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Chemistry of Ring-Fused Oxazine-2,4-diones

Yann Brouillette,[a] Jean Martinez,[a] and Vincent Lisowski*[a]

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Isatoic anhydride has attracted a great deal of attention in the last decades. Substitution of its benzene moiety by many different ring systems has given rise to a large array of analogues. A review on the methods of preparation of all known ring-fused oxazine-2,4-diones is given herein. The different reactivity of these analogues is exhaustively depicted and illustrates the rich versatility of this class of starting material.

[a] Institut des Biomolécules Max-Mousseron, UMR 5247, CNRS, Universités Montpellier I et II, UFR de Sciences Pharmaceutiques et Biologiques,
15 Avenue Charles Flahault, 34093 Montpellier, France
Fax: +33-4-67 54 86 54
E-mail: vincent.lisowski@univ-montp1.fr

1 Introduction

In 1980, an exhaustive review of the chemistry of isatoic anhydride (**1**), and its pyridine analogues, was depicted by Gary M. Coppola.[1] A year later, T. Kappe and W. Stadlbauer published another review on the uses of isatoic anhydrides in heterocyclic synthesis.[2] Since then, the elaboration of all sorts of ring-fused oxazinediones has emerged. Their different versatile reactivity has demonstrated importance in the synthetic organic and medicinal chemistry fields. In 2001, a review by M.-G. A. Shvekhgeimer entirely devoted to the synthesis of various nitrogen-containing heterocyclic systems, all from isatoic anhydrides, confirmed novel usefulness of this motif.[3] Despite its lacking of timeliness, the chemistry of isatoic anhydride analogues has also emerged as an interesting versatile building block for the synthesis of new heterocyclic scaffolds. The nomenclature associated with isatoic anhydride (**1**) is inconsistent and results in various methods for numbering the ring skeleton. Even though *Chemical Abstracts* refers to it as the heterocyclic system 1,3-benzoxazine-2,4(1*H*)-dione and numbers it accordingly, most literature references rather use its trivial name, isatoic anhydride (Figure 1).[1] Two 1,3-oxazinedione isomers exist and the International Union of Pure and Applied Chemistry (IUPAC) nomenclature numerates them as 3*H*-1,3-oxazine-2,6-dione (**2**) and 3*H*-1,3-oxazine-2,4-dione (**3**; Figure 1). However, once fused to a ring, oxazine **2** changes the numbering of its carbonyl groups to be numerated as 1*H*-cyclo[*d*][1,3]oxazine-2,4-dione (**4**). In most published reports, the numbering priority is attributed to the oxazine, independently of the nature of the fused cycle. To ease the reading of the following manuscript, the nomenclature used herein will adopt this numbering.

The purpose of this review is to summarize the wide variety of chemistry surrounding isatoic anhydride analogues **4**, and thus, constitutes an update to the work reported by Coppola. Although nonfused 3*H*-1,3-oxazine-2,6-diones (**2**; the oxygen isoster of uracil)[4] and its derivatives have

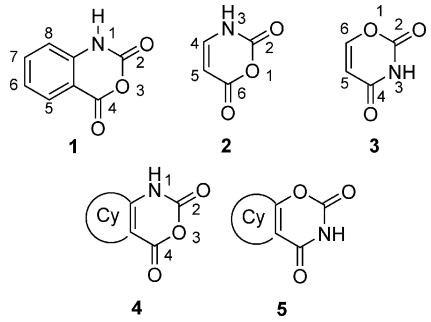


Figure 1. Numbering of oxazinediones **1**–**5**.

shown antileukemic[5,6] and growth-inhibiting properties,[7] nonfused oxazinediones **2** and **3**[4,8] and cyclo[*e*][1,3]oxazine-2,4-diones **5**[9,10] will not be part of this review. This work will focus on the synthesis and the reactivity of cyclo[*d*][1,3]oxazine-2,4-diones of type **4**.

