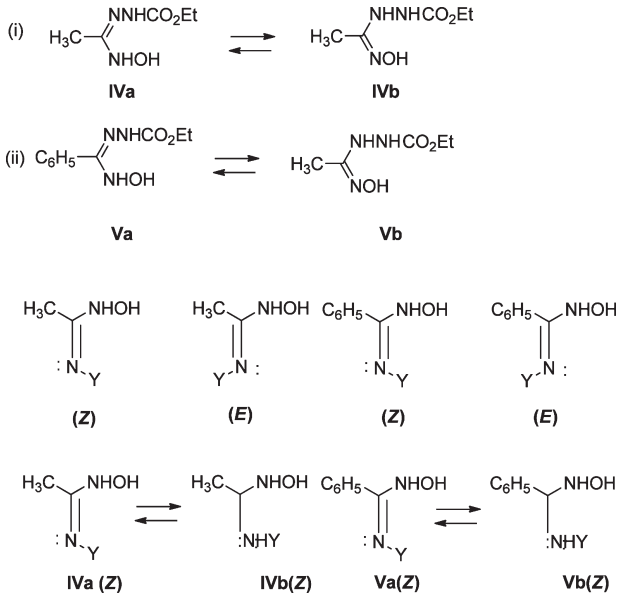


Figure 2. Tautomerization and conformation of *N*-hydroxamide ethoxycarbonylhydrazones.

Table 1. IR and NMR Data of *N*-Hydroxyamidoxime Derivatives

compd.	IR (cm^{-1})	^{1}H NMR (δ)	^{13}C NMR (δ)
3a	ref 10	ref 10	ref 10
3c	ref 17	*a*	*a*

[a] Not reported.

2.2. *N*-Aminoamidoximes

Ikizler reported two tautomeric forms **IV** and **V** of *N*-hydroxamide ethoxycarbonylhydrazones in DMSO as shown in Figure 2.[13]

For compounds **IV** and **V**, *syn* (*Z*) and *anti* (*E*) stereoisomers are possible and quantum-chemical calculations show that the *syn* (*Z*) isomers are more stable. Conformational analyses of these molecules were examined by using the AM1 semiempirical method.

2.3. Hydrazidines

To the best of our knowledge, there are no experimental reports regarding the structure and configuration of hydrazidines.

3. SPECTROSCOPIC DATA

Spectroscopic (IR, UV, ^{1}H/^{13}C NMR), CHN elemental analysis, and mass spectrometry data for *N*-hydroxyamidoximes,

Table 2. UV, IR, NMR, CHN, and Mass Spectrometry Data of *N*-Aminoamidoxime Derivatives[a]

compd	UV data, λ_{max} (nm)	IR (cm^{-1})	^1H NMR (δ)	CHN analysis	EIMS (30 eV)
28c	*b*	ref 50	ref 50	ref 50	*b*
28f	*b*	ref 52	ref 52	ref 52	ref 52
28g	*b*	ref 52	ref 52	ref 52	ref 52
28h	*b*	ref 52	ref 52	ref 52	ref 52
28i	*b*	ref 52	ref 52	ref 52	ref 52
38a	ref 55	ref 55	ref 55	*b*	*b*
38b	ref 55	ref 55	ref 55	*b*	*b*
38c	ref 55	ref 55	ref 55	*b*	*b*
38d	ref 55	ref 55	ref 55	*b*	*b*
38e	ref 55	ref 55	ref 55	*b*	*b*
38g	ref 55	ref 55	ref 55	*b*	*b*
46a	*b*	ref 51	ref 51	*b*	*b*
46b	*b*	ref 51	ref 51	*b*	*b*
46c	*b*	ref 51	ref 51	*b*	*b*

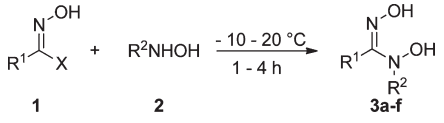
[a] References 55 and 51 report the ^{13}C NMR data for **38a** and **46c**, respectively. [b] Not reported.

Table 3. IR, NMR, and CHN Data of Hydrazidines

compd	IR (cm^{-1})	^1H NMR (δ)	CHN analysis
60c	*a*	ref 66	ref 66
60d	*a*	ref 66	ref 66
60e	*a*	ref 66	ref 66
60f	*a*	ref 66	ref 66
67	*a*	ref 70	ref 70
68	*a*	ref 70	ref 70
51a	ref 61	ref 60	ref 60
51b	*a*	ref 60	ref 60
51c	*a*	ref 60	ref 60
51d	*a*	ref 60	ref 60

[a] Not reported.

Scheme 1. Reaction of Oximidoyl Chlorides/Amidoxime 1 with Hydroxylamines 2



N-aminoamidoximes, and hydrazidines are reported in Tables 1, 2, and 3, respectively.

4. *N*-HYDROXYAMIDOXIMES AND THEIR DERIVATIVES

4.1. Preparative Methods

4.1.1. From Oximidoyl Chlorides/Amidoxime and Hydroxylamines. The most common method for the synthesis of *N*-hydroxyamidoximes starts from α-chloro or amino oximes. Ley first reported the preparation of *N*-hydroxyamidoximes **3a,b** from hydroxylamine and hydroxyimidoyl chloride, and

Table 4. Preparation of *N*-Hydroxyamidoximes 3a−f

product 3		reactant 1		reactant 2		
no.	yield (%)	R^1	X	R^2	solvent	refs
a	*a*	C_6H_5	Cl	H	EtOH	10, 14−16
b	*a*	4-pyridyl	Cl	H	MeOH	17
c	*a*	2-pyridyl	Cl	H	MeOH	17
d	*a*	3-$NO_2C_6H_4$	Cl	H	EtOH	12
e	50	2,6-$Cl_2C_6H_3$	Cl	H	EtOH/Ether	18
f	85	H	NH_2	H	MeOH/Ether	14, 19

[a] Not reported.

Scheme 2. Reaction of Nitrile Oxides 5 with Hydroxylamines 4

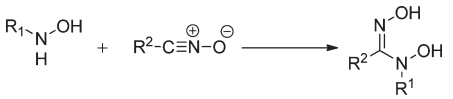


Table 5. Preparation of *N*-Hydroxyamidoximes 6a−d from Hydroxylamines 4 and Nitrile Oxides 5

product 6				conditions		
no.	yield (%)	R^1	R^2	solvent	*T* (°C)	time (h)
a	66	H	C_6H_5	petroleum ether	0	3
b	68	*t*-Bu	C_6H_5	petroleum ether	0	2−3
					20	3
c	53	*t*-Bu	*t*-Bu	$CHCl_3$	0	5
					20	24
d	45	*t*-Bu	2,4,6$(OMe)_3C_6H_2$	$CHCl_3$	20	*a*

[a] Not reported.

subsequently, Armand prepared the *N,N′*-dihydroxyformimidamide **3f** in good yield (85%) from *N′*-hydroxyformimidamide and hydroxylamine (Scheme 1, Table 4).

4.1.2. From Nitrile Oxides and Hydroxylamines. Aurich and Stork reported that nitrile oxides **5** react with hydroxylamines **4** to give N^2-hydroxyamidinyl N^1-oximes **6a−d** (Scheme 2, Table 5).[20]

4.1.3. From Di(benzotriazol-1-yl)imines and Hydroxylamines. Katritzky et al. also synthesized *N*-hydroxyamidoximes **8a,b** in moderate to high yields by the reaction of di(benzotriazol-1-yl)imines **7a,b** with hydroxylamine **2** in the presence of triethylamine. The reaction mixture was heated under reflux for 30−45 min (Scheme 3, Table 6).[21]

4.1.4. Synthesis of Mono- and Di-*O*-alkyl Derivatives of *N*-Hydroxyamidoximes. Di-*O*-alkyl derivatives of *N*-hydroxymethylamidoxime **11a** were obtained in moderate yield by treatment of 1*H*-1,2,3-benzotriazol-1-ylmethanone oxime **9a** with benzyloxyhydroxylamine **10a** under microwave conditions.[22] Eloy et al. reported the preparation of *O*-alkyl-substituted sulfamidobenzamidoxime **11b** by reaction of an alcoholic solution of sulfamidobenziminoethyl ether hydrochloride **9b** (X = OEt) with *O*-methylhydroxylamine **10b** under pressure

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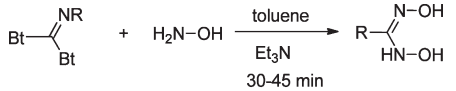
Scheme 3. Reaction of Di(benzotriazol-1-yl)imines 7a,b with Hydroxylamine 2

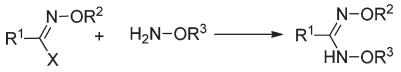


7a-b 2 8a-b

Table 6. Preparation of *N*-Hydroxyamidoximes 8a,b from Di(benzotriazol-1-yl)imines 7a,b

	product **8**		
no.	yield (%)	R	
a	61	H	
b	91	$C_6H_4CO_2Et$	

Scheme 4. Reaction of Amidoxime 9a/Imines 9b−d with Hydroxylamines 10a−d



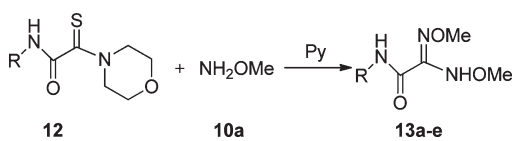
9a-d 10a-d 11a-d

Table 7. Preparation of *O*-Substituted *N*-Hydroxyamidoximes 11a−d[a]

Product		Reactant					
11		**9**			**10**	Conditions	Refs
no	Yield (%)	R^1	X	R^2	R^3		
a	64	CH_3	Bt	H	Bn	Na_2SO_4 anhydrous *mw* 110 °C, 10 min	22
b	n/r		OEt	H	CH_3	EtOH under pressure	1
c	73	H	NMe_2	Bn	$CH_2C_6H_5$	CH_3CN, AcOH reflux, 10 h	23
d	47	H	NMe_2	Bn	$CH{\equiv}CCH_2$	CH_3OH, reflux,10h	23

[a] n/r indicates not reported.

Scheme 5. Reaction of Monothiooxamides 12 and *O*-Methylhydroxylamine 10a



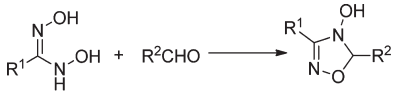
12 10a 13a-e

(Scheme 4, Table 7).[1] Diaz et al. also prepared the di-*O*-alkyl derivative of *N*-hydroxymethylamidoxime **11c,d** from benzyl amine **10c** and propargylamine **10d** reacting with *N,N*-dimethyl(form)amidines **9c,d**.[23]

Table 8. Preparation of Derivatives of *N*-Hydroxyamidoximes 13a−e from Monothiooxamides 12 and *O*-Methylhydroxylamine 10a

	product **13**	
no.	yield (%)	R
a	30	C_6H_5
b	47	4-$MeOC_6H_4$
c	44	6-Cl-2,4$(MeO)_2C_6H_2$
d	12	2,3-$Me_2C_6H_3$
e	42	$CH_2C_6H_5$

Scheme 6. Reaction of *N*-Hydroxyamidoximes 14 with Aldehydes 15



14 15 16a-d

Table 9. Preparation of 4-Hydroxyoxadiazolines 16a−d

			conditions		
product **16**	R^1	R^2	solvent	*T* (°C)	time (min)
a	C_6H_5	C_2H_5	Et_2O	20	10
b	C_6H_5	4-$NO_2C_6H_4$	CH_3OH	40	60
c	CH_3	C_2H_5	CH_3OH	20	10
d	CH_3	4-$OCH_3C_6H_4$	CH_3OH	40	*a*

[a] Not reported.

Zavarzin et al. prepared *N*-methoxy derivatives of amidoximes **13a−e** from monothiooxamides **12** with *O*-methylhydroxylamine **10a** in pyridine under reflux (Scheme 5, Table 8).[24,25]

4.2. Chemistry of *N*-Hydroxyamidoximes

4.2.1. Reaction with Aldehydes. Desherces et al. used *N*-hydroxyamidoximes **14** as precursors for the synthesis of 4-hydroxyoxadiazolines **16a−d** by condensation with aldehydes **15** (Scheme 6, Table 9).[26]

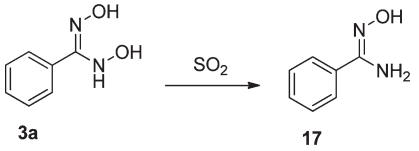
4.2.2. Reduction of *N*-Hydroxyamidoximes. Ley and Ulrich showed that *N*-hydroxybenzamidoxime **3a** may be reduced by sulfur dioxide to benzamidoxime **17** (Scheme 7).[12]

4.2.3. Oxidation of *N*-Hydroxyamidoximes. Armand and Minvielle reported that periodate oxidation of hydroxyamidoximes **3** gave the corresponding nitrosolate potassium salts **19a−d**. In acidic media, nitrosolic salts **19a,b** give nitrosolic acids **20a,b**, and nitrosolic salts **19c,d** react with 1 equiv of N_2O_4 to yield nitrolic acids **20c,d** (Scheme 8, Table 10).[19]

4.3. Applications

4.3.1. As a Prodrug Model. Clement and Reeh reported that drugs containing amidine functions are efficiently absorbed by the gastrointestinal tract after oral administration.[30] *N*-Hydroxybenzamidoxime derivatives **3a** represent a new class of prodrug to improve the oral bioavailability of medications containing amidine functions, because they have lower basicity but higher lipophilicity than amidine derivatives and can be quickly

Scheme 7. Conversion of *N*-Hydroxybenamidoxime 3a into Benzamidoxime 17



Scheme 8. Reaction of *N*-Hydroxyamidoximes 3 with Potassium Periodate 18

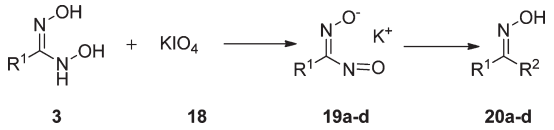
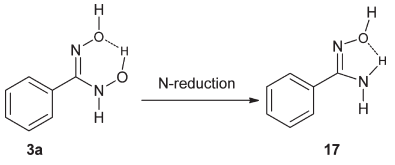


Table 10. Oxidation of *N*-Hydroxyamidoximes 3

	product **20**			conditions		
no.	yield (%)	R^1	R^2	solvent	T (°C)	refs
a	*a*	C_6H_5	NO	alkaline media	*a*	19, 28
b	*a*	H	NO	alkaline media	*a*	19
c	80	CH_3	NO_2	1 equiv of N_2O_4, MeCN, or Et_2O	10	29
d	85	C_2H_5	NO_2	1 equiv of N_2O_4, MeCN, or Et_2O	10	29

[a] Not reported.

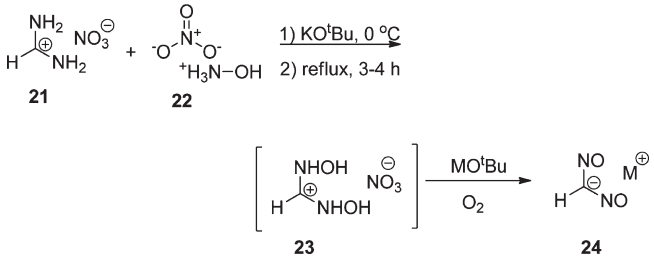
Scheme 9. *In Vivo* Biotransformation of *N*-Hydroxybenzamidoxime 3a



absorbed, then reduced rapidly to benzamidoxime **17** *via N*-reductases *in vivo* after oral administration (Scheme 9). The bioavailability of *N*-hydroxyamidoxime exceeds that of benzamidine after the oral application.[10]

4.3.2. Applications in Inorganic Chemistry. Wieland and Hess obtained nitrosolates from unstable *N*-hydroxyamidoximes by disproportion in NH_3 or by oxidation with KIO_4 in basic solution.[27,31] For R = H, these procedures lead to the formation of potassium dinitrosomethanide when KOH is used.[31] Recently, theoretical calculations predict that salts of nitrosodicyanomethanide $[(ON)C(CN)_2]^-$ and nitrodicyanomethanide $[(O_2N)C(CN)_2]^-$ are potential propellants similar to nitrite and nitrate salts.[32] Brand et al. developed a two-step synthesis of DNM salts (DNM = dinitrosomethanide) from formamidinium nitrate. Treating a methanolic solution of **21** and hydroxylammonium nitrate **22** (2 equiv) with a methanolic solution of KO^{t}Bu (2 equiv) resulted in the formation of the labile intermediate *N*,*N*′-dihydroxyformamidinium nitrate **23**

Scheme 10. Synthesis of Dinitrosomethanide (DNM) Salt 24



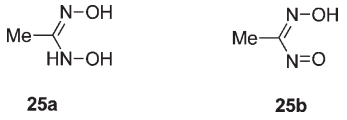


Figure 3. Acetohydroximic oxime and ethylnitrosolic acid.

(Scheme 10). The reaction of **23** with MO^{t}Bu (2 equiv) in the presence of oxygen yields the deep blue DNM salt **24**.[33]

N-Hydroxyamidoxime derivatives are efficient ligands for transition metals in redox systems.[34] The study of reactions between the two redox systems Fe(II)/Fe(III) and acetohydroximic oxime **25a** or ethylnitrosolic acid **25b** shows a strong stabilization of Fe(II) by ethylnitrosolate (Figure 3). The systems Fe(II)−**25a**, Fe(III)−**25a**, and Fe(III)−**25b** are unstable and evolve toward Fe(II)−**25b**.[35]

4.3.3. Biochemical Applications. *N*-Hydroxyamidoxime derivatives demonstrate various biological and chemical activity as shown in Table 11.

5. *N*-AMINOAMIDOXIMES AND THEIR DERIVATIVES

5.1. Preparative Methods

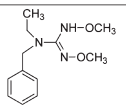
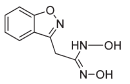
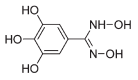
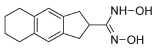
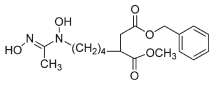
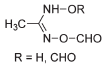
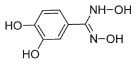
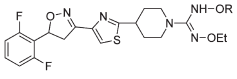
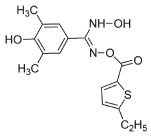
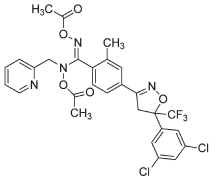
N-Aminoamidoximes are important precursors for the preparation of 1,2,4-triazoles and *vic*-dioximes, the latter being useful for the complexation of a variety of metal ions (*vide infra*).