2 Synthesis of Ring-Fused Oxazine-2,4-diones

At the time of the investigation of this review, few methods mainly covered the possible protocols for the obtainment of new ring-fused oxazinediones **4**. To show the diversity of the scaffolds accessible today, the synthesis of all known ring-fused oxazinediones **4** was gathered and illustrated herein. The oxazines were classified in correlation with their fused cycle and divided into two categories: the aromatic and the nonaromatic groups.

2.1 Aromatic

To distinguish the different types of aromatic rings fused to oxazinediones **4** described herein, the arenes were separated from the heterocycles.

2.1.1 Arenes

The arene class mainly consists of the benzene ring, but also includes the naphthalene, acenaphthalene and anthracene-9,10-dione ring systems.

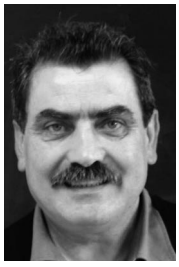
2.1.1.1 Benzene

The story began in 1884, when H. Kolbe first used the name isatoic acid to identify the product from the chromic acid oxidation of isatin.[11,12] Erroneously considered an acid, the product was actually found to be an anhydride and, therefore, later named isatoic anhydride.

Since then, isatoic anhydride (**1**) has been used in "the manufacture of agricultural chemicals, dyes, pigments, cross-linking agents, chain stoppers in resins and for other uses in rubber and polymer chemistry. It was also used as a modifier in protein and carbohydrate substrates (wool, paper, textiles), as a petroleum additive (fuels and lubricants), as a blowing agent for polymer foams, as a flame-proofing agent and a corrosion inhibitor, in metal finishing, for food and beverages, soaps and detergents, perfumes, cosmetics, and in medicines and pharmaceuticals".[1,2]

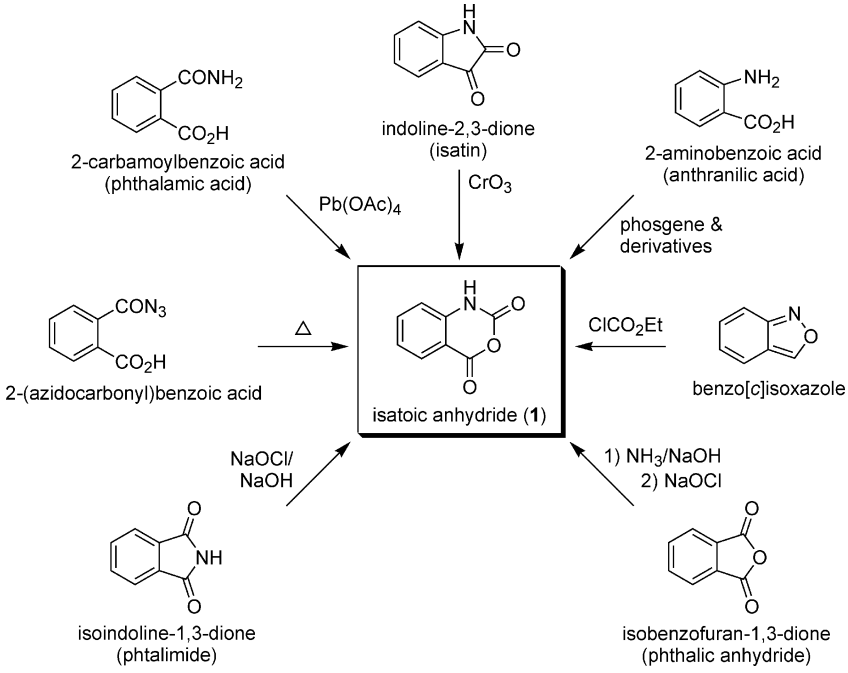
Recently, more experimental and theoretical investigations were carried out to explore the physical chemistry of isatoic anhydride.[13] The reactions commonly used for

Yann Brouillette, PhD, was born in Montreal (Quebec, Canada) in 1981. He completed his Masters degree in 2005 under the supervision of Professor William D. Lubell at the University of Montreal, where he studied the synthesis of pyrrole analogues on solid supports. He then joined the research group of Professor Jean Martinez at the University of Montpellier, France, where he recently defended his PhD thesis on the reactivity study of thiaisatoic anhydrides in solution and on solid phase.