5.1.1. From Imidoyl Chlorides or Amidoxime and Hydrazines. Armand and Bassinet reported the preparation of *N*-aminoamidoximes **28a**,**b** by reaction of imidoyl chloride with hydrazine.[47] The method is straightforward, but the yields are low. Later, Mullican and co-workers prepared 3,5-bis(*t*-butyl)-4-hydroxy-*N*-aminoamidoxime derivative **28c** in 89% yield by reaction of imidoyl chloride with hydrazine.[48] We have described the synthesis of the *p*-nitrophenyl derivative of aminoamidoxime **28d** via benzotriazolyl oxime in 71% yield under microwave conditions.[22] Saikavakali and Irez prepared *anti*-glyoximehydrazine **28e** from the hydrazimic chloride precursor.[49] Hydrazine (3-arylsydnon-4-yl) methanone oxime derivatives **28f**−**i** were reported by Shih et al. in good yields (83−96%) from the corresponding carbohydroximic acid chlorides (Scheme 11, Table 12).[50]

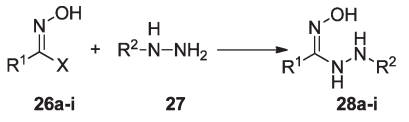
5.1.2. From Nitrile Oxide and Hydrazines. Ekcstein et al. described the reaction of diphenyl acetonitrile oxide **29** with hydrazines **27a** and **30** in ether under reflux to give aminoamidoximes **31a**,**b** (Scheme 12).[51]

5.1.3. From Amidoximes and Semicarbazides. Armand reported the formation of *N*-aminoamidoximes **34** by heating amidoximes **32** with an aqueous solution of semicarbazides **33** (Scheme 13, Table 13).[52]

Table 11. Activity of Some of *N*-Hydroxyamidoxime Derivatives

no.	Structure	Applications	Refs
1		Treatment of hypertension	36
2		Antidepressant, hypotensive, and dopa-potentiating activities	37
3		Inhibitor of ribonucleotide reductase	38
4		Blood platelet- aggregation inhibitors	39
5		Against recombinant human inducible nitric oxide synthase	40
6		Oxidizer	41
7	 R = H, CHO	improving the bioavailability of the medicament (Leishmaniasis)	42
8		Preventing neuroinflammatory, autoimmune disease	43
9	 R = H, Me	Fungicidal	44
10		Immuno-modulating agents	45
11		Pesticidal activity	46

Scheme 11. Reaction of Imidoyl Chlorides or Amidoxime 26a−i with Hydrazines 27



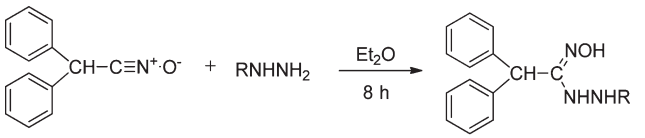
5.1.4. From Ethoxycarbonyl Hydrazones and Hydroxylamine. Ikizler and Sancak prepared a series of hydroxamic acid ethoxycarbonylhydrazides **38a−g** by heating ester ethoxycarbonylhydrazones **35a−g** or amide ethoxycarbonylhydrazones **35a**, **35b**, and **35f** with hydroxylamine **2** (Scheme 14, Table 14). Compound **38a** was also synthesized from ethyl carbazate **36** and **37** in 63% yield.[53]

Table 12. Preparation of *N*-Aminoamidoxime Derivatives 28a−i from α-Substituted Oximes 26a−i and Hydrazines 27[a]

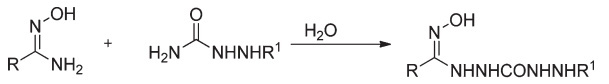
Product		Reactant				
28		26		27	Conditions	Refs
no	Yield (%)	R^1	X	R^2		
a	21-30	CH_3	Cl	H	n/r	47
b	21-30	CH_3	NH_2	H	n/r	47
c	89		Cl	H	Et_3N/EtOH, 0-15 °C, 2h	48
d	71	C_6H_5	Bt	*p*-$NO_2C_6H_4$	Na_2SO_4 anhydrous, 110 °C, *mw*, 10 min	22
e	n/r	CH=N(OH)	Cl	H	EtOH/H_2O, NaOH, 0°C	49
f	96	C_6H_5-ODAO	Cl	H	EtOH, 4.5 h	50
g	83	4-MeC_6H_4-ODAO	Cl	H	EtOH, 4.5 h	50
h	88	4-$MeOC_6H_4$-ODAO	Cl	H	EtOH, 4.5 h	50
i	86	4-$EtOC_6H_4$-ODAO	Cl	H	EtOH, 4.5 h	50

[a] n/r indicates not reported.

Scheme 12. Reaction of Nitrile Oxide 29 with Hydrazines 27a and 30



Scheme 13. Reaction of Amidoximes 32 with Semicarbazides 33



5.2. Chemistry of *N*-Aminoamidoximes

5.2.1. Synthesis of Triazolone Derivatives. *N*-Aminoamidoxime derivatives **39a−f** cyclize to 3-substituted 4-hydroxy-4,5-dihydro-1,2,4-triazol-5-one **40a−f** in basic medium in moderate to good yields (57−79%) (Scheme 15, Table 15).[53]

5.2.2. Reaction with Aldehydes. In the presence of an acid catalyst, methanone oxime derivatives **41** react with aromatic or aliphatic aldehydes **42** to give a series of 5-aryl-3-(3-arylsydnon-4-yl)-1*H*-[1,2,4]triazoles **43a−c′** (Scheme 16, Table 16). In this reaction, the solvent type and quantity of sulfuric acid used influence the nature of the products. When ethanol was used as solvent, two or more products were obtained because the reaction intermediate tended to precipitate and therefore not cyclize completely. However, with acetonitrile as solvent,

dx.doi.org/10.1021/cr200076q |*Chem. Rev.* 2012, 112, 1633–1649

Table 13. Preparation of *N*-Aminoamidoxime Derivatives 34 from Amidoximes 32 and Semicarbazides 33

	reactant		conditions	
product **34**, yield (%)	**32**, R	**33**, R^1	*T* (°C)	time (h)
a	H	H	20−40	12
a	CH_3	H	20−40	12
a	C_2H_5	H	20−90	13
a	CH_3	C_6H_5	20−140	12
a	C_2H_5	C_6H_5	20−140	12

[a] Not reported.

Scheme 14. Reaction of Ethoxycarbonyl Hydrazones 35a−g with Hydroxylamine 2 and Ethyl Carbazate 36 with Ethyl Acetohydroxamate 37

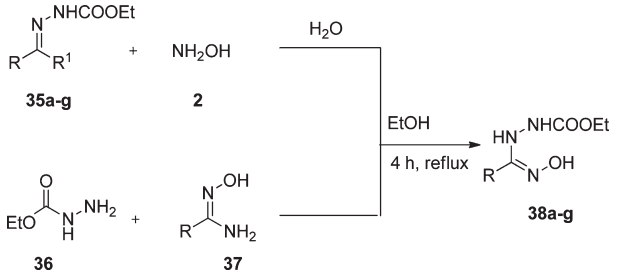


Table 14. Preparation of *N*-Aminoamidoxime Derivatives 38a−g

product **38**		reactant **35**	
no.	yield (%)	R	R^1
a	65	CH_3	OC_2H_5
b	67	C_2H_5	OC_2H_5
c	68	C_3H_7	OC_2H_5
d	70	$C_6H_5CH_2$	OC_2H_5
e	56	*p*-$ClC_6H_4CH_2$	OC_2H_5
f	54	C_6H_5	OC_2H_5
g	61	*p*-ClC_6H_4	OC_2H_5
a	42	CH_3	NH_2
b	30	C_2H_5	NH_2
f	34	C_6H_5	NH_2

the intermediate remained in solution and the cyclization went to completion. Moreover, concentrated sulfuric acid improved the yield of a single product and reduced the reaction time to between 5 and 7 h.[50]

5.3. Applications

5.3.1. As Metal Ligands for Coordination Compounds. Sarikavakli et al. reported that *vic*-dioximes **46a−d** were formed by reaction of *N*-aminoamidoximes **44** with aldehydes or ketones **45** (Schemes 17 and 18). The products complex transition metal ions (Ni, Cu, Co) to form novel *vic*-dioxime derivatives of hydrazone metal complexes (Tables 17 and 18). *vic*-Dioximes form mononuclear complexes with Ni(II), Co(II), and Cu(II) with a metal to ligand ratio of 1:2, whereas Zn(II) and *vic*-dioximes

Scheme 15. Cyclization of *N*-Aminoamidoximes 39a−f to 1,2,4-Triazol-5-ones 40a−f

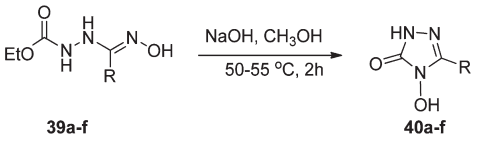
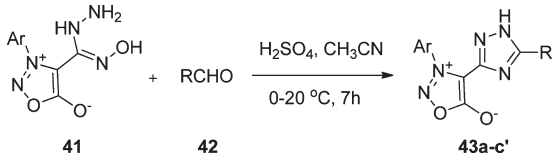


Table 15. Preparation of Compound 40

product **40**		
no.	yield (%)	R
a	79	CH_3
b	66	C_2H_5
c	71	C_3H_7
d	60	$CH_2C_6H_5$
e	57	*p*-$ClCH_2C_6H_4$
f	73	C_6H_5

Scheme 16. Reaction of *N*-Aminoamidoxime Derivatives 41 with Aldehydes 42



form complexes with a metal to ligand ratio of 1:1. The Ni(II) and Cu(II) complexes are square planar, but the complexes of Co(II) are octahedral, and the Zn(II) complexes are tetrahedral. *vic*-Dioximes can also form stable metal complexes of inner transition or actinide metal ions, and the ligands or their metal complexes have played a significant role in stereochemistry, isomerism, magnetism, spectroscopy, cation and ligand exchange chromatography, analytical chemistry, catalysis, pigments, and dyes.[55] *vic*-Dioxime complexes like Co(dimethylglyoxime)$_2^{n\pm}$ are model coordination compounds for studying the structure of vitamin B12 and coenzyme B13, which have important roles in biology.[56]

6. HYDRAZIDINES AND THEIR DERIVATIVES

6.1. Preparative Methods

6.1.1. From Amidrazones and Hydrazine. Neunhoffer and co-workers reported that the reaction of the amidrazones **50** with anhydrous hydrazine **27a** at 40 °C gave hydrazidines **51a−d** in moderate to good yields. (Scheme 19, Table 19).[57,58]

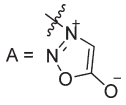
6.1.2. From Imidate Salt and Hydrazine. Doyle et al. described the preparation of hydrazidine **51a** in low yield (32%) from excess of hydrazine **27a** and imidate salt **52** under anhydrous conditions at temperatures below 0 °C (Scheme 20).[59]

6.1.3. From Isonicotinylhydrazide and Diethoxy-*N*,*N*-dimethylethanamine. Glushkov et al. prepared hydrazidine derivative **57** from 1,1-diethoxy-*N*,*N*-dimethylethanamine **55** and isonicotinylhydrazide **54** (isoniazid), a medication in the

dx.doi.org/10.1021/cr200076q |*Chem. Rev.* 2012, 112, 1633–1649

Table 16. Synthesis of Triazole Derivatives 43a−c′

product		reactants	
43		41	42
no.	yield (%)	Ar	R
a	90	C_6H_5	C_6H_5
b	64	4-$CH_3C_6H_4$	C_6H_5
c	68	4-$CH_3OC_6H_4$	C_6H_5
d	84	4-$C_2H_5OC_6H_4$	C_6H_5
e	93	C_6H_5	4-$CH_3OC_6H_4$
f	83	4-$CH_3C_6H_4$	4-$CH_3OC_6H_4$
g	72	4-$CH_3OC_6H_4$	4-$CH_3OC_6H_4$
h	85	4-$C_2H_5OC_6H_4$	4-$CH_3OC_6H_4$
i	92	C_6H_5	4-ClC_6H_4
j	73	4-$CH_3C_6H_4$	4-ClC_6H_4
k	72	4-$CH_3OC_6H_4$	4-ClC_6H_4
l	76	4-$C_2H_5OC_6H_4$	4-ClC_6H_4
m	45	C_6H_5	2-furyl
n	50	4-$CH_3C_6H_4$	2-furyl
o	70	4-$CH_3OC_6H_4$	2-furyl
p	68	4-$C_2H_5OC_6H_4$	2-furyl
q	50	C_6H_5	2-thienyl
r	64	4-$CH_3C_6H_4$	2-thienyl
s	63	4-$CH_3OC_6H_4$	2-thienyl
t	67	4-$C_2H_5OC_6H_4$	2-thienyl
u	70	C_6H_5	*n*- C_5H_{11}
v	67	C_6H_5	*n*- C_6H_{13}
w	76	C_6H_5	*n*- C_6H_{11}
x	63	C_6H_5	4-$CH_3OC_6H_4$-A
y	60	C_6H_5	4-$C_2H_5OC_6H_4$-A
z	42	4-$CH_3C_6H_4$	C_6H_5-A
a′	45	4-$CH_3C_6H_4$	4-$CH_3OC_6H_4$-A
b′	40	4-$CH_3OC_6H_4$	4-$CH_3OC_6H_4$-A
c′	41	4-$C_2H_5OC_6H_4$	4-$CH_3OC_6H_4$-A



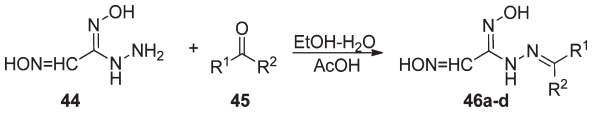
prevention and treatment of tuberculosis.[60] The two-step reaction first afforded the amidine derivative **56**, which was converted to the hydrazidine hydrochloride salt derivative **57** by reaction with another equivalent of **54** in acid−ethanol solution under reflux (Scheme 21).

6.1.4. From Hydrazonyl Bromide and Hydrazines. Hegarty and co-workers synthesized a series of N^4-substituted hydrazidines **60a**−**i** from the hydrazonyl bromide **58** and hydrazine **59** in alcohol. Subsequently, Takahashi et al. prepared N^2-acyl-N^4-substituted hydrazidines **60j**−**p** with hydrazonyl bromide and hydrazines in THF at room temperature (Scheme 22, Table 20).[61]

6.2. Chemistry of Hydrazidines

6.2.1. Reaction with Aldehydes. The hydrazidine derivatives **61**, **51**, and **60** react with aryl aldehydes **42a**, **63**, and **65** to afford monobenzylidinehydrazidine **62** (Scheme 23),

Scheme 17. Reactions of *N*-Aminoamidoxime 44 with Aldehydes/Ketones 45



Scheme 18. Reaction of *N*-Aminoamidoximes 47 and Metal Hydrates 48

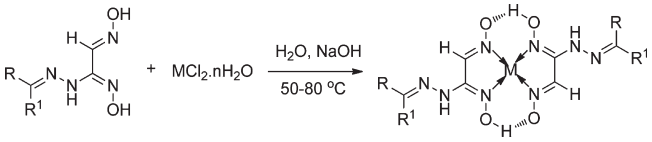


Table 17. Preparation of *vic*-Dioxime Derivatives 46a−d

product		reactant				
46		45		conditions		
no.	yield (%)	R^1	R^2	*T* (°C)	time (h)	refs
a	60	2-furyl	H	5	0.5	49
b	82	2-pyridyl	H	5	0.5	49
c	70	4-$NO_2C_6H_4$	CH_3	5−20	4−8	54
d	75	4-$CH_3C_6H_4$	CH_3	5−20	4−8	54

dibenzylidinehydrazidines **64** (Scheme 24, Table 21), and **66a**−**e** (Scheme 25, Table 22).[64]

Dibenzylidinehydrazidines **66a**−**e** were cyclized by mercuric oxide in ethanol under reflux to yield 3-alkyl-5-aryl-4-aminoaryl-1,2,4-triazoles **67a**−**e** (Scheme 25, Table 22).

6.2.2. Reaction with Ketones. Compounds **70** were prepared in good yields by condensation of *N*,*N*′-diaminoguanidine **68** with α-bromo ketones **69** containing various R^1 and R^2 groups (Scheme 26, Table 23).[65]

Butler designed the synthesis of mono- and dipyrazolomethylenehydrazono derivatives **73** and **74** and **75** by reaction of triaminoguanidine **71** with diketone **72**, the proportions of products **73**−**75** varying with the conditions of the reaction. In the presence of sufficient **72**, the dipyrazolylmethylenehydrazono derivative **74** was obtained as the main product, whereas at a molar ratio of 1:2 (triaminoguanidine and acetylacetone), dipyrazolylketone hydrazone **75** was isolated in highest yield (Scheme 27).[66]

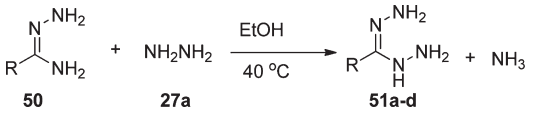
Neunhoeffer et al. also described the reaction of hydrazidines **51** with diketones **76**−**79** for the preparation of fused and nonfused six-membered heterocyclic systems such as tetraphenylpyrazine **81** and 1,2,4-triazines **83**. The reaction of methylhydrazidine **51** with benzoin **76** forms the monocondensation product **80** first, then 2,3,5,6-tetraphenylpyrazine **81** upon heating. The reaction of hydrazidine **51** with benzil 77 gives 4-amino-1,2,4-triazines **83**, preferentially. However, reaction with 4,4-dimethyl-1,2-cyclopentandione **78** gave octaaza[14]-annulen **84**.[71] The reaction of benzylhydrazidine **51** with 2-hydroxy-4,4-dimethyl-2-cyclopenten-1-one **79** gave

dx.doi.org/10.1021/cr200076q |*Chem. Rev.* 2012, 112, 1633–1649

Table 18. Synthesis of Metal Complex of *vic*-Dioxime Derivatives 49a−l

product		reactant							
49		47	48			conditions			
no.	yield	R	R^1	M	*n*	solvent	*T* (°C)	time (min)	refs
a	83	2-furyl	H	Ni	6	EtOH	80	15	49
b	66	2-furyl	H	Co	6	EtOH	80	15	49
c	75	2-furyl	H	Cu	2	EtOH	80	15	49
d	67	2-pyridyl	H	Ni	6	H_2O	80	15	49
e	54	2-pyridyl	H	Co	6	H_2O	80	15	49
f	70	2-pyridyl	H	Cu	2	H_2O	80	15	49
g	68	4-$NO_2C_6H_4$	Me	Ni	6	EtOH	60	120	54
h	55	4-$NO_2C_6H_4$	Me	Co	6	EtOH	60	120	54
i	72	4-$NO_2C_6H_4$	Me	Zn	2	EtOH	50	120	54
j	80	4-$CH_3C_6H_4$	Me	Ni	6	EtOH	60	120	54
k	56	4-$CH_3C_6H_4$	Me	Co	6	EtOH	60	120	54
l	52	4-$CH_3C_6H_4$	Me	Zn	2	EtOH	50	120	54