Professor Jean Martinez studied chemistry at the École Nationale Supérieure de Chimie de Montpellier (France). After receiving his PhD in 1972 he was awarded a permanent position at the CNRS. He completed his "Thèse d'État" in 1976 under the direction of Professor F. Winternitz and performed postdoctoral studies with Professor E. Bricas in Orsay (France) and with Professor M. Bodanszky at Case Western University (Ohio, USA). On his return to France, he pursued his research activities in the field of peptides and successively became head of various research laboratories in Montpellier, including the "Chemistry and Pharmacology of Biologically Active Molecules" Laboratory. In 1998, he was appointed Professor of Organic Chemistry at the Faculty of Sciences and in 2001 Professor of Medicinal Chemistry at the School of Pharmacy. He is actually Director of the "Max-Mousseron Institute for Biomolecules", where he is also head of the "Department of Amino acids, Peptides and Proteins". He is currently President of the European Peptide Society. His research interests are peptide chemistry and pharmacology, stereoselective synthesis of biomolecules, chemistry on polymeric supports, mass spectrometry, artificial protein synthesis, computer-assisted peptide search, and green chemistry.

Vincent Lisowski, PhD, was born in Aunay/Odon (France) in 1974. He first received his PharmD degree in 1998 before he obtained his PhD in 2002 from the University of Basse-Normandie, under the supervision of Professor Sylvain Rault in the field of thiophene chemistry. After a postdoctoral position at the pharmaceutical faculty of Caen, where he developed medicinal projects in the field of cancer and Alzheimer's disease, he joined the group of Professor Jean Martinez as an Assistant Professor at the University of Montpellier in 2003. His research interests focus on new methodologies in solid-phase organic synthesis in the field of heterocyclic and peptide chemistry.



Scheme 1. Most common preparation methods for the synthesis of isatoic anhydride.[2]

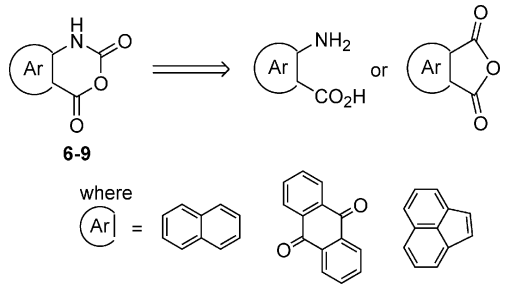
the preparation of isatoic anhydride (**1**) are summarized in Scheme 1.[1,2] The first preparation of isatoic anhydride was accomplished by chromic acid oxidation of isatin.[11,12,14] The oxidizing reagents commonly used for this general procedure include chromium trioxide and organic peroxy acids.[15–18] Due to their ready availability, anthranilic acids have become the precursor of choice in the synthesis of isatoic anhydrides. Their cyclization can be carried out with carbonylation reagents (such as phosgene,[19] diphosgene[20] and ethyl chloroformate[21]). The reaction mechanism and the formation of byproducts of this type of ring closure have been acutely investigated.[22] Direct submission of benzo[*c*]isoxazole with ethyl chloroformate also leads to **1**. Treatment of phthalic anhydride with ammonia and NaOH leads to phthalamic acid, which rearranges with NaOCl to form **1**. Similar results were attained starting from phthalimides (or *N*-chlorophthalimide).[23] Reaction of phthalic acids or anhydrides with azides also consists of a general route to isatoic anhydrides.[24,25] Finally, oxidation of phthalimic acids with lead(IV) acetate allows access to **1** as well.[26]

To the best of our knowledge, no new synthetic method for the preparation of **1** has been reported since publication of the reviews on its chemistry.[1,2] Modifications to known procedures gave birth to new protocols. For example, the oxidation of isatins has been reinvestigated for a recent green synthesis of isatoic anhydride by using cheap and environmentally friendly urea–hydrogen peroxide complex and ultrasonic irradiation.[27] The reaction of phthalimides was also reinvestigated with *N*-(mesyloxy)phthalimides for a better mechanistic understanding of the acidic reaction conditions.[28] Today, **1** is commercially available, along with its *N*-methylated analogue.