Scheme 19. Synthesis of Hydrazidine Derivatives 51a−d from Amidrazones 50

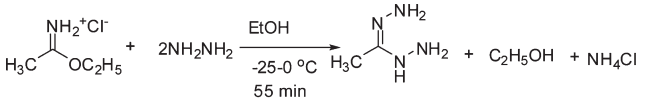


50 27a 51a-d

Table 19. Preparation of Hydrazidine Derivatives 51a−d

product **51**		
no.	yield (%)	R
a	98	CH_3
b	66	C_2H_5
c	66	*n*-C_3H_7
d	42	*i*-C_3H_7

Scheme 20. Synthesis of Hydrazidine Derivative 51a from Imidate Salt 52



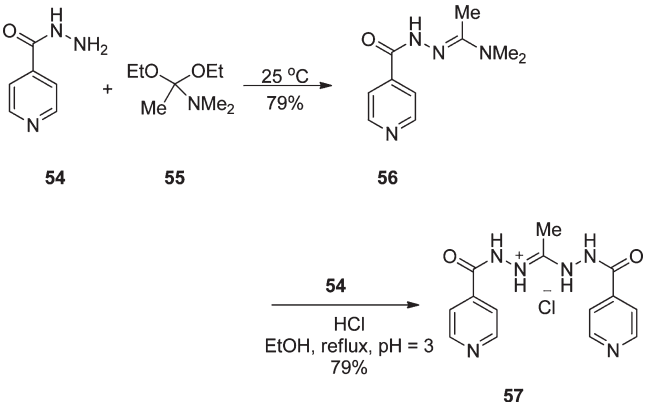
52 27a 51a 53

4-amino-1,2,4-triazines **85**, tetrahydrotetrazine **86**, and octaaza[14]-annulen **87** (Scheme 28).[64]

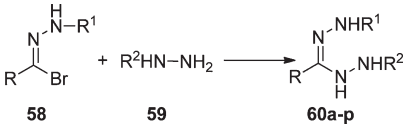
6.2.3. Reaction with Formic Acid. 3-Alkyl and arylamino-1,2,4-triazoles **90a** and **90e** were obtained on heating of **60a,e** in formic acid. The reaction presumably proceeds via formylated hydrazidine **89a,e** to cyclized products **90a,e** (Scheme 29, Table 24).[61]

6.2.4. Reaction with Orthocarboxylic Triesters. Hydrazidines **51** can be used as important synthetic auxiliaries for the synthesis of 4-amino-1,2,4-triazoles **92** by reaction with triethoxycarboxyate **91** (Scheme 30, Table 25).[58]

Scheme 21. Synthesis of Hydrazidine Hydrochloride Salt Derivative 57 from Isonicotinylhydrazide 54



Scheme 22. Reaction of Hydrazonyl Bromide 58 with Hydrazines 59



58 59 60a-p

6.2.5. Synthesis of Triazinone Derivatives. Draber et al. reacted benzylhydrazidine **51** with α-ketocarboxylic acid **93a** and obtained 4-amino-6-benzyl-3-methyl-1,2,4-triazine-5-one **94a** in 56% yield.[67] Later, Neunhoeffer reported a series of six-membered heterocycles, triazinones **94b−i**, from hydrazidines **51** and α-ketocarboxylic esters **93b−i** (Scheme 31, Table 26).[64,68]

6.2.6. Reaction with Diketoesters. The reaction of **51** with dimethyl oxalate **95** yields the diketo-triazine **98** but in only 7% isolated yield. Hydrazidines **51** react with phenylglyoxylmethylester **96** to form 4-amino-3-methyl-6-phenyl-1,2,4-triazin-5(4*H*)-one **100a,b** *via* the monocondensation intermediate **99**.

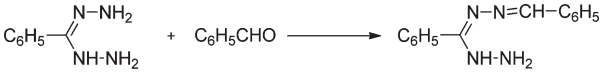
dx.doi.org/10.1021/cr200076q |*Chem. Rev.* 2012, 112, 1633–1649

Table 20. Preparation of Hydrazidines 60a−p

product **60**	reactant **58**		reactant **59**		
no.	yield (%)	R	R^1	R^2	conditions
a	87[a]	C_6H_5	2-Br-4-$NO_2C_6H_3$	H	EtOH/H_2O/20 °C
b	*b*	4-*i*-PrC_6H_4	2-Br-4-$NO_2C_6H_3$	H	EtOH/H_2O/20 °C
c	*b*	4-Cl-C_6H_4	2-Br-4-$NO_2C_6H_3$	H	EtOH/H_2O/20 °C
d	*b*	C_6H_5	4-$NO_2C_6H_4$	H	EtOH/H_2O/20 °C
e	*b*	4-Me-C_6H_4	4-$NO_2C_6H_4$	H	EtOH/H_2O/20 °C
f	*b*	4-Br-C_6H_4	4-$NO_2C_6H_4$	H	EtOH/H_2O/20 °C
g	*b*	CH_3	2,4-$(NO_2)_2C_6H_3$	H	EtOH/H_2O/20 °C
h	*b*	Me_3C	2,4-$(NO_2)_2C_6H_3$	H	EtOH/H_2O/20 °C
i	82[c]	1-MePr	2,4-$(NO_2)_2C_6H_3$	H	acetone/H_2O/70 °C/2 h
j	44[d]	C_6H_5	2-Br-4-$NO_2C_6H_3$	C_6H_5(C=O)	THF/Et_3N/2 h
k	*b*	C_6H_5	2-Br-4-$NO_2C_6H_3$	4-$Me_2NC_6H_4$(C=O)	*b*
l	*b*	4-Cl-C_6H_4	2-Br-4-$NO_2C_6H_3$	C_6H_5(C=O)	*b*
m	*b*	1-MePr	2,4-$(NO_2)_2C_6H_3$	C_6H_5(C=O)	*b*
n	*b*	4-*i*-PrC_6H_4	2-Br-4-$NO_2C_6H_3$	4-*i*-PrC_6H_4(C=O)	*b*
o	*b*	C_6H_5	2-Br-4-$NO_2C_6H_3$	H(C=O)	*b*
p	*b*	CH_3	2,4-$(NO_2)_2C_6H_3$	H(C=O)	*b*

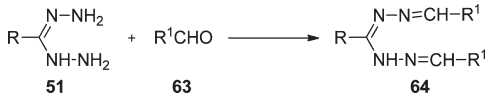
[a] Reference 62. [b] Not reported. [c] Reference 63. [d] Reference 61.

Scheme 23. Reactions with Benzaldehyde 42 To Give Monobenzylidinehydrazidine 62



61 **42a** **62**

Scheme 24. Reactions with Aldehydes 63 To Give Di-benzylidinehydrazidine Derivatives 64



51 **63** **64**

The reaction of **51** with thioxamidyl methyl ester **97** in the presence of triethylamine as base gives the monocondensation intermediate **101**, which cyclizes to **102** upon heating (Scheme 32).[68]

6.2.7. Reaction with Benzoyl Cyanide. Methylhydrazidine **51a** reacts with benzoyl cyanide **103** to give 4-amino-5-imino-1,2,4-triazine **104** in 48% yield presumably by a combination of condensation and addition reactions (Scheme 33).[68]

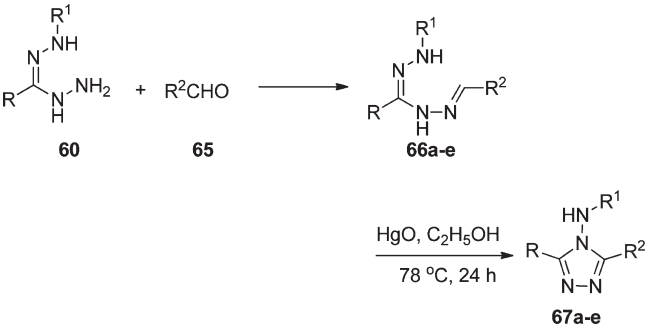
6.2.8. Reaction with Anhydrides. Degen used hydrazidines for the preparation of tetrazines. Reaction of **51a** with nitrophthalic anhydride **105** yields two isomeric nitro-1,2,4,5-tetrazino[3,2-*a*]-isoindol-6(4*H*)-ones **112** and **113**. The reaction of methylhydrazidine **51a** with **106** affords 7,8-dichloro-3-methyl-1,8-dihydro-pyrrolo[1,2-*b*]-1,2,4,5-tetrazine-6(4*H*)-one **114a,b**. Similarly, the reaction of **51a** with phthalaldehydic acid **107** yields 3-methyl-1,10-dihydro-1,2,4,5-tetrazino[3,2-*a*]isoindol-6(4*H*)-one) **115**, which can be converted to 3-methyl-1,2,4,5-tetra-amino[3,2-*a*]isoindol-6(4*H*)-one **116** by mild oxidation. Compound **116** can also be obtained by

Table 21. Synthesis of Di-benzylidinehydrazidine Derivatives 64

product **64**	reactant **51**	reactant **63**	
yield (%)	R	R^1	conditions
98[a]	CH_3	C_6H_5	EtOH, 40 °C, 7 min
66[a]	C_2H_5	C_6H_5	EtOH, 40 °C, 7 min
66[a]	*n*-C_3H_7	C_6H_5	EtOH, 40 °C, 7 min
42[a]	*i*-C_3H_7	C_6H_5	EtOH, 40 °C, 7 min
96[b]	CH_3	4-$NO_2C_6H_4$	MeOH, Et_3N, 20 °C, 48 h
45[b]	CH_3	4-$CH_3OC_6H_4$	EtOH, Et_3N, 26 h

[a] Reference 59. [b] Reference 64.

Scheme 25. Reactions with Aldehydes 65 To Give Triazole Derivatives 67a−e



60 **65** **66a-e** **67a-e**

dx.doi.org/10.1021/cr200076q |*Chem. Rev.* 2012, 112, 1633–1649

Table 22. Synthesis of Triazole Derivatives 67a−e

			reactant			
			60		65	
no.	yield (%) of **66**	yield (%) of **67**	R	R^1	R^2	conditions EtOH/78 °C, *T* (min)
a	*ca.* 100[a]	48[c]	C_6H_5	2-Br-4-$NO_2C_6H_3$	C_6H_5	5
b	*b*	*b*	4-Cl-C_6H_4	2-Br-4-$NO_2C_6H_3$	C_6H_5	5
c	39[a]	*b*	4-*i*-PrC_6H_4	2-Br-4-$NO_2C_6H_3$	4-*i*-PrC_6H_4	Et_3N, 120
d	*b*	*b*	C_6H_5	2-Br-4-$NO_2C_6H_3$	4-$Me_2NC_6H_4$	30[c]
e	*b*	*b*	1-MePr	2,4-$(NO_2)_2C_6H_3$	C_6H_5	5[d]

[a] Reference 62. [b] Not reported. [c] Reference 61. [d] Reference 63.

Scheme 26. Reaction of Diaminoguanidine 68 with α-Bromo Ketones 69

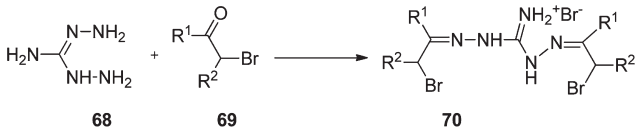
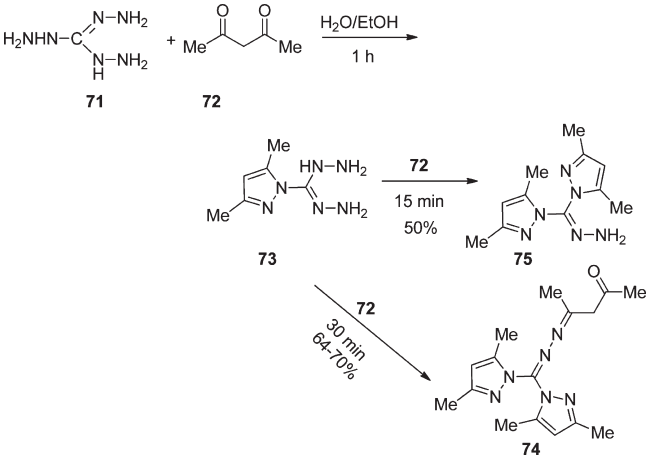


Table 23. Preparation of Compound 70

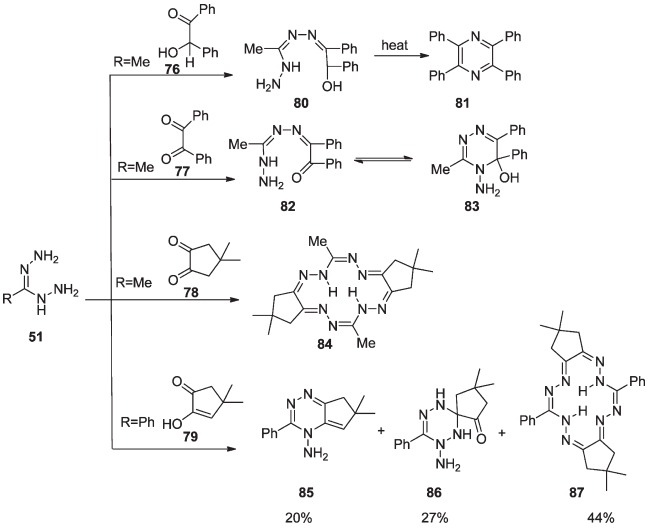
product **70**		
yield (%)	R^1	R^2
78	CH_3	H
78	CH_3	CH_3
96	C_6H_5	H
86	4-ClC_6H_4	H

Scheme 27. Reaction with Diketone 72



the reaction of **51a** with phthalic acid derivatives **107**, **108**, **109**, and **110** (Scheme 34).[69] In addition, methylhydrazidine **51a** was used for the preparation of 3-methylpyrrolo[1,2]-1,2,4,5-tetrazine **118** *via* cyclization with *cis*- or *trans*-2,5-dimethoxy-2,5-dihydrofuran **111** (Scheme 34).[70]

Scheme 28. Reaction of 51 with Diketones 76−79



Scheme 29. Reaction of 60a,e with Formic Acid 88

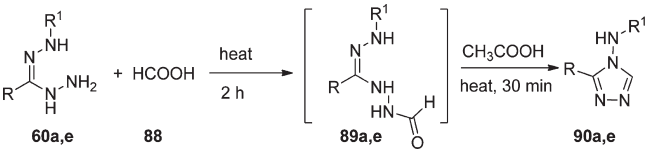


Table 24. Preparation of Triazole Derivatives 90a and 90e

	product **90**		
no.	yield (%)	R	R^1
a	56	C_6H_5	2-Br-4-$NO_2C_6H_3$
e	69	CH_3	2,4-$(NO_2)_2C_6H_3$

Neunhoeffer et al. also prepared tetrazine derivatives **120** and **122** by the reaction of benzylhydrazidine **61** with anhydrides **106b** and **119** (Scheme 35).[64]

6.2.9. Reaction with Cyclopentadiene Derivatives. Methylhydrazidine **51a** reacts with 2,3-dihydroxycyclo-pentadiene-1,4-dicarboxylate-dimethylester **123** to give 4-amino-4,

dx.doi.org/10.1021/cr200076q |*Chem. Rev.* 2012, 112, 1633–1649

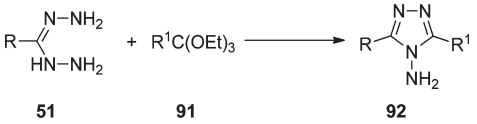
6-dihydro-3-methyl-1*H*-cyclopenta[*e*]1,2,4-triazin-5,7-dicarboxylester **124** (Scheme 36, Table 27).[71]

6.2.10. Reactions with Dimethyl Acetylenedicarboxylate. Tetrazines **126a**−**e** were synthesized in good yields by the reaction of hydrazidines **60** and dimethyl acetylenedicarboxylate **125** in THF under reflux (Scheme 37, Table 28).[61]

In the presence of triethylamine, **51a** reacted with dimethylacetylenedicarboxylate **125** in methanol to afford crystalline pyrazolinone **127** in 37% yield (Scheme 38).[68]

6.2.11. Reaction with Thioesters. *S*-Methylisothiocarbonohydrazide salt is used as a bis-aminoguanidine equivalent in the synthesis of 6-aryl-3-aminotetrazines from dithioesters (Scheme 39, Table 29).[72] For example, dithioesters **129** can react with *S*-methylisothiocarbonohydrazide hydroiodide salt **128** to form dihydrotetrazines **130**, which can be oxidized to (methylthio)tetrazines **131**. The methylthio group serves to deactivate the internal latent guanidine nitrogens for cyclization, as well as to provide a handle for the subsequent amination to form 6-aryl-3-aminotetrazines **132a**−**k′**.[73]

Scheme 30. Reaction with Orthocarboxylic Triesters 91

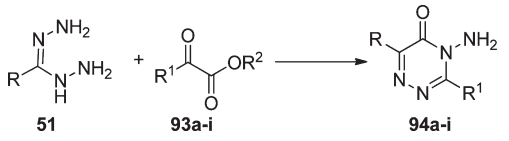


51 **91** **92**

Table 25. Preparation of 4-Amino-1,2,4-triazoles 92

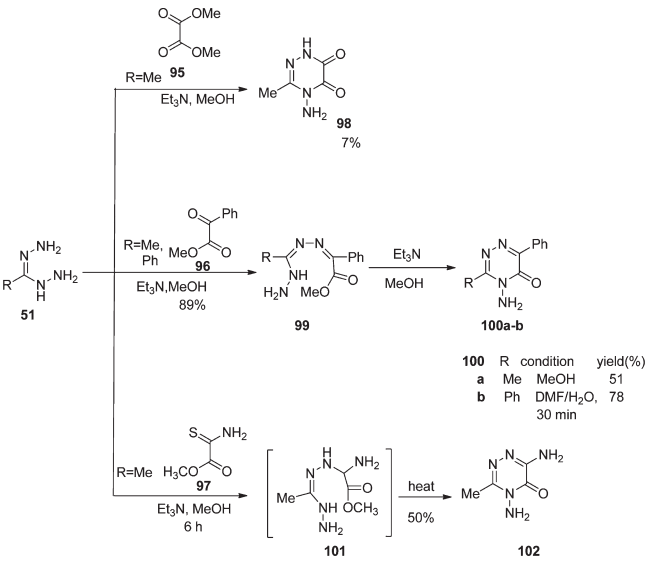
product **92**		
yield (%)	R	R^1
95	CH_3	H
97	C_2H_5	H
92	*n*-C_3H_7	H
90	*i*-C_3H_7	H
93	CH_3	CH_3