Although **1** has been known for over a century, only within the last 50 years have the polycyclic derivatives been further investigated. 1*H*-Benzo[*d*][1,3]oxazine-2,4-dione **1** was the first and remains the most commonly used ring-fused oxazine-2,4-dione **4** today.

2.1.1.2 Naphthalene, Anthracene-9,10-dione and Acenaphthalene Analogues

Naphthalene isomers **6** and **7** fused to the oxazinedione were obtained by treatment of the 1- or 3-amino-2-naphthoic acids with phosgene,[29,30] or ethyl chloroformate with subsequent reflux in acetyl chloride.[31] 1*H*-Anthra[1,2-*d*]-[1,3]oxazine-2,4,7,12-tetraone (**8**; or phthaloylisatoic anhydride) and its substituted derivatives were readily prepared by phosgenation of 1-amino-2-anthraquinonecarboxylic acids in substituted benzene solvents.[32,33] Acenaphtho[1,2-*d*]-[1,3]oxazine-2,4-dione (**9**) was synthesized in 99% yield by a Curtius rearrangement[34–37] of 1,2-acenaphthylenedicarboxylic anhydride, after reaction with sodium azide, in re-



Scheme 2. Polyaromatic oxazinediones synthetic pathway.

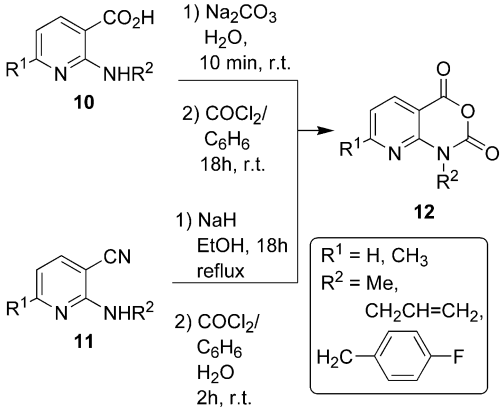
fluxing acetonitrile for 2 h. Acetonitrile was used as the solvent for its high polarity and subsequent ability to increase the nucleophilicity of the azide ion (Scheme 2).[38]

2.1.2 Heterocycles

For the past 30 years, substitution of the benzene ring of isatoic anhydride by heterocycles has been attracting more attention. A vast amount of aromatic heterocycles fused to the oxazine-2,4-dione were synthesized, among which we find pyridine, pyrimidine, quinoxaline, pyrrole, indole, pyrazole, imidazole, isoxazole, furan, thiophene, benzo[*b*]thiophene, oxazole and thiazole. The aza derivative of benzene, pyridine, is the most commonly acknowledged six-membered heteroaromatic anhydride.

2.1.2.1 Pyridine

Since the latest review on azaoxazinediones,[1,26,39] four new methods of preparation have emerged for the synthesis of azaisatoic anhydride (**12**; $R^1 = R^2 = H$). G. M. Coppola described the preparation of 1-*N*-alkyl-substituted derivatives **12** in yields of 14–82% by treatment of the corresponding sodium 2-aminopyridine-3-carboxylate, obtained either from acid **10** or nitrile **11**, with phosgene (solution in benzene; Scheme 3).[40] This synthetic procedure introduced *N*-alkyl substituents (R^2) onto the azaisatoic anhydride directly before ring closure.

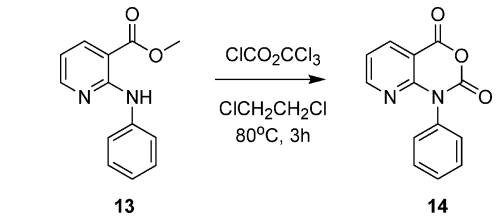


Scheme 3. Synthesis of *N*-alkylated-1*H*-pyrido[2,3-*d*][1,3]oxazine-2,4-dione **12** by using phosgene.