Scheme 31. Reaction with α-Keto Acid or Esters 93a−i

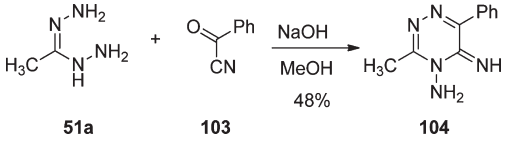


51 **93a-i** **94a-i**

Scheme 32. Reaction of 51 with Diketoesters 95−97



Scheme 33. Synthesis of Triazine 104



51a **103** **104**

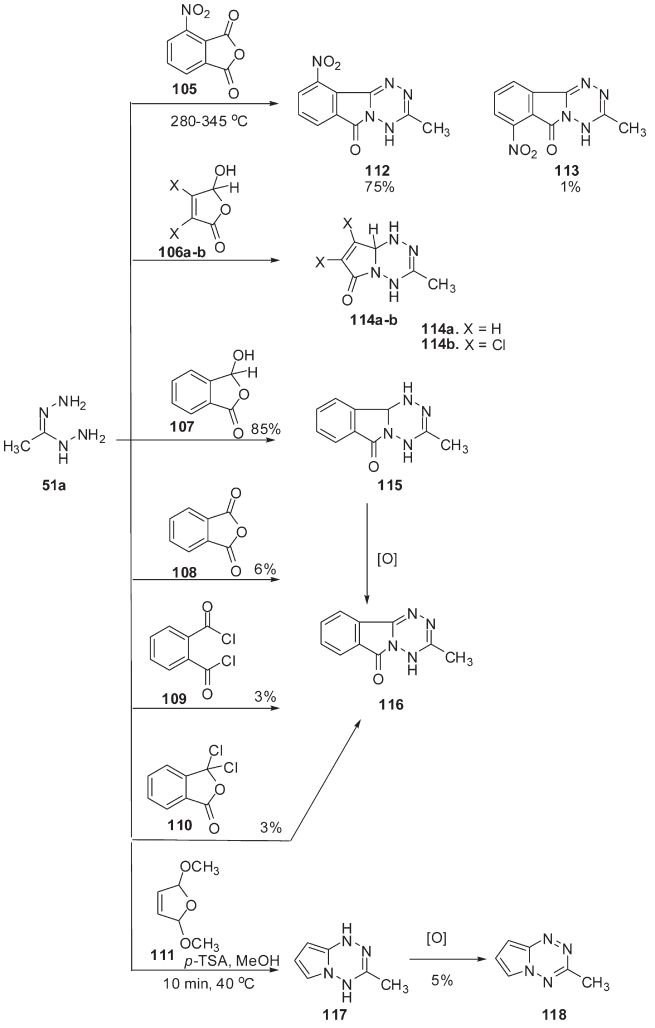
Table 26. Synthesis of Tetrazine Derivatives 94a−i

			reactant		
product **94**			**51**	**93**	
no.	yield (%)	conditions	R	R^1	R^2
a	56[a]	EtOH/H_2O, 20 °C, 4 h	$C_6H_5CH_2$	CH_3	H
b	51[b]	MeOH, Et_3N, 16 h, 20 °C	CH_3	C_6H_5	CH_3
c	78[b]	DMF, 120 °C, 30 min	C_6H_5	C_6H_5	CH_3
d	60[c]	MeOH, Et_3N, 15 h, 20 °C	C_6H_5	H	CH_3
e	43[c]	MeOH, Et_3N, 15 h, 20 °C	4-$CH_3C_6H_4$	H	CH_3
f	49[c]	MeOH, Et_3N, 15 h, 20 °C	4-$CH_3OC_6H_4$	H	CH_3
g	48[c]	MeOH, Et_3N, 50 °C, 18 h	C_6H_5	CH_3	CH_3
h	66[c]	MeOH, Et_3N, 50 °C, 6 h	4-$CH_3C_6H_4$	CH_3	CH_3
i	55[c]	MeOH, Et_3N, 50 °C, 77 h	4-$CH_3OC_6H_4$	CH_3	CH_3
j	60[c]	EtOH, 20 °C, 24 h,	C_6H_5	CO_2CH_3	CH_3
k	66[c]	EtOH, 20 °C, 24 h	4-$CH_3C_6H_4$	CO_2CH_3	CH_3
l	87[c]	EtOH, 20 °C, 24 h,	4-$CH_3OC_6H_4$	CO_2CH_3	CH_3

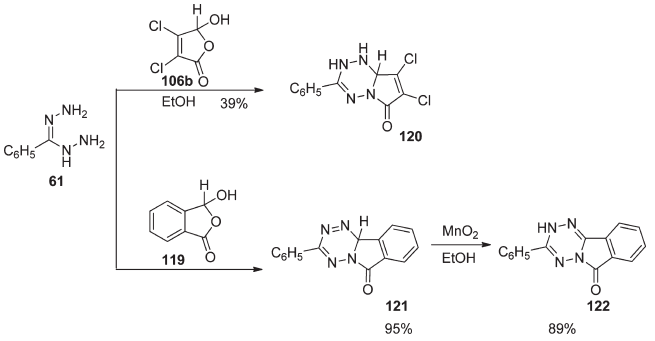
[a] Reference 67. [b] Reference 68. [c] Reference 64.

dx.doi.org/10.1021/cr200076q |*Chem. Rev.* 2012, 112, 1633–1649

Scheme 34. Reaction of 51a with Anhydrides 105−111



Scheme 35. Synthesis of Tetrazine Derivatives 120 and 122



6.2.12. Synthesis of Tetrazine Derivative. Glushkov reported the formation of 3-methyl-6-pyridyl-1,2,4,5-tetrazine **134** by cyclization of hydrazidine derivative **133** at room temperature (Scheme 40).[60]

6.3. Applications

6.3.1. As New Fibrous Adsorbents. Fibrous complexing adsorbents offer vital advantages over granular adsorbents and have found wide utility for trace element preconcentration in chemical analysis. For example, the concentration of Cr(III) and Cr(VI) at 5−30 μg/L in aqueous solution have been determined by emission spectrometry following preconcentration on polyethylenepolyamine-modified PAN fibers.[74] The complexing fibrous adsorbents like POLYORGS 33, POLYORGS 34, and POLYORGS 35 were prepared by treating a freshly formed poly(acrylonitrile) fiber with a mixture of hydroxylamine and hydrazine hydrate, modified amidoximes, and hydrazidines, respectively. It was shown that these adsorbents can be used for the dynamic preconcentration of heavy,

Scheme 36. Synthesis of Triazine Derivatives 124

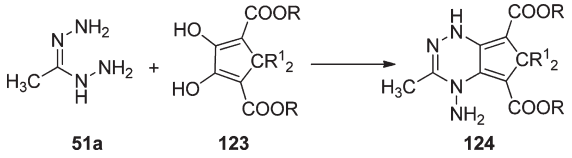


Table 27. Synthesis of Triazine Derivatives 124

		reactant **123**	
product **124**[a] yield (%)	conditions	R	R^1
b	EtOH, Et_3N, 20 °C, 3 h	CH_3	H
50	EtOH, Et_3N, 20 °C, 3 h	C_2H_5	H
55	MeOH, Et_3N, 20−64−20 °C, 81 h	CH_3	CH_3

[a] Reference 70. [b] Not reported.

Scheme 37. Reactions of Hydrazidines 60 with Dimethyl Acetylenedicarboxylate 125

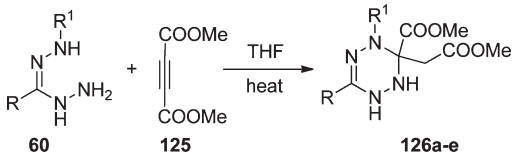
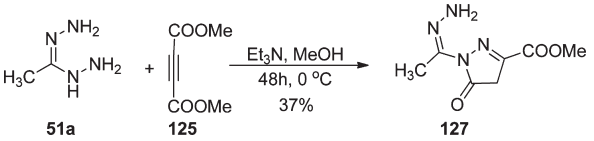


Table 28. Synthesis of Tetrazine Derivatives 126a−e

	product **126**		
no.	yield (%)	R	R^1
a	77	C_6H_5	2-Br-4-$NO_2C_6H_3$
b	86	4-ClC_6H_4	2-Br-4-$NO_2C_6H_3$
c	80	C_6H_5	4-$NO_2C_6H_4$
d	88	1-MePr	2,4-$(NO_2)_2C_6H_3$
e	87	CH_3	2,4-$(NO_2)_2C_6H_3$