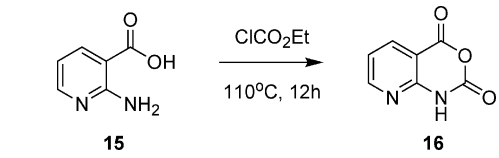
Because phosgene is not easily available in Japan, this situation prompted Kuroda et al. to develop a more convenient synthetic approach. Methyl 2-(phenylamino)pyridine-3-carboxylate (**13**) was treated with trichloromethyl chloroformate (TCF) in 1,2-dichloroethane to give *N*-phenyl-3-azaisatoic anhydride (**14**) in 87% yield (Scheme 4).[41] This methodology was later extended to a collection of *N*-aryl- and *N*-alkyl-substituted methyl aminopyridines-3-carboxylates[42] and carried out in a TCF/dioxane solution.[43]

A large excess of ethyl chloroformate was also used for the conversion of 2-aminopyridine-3-carboxylic acid (**15**) into 1*H*-pyrido[2,3-*d*][1,3]oxazine-2,4-dione (**16**) in 65% yield (Scheme 5).[44]

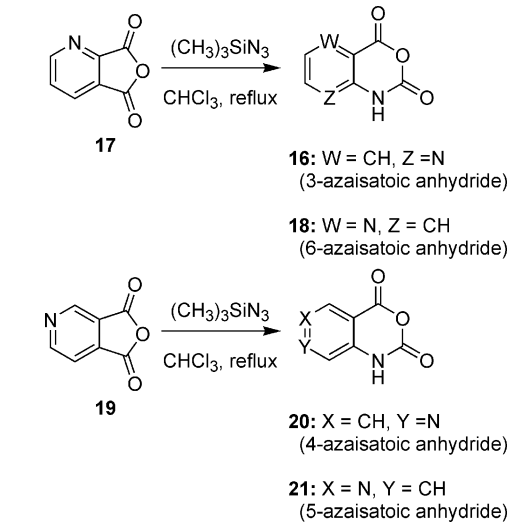
Finally, the reaction of 2,3-pyridinedicarboxylic anhydride (**17**) with a slight excess of trimethylsilyl azide in refluxing chloroform was reported to solely afford 3-azaisatoic anhydride **16** isomer.[45] The same reaction was also reported to give 6-azaisatoic anhydride **18** by simple substitution of the chloroform solvent by ether.[46] These observations were later clarified and revealed that when carried out in chloroform, the methodology could be expanded to obtain all four possible isomers. Therefore, a 2:1 mixture of 3- and 6-azaisatoic anhydrides (**16** and **18**) was obtained from 2,3-pyridinedicarboxylic anhydride (**17**), and a 1:1 mixture of 4- and 5-azaisatoic anhydrides (**20** and **21**) was obtained from 3,4-pyridinedicarboxylic anhydride (**19**; Scheme 6).[47]



Scheme 4. Synthesis of *N*-phenyl-3-azaisatoic anhydride (**14**) by using TCF.



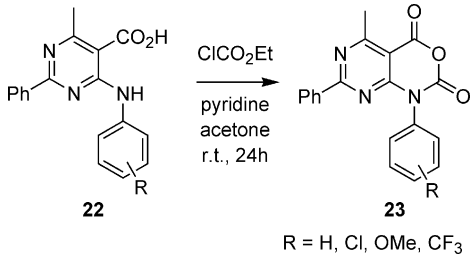
Scheme 5. Synthesis of 1*H*-pyrido[2,3-*d*][1,3]oxazine-2,4-dione (**16**) by using ethyl chloroformate.



Scheme 6. Synthesis of all four isomers of azaisatoic anhydrides.

2.1.2.2 Pyrimidine

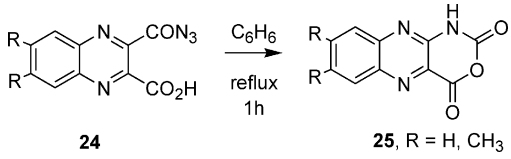
Less common, pyrimidine fused to an oxazinedione was also reported. A series of nine 5-methyl-7-phenyl-1*H*-pyrimido[4,5-*d*][1,3]oxazine-2,4-dione analogues **23** was produced in yields of 21 to 58% by reaction of 4-methyl-2-phenyl-6-arylaminopyrimidine-5-carboxylic acids **22** with ethyl chloroformate (Scheme 7).[48,49]



Scheme 7. Synthesis of 1*H*-pyrimido[4,5-*d*][1,3]oxazine-2,4-diones **23**.