Scheme 38. Synthesis of Pyrazolinone 127



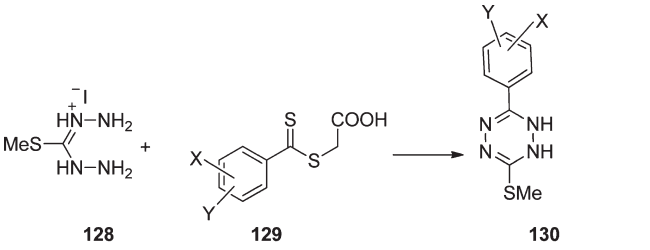
dx.doi.org/10.1021/cr200076q |*Chem. Rev.* 2012, 112, 1633–1649

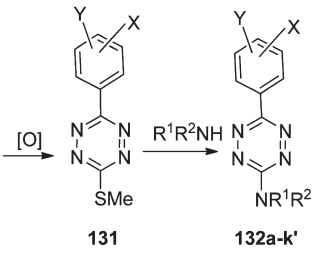
noble, and rare metals and radionuclides from aqueous salt solutions.[75]

6.3.2. As Antituberculosis Agents. Some hydrazidine analogues of isonicotinylhydrazine demonstrate *in vivo* antituberculosis activity, with hydrazidine derivatives[56] possessing the best activity against the tuberculosis pathogen.[60]

6.3.3. As Environmentally Friendly Dyes. Dozens of patents and journals describe various hydrazidine- or formazan-derived compounds as dye ligands that bind to metal such as Cu, Fe, Ni, and Co, and they have important applications in the textile industry.[76−78] Freeman et al. synthesized some Fe-complexed hydrazidine derivatives, **135** and **136**, to provide environmentally friendly dyes (Figure 4). They can also coordinate metals such as Cr and Co without adversely affecting technical and mutagenic properties, again offering applications in the textile industry.[76,77] Cu complexes of some hydrazidine derivatives, for example, *N*,*N*′-bis(*O*-hydroxyphenyl)-*C*-phenylformazan **137**, are suitable dyeing agents for the dyeing of protein fibers in neutral or slightly acid media. They have fairly strong affinity to woolen materials as dyeing agents.[79]

Scheme 39. Reaction of 128 with Thioester 129





Scheme 40. Synthesis of Tetrazine Derivative 134

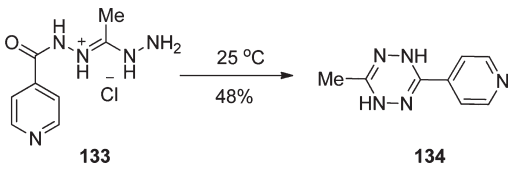
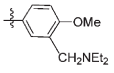
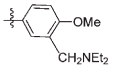
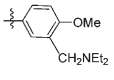
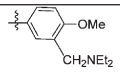
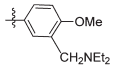
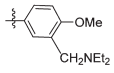
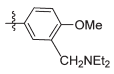
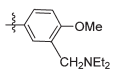


Table 29. Preparation of 6-Aryl-3-aminotetrazines 132a−k′

Product **132**				
no	Yield (%)	X, Y	R^1	R^2
a	67	3,4-Cl_2	H	$(CH_2)_3NMe_2$
b	44	3,4-Cl_2	Me	Bu
c	57	3,4-Cl_2	Me	Et
d	14	3,4-Cl_2	H	
e	95	4-Br	Me	Me
f	100	4-Br	H	Me
g	55	4-Br	H	H
h	71	4-Me	H	H
i	87	4-Me	H	Me
j	70	4-Me	Me	Me
k	29	4-Me	H	
l	45	4-NO_2	Me	Me
m	66	3,4,5-$(OMe)_3$	H	Me
n	61	3,4,5-$(OMe)_3$	Me	Me
o	53	3,4,5-$(OMe)_3$	H	H
p	29	3,4,5-$(OMe)_3$	H	
q	69	3-CF_3	H	H
r	83	3-CF_3	H	Me
s	73	3-CF_3	Me	Me

Product **132**				
no	Yield (%)	X, Y	R^1	R^2
t	33	3-CF_3	H	
u	82	4-OMe	H	H
v	87	4-OMe	H	Me
w	82	4-OMe	Me	Me
x	35	4-OMe	H	
y	68	4-CF_3	H	H
z	67	4-CF_3	H	Me
a'	87	4-CF_3	Me	Me
b'	35	4-CF_3	H	
c'	82	4-F	H	H
d'	100	4-F	H	Me
e'	90	4-F	Me	Me
f'	91	4-NHAc	H	
g'	88	3-C_6H_5	H	H
h'	61	3-C_6H_5	H	Me
i'	63	3-C_6H_5	Me	Me
j'	26	3-C_6H_5	H	
k'	27	4-NMe_2	Me	Me

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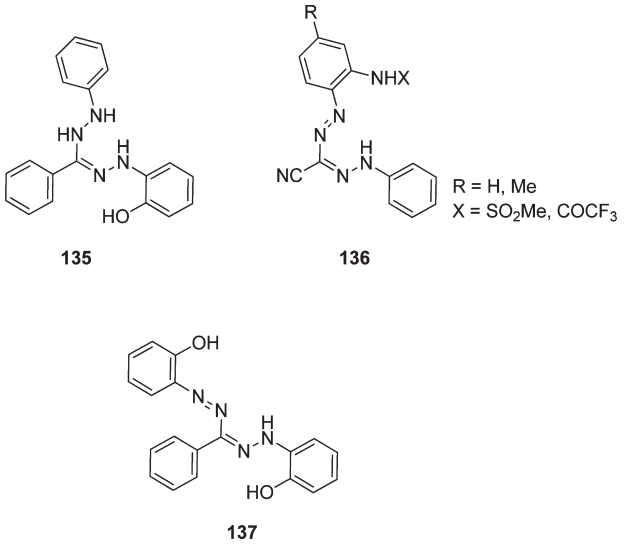

135 136 137

Figure 4. Environmentally friendly dye ligands.

7. CONCLUSIONS

In summary, *N*-hydroxy- and *N*-amino-amidoximes and hydrazidines are important amidine derivatives with synthetic utility and various biological applications. Typically they can react or cyclize with electrophiles such as aldehydes, ketones, carboxylates, and acids. They have been used extensively as starting materials for the preparation of nitrogen-rich heterocycles. In practice, they have applications in drugs, dyes, polymers, and many other materials. With this work, we provide a first comprehensive review on the titled compounds that will be valuable to scientists who are interested in synthetic, biological, and pharmacological applications of all three classes of compounds.

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BIOGRAPHIES

Alan Katritzky is Kenan Professor of Chemistry and Director for Center of Heterocyclic Compounds at the University of Florida. He was based in the U.K. at the Universities of Oxford, Cambridge, and East Anglia before crossing the Atlantic to take up his present post in 1980. He has taught, researched, and consulted in many areas of organic and physical-organic chemistry, including structure−property and −activity relationships since 1990. His distinctions include 14 honorary doctorates from 12 European and Asian countries and membership of five National Academies. He has traveled widely and published extensively in the primary and secondary literature (*h* index of 80).

Longchuan Huang was born and raised in China. She received a Ph.D in organic chemistry from University of Florida under the guidance of Professor Alan R. Katritzky in December 2010. Her Ph.D. research was focused on heterocyclic synthesis. Recently, she has joined the group of Professor Amos B. Smith III as a postdoctoral research fellow at University of Pennsylvania in January 2011.

Mamta Chahar was born in 1978 in Agra, India. She received her Ph.D. degree in Organic Chemistry from the Indian Institute of Technology Delhi, New Delhi, India, in 2008, under the direction of Professor Pramod S. Pandey. The main focus of her Ph.D. research was synthesis of steroid-based receptors and study of their anion binding. Then, she joined Indian Oil Industry, R&D, India, as a Research Associate (2008−2009). In 2009, she joined the group of Prof. Alan R. Katritzky at the Center of Heterocyclic Compounds, University of Florida, Gainesville, FL, as a postdoctoral fellow. Her research focused on the synthesis and applications of heterocyclic compounds and peptide chemistry.

Dr. Rajeev Sakhuja was born in New Delhi, India, in 1978. He obtained his Ph.D. degree in synthetic organic chemistry in 2007 under the supervision of Prof. Subhash C. Jain at Delhi University, Delhi, India. The main focus of his doctoral research was to study the reactivity and catalytic activity of azaphenothiazines, synthesize novel nitrogen and sulfur heterocycles, and phytochemically investigate some medicinally important plants. Then he joined Ranbaxy Research Laboratories, Gurgaon, India, as a Research Associate (2007−2008) and worked on the synthesis of telbivudine, an antiviral drug. Thereafter he started his postdoctoral research with Prof. Alan R. Katritzky at the Center of Heterocyclic Compounds, University of Florida, Gainesville, FL (2008−2010), where he focused on the synthesis of novel photochromic 2*H*-chromene based organogelators, cytotoxic napthoquinone dipeptides, and Boltorn 1,2,3-triazole dendrimers. Currently, he is working as a postdoctoral fellow with Professor Raymond Booth at Department of Medicinal Chemistry, University of Florida, where his research is focused on developing novel phenyl-dimethylaminotetralin (PAT) derivatives possessing anorectic and antipsychotic efficacy in rodents via actions at brain serotonin receptors.

After retiring from his academic position at King's College, London, in 1999, Dennis Hall joined Alan Katritzky's research group at the University of Florida where he acts as a group leader, Administrator for the on-line journal *Arkivoc*, and co-organizer of the Florida Heterocyclic/Synthesis conferences (Flohet). Since joining the Katritzky team, he has coauthored some 30 papers in the fields of heterocyclic chemistry, QSAR, insect control, and synthetic ion channels.

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