2.1.2.3 Quinoxaline

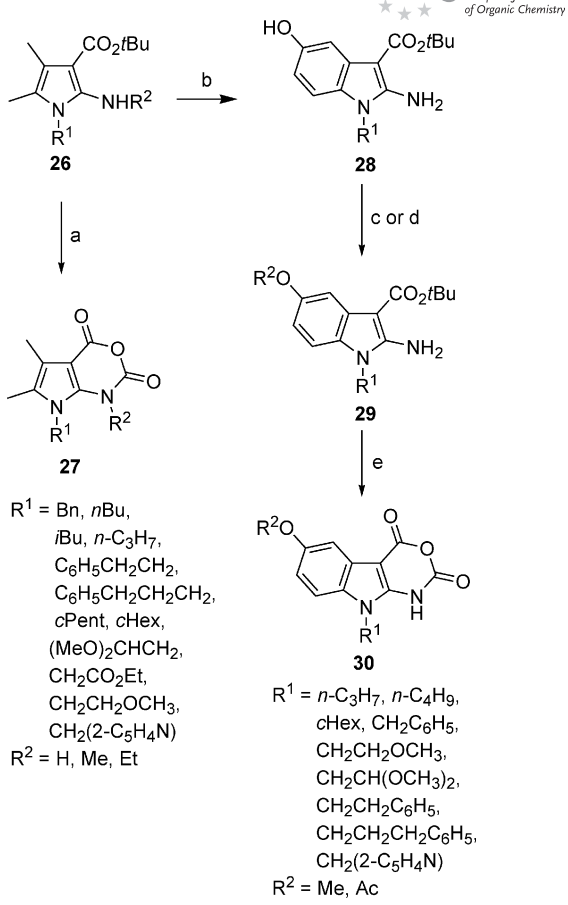
One example of 1*H*-quinoxalo[3,2-*d*][1,3]oxazine-2,4-dione (**25**) was described by a typical Curtius rearrangement of azide **24** followed by cyclization in refluxing benzene (Scheme 8).[50]



Scheme 8. Synthesis of 1*H*-quinoxalo[3,2-*d*][1,3]oxazine-2,4-dione (**25**).

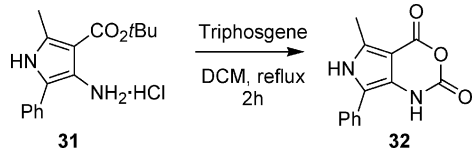
2.1.2.4 Pyrrole and Indole

For the moment, two out of the three possible fusions between the pyrrole and the oxazinedione have been reported. A series of 7-substituted 5,6-dimethyl-2,4-dioxo-1,2,4,7-tetrahydropyrrolo[2,3-*d*][1,3]oxazines **27** (R^2 = H) were prepared by cyclization of *N*1-substituted 2-amino-3-*tert*-butoxycarbonyl-4,5-dimethylpyrroles **26** with phosgene (solution in toluene) in yields ranging from 32 to 94% (Scheme 9).[51] Ring closure followed by formation of the pyrrolo[2,3-*d*][1,3]oxazinediones **27** by using triphosgene instead of phosgene was reported to give superior yields with less exposure to toxicity.[52–54] Cyclization of **26** bearing secondary amines (R^2 = Me, Et) was also reported to proceed in the same way, but necessitated an additional hour of reflux in the presence of TFA to afford the corresponding oxazinedione **27**.[55] Indole-fused oxazinediones were obtained in a four-step process starting from the same *N*1-substituted pyrroles **26** (Scheme 9). Pyrroles **26** were converted into the corresponding enone 2-amino-3-*tert*-butoxycarbonyl-5-hydroxyindoles **28** by cycloaddition of ethyl propiolate[56] and subsequent reductive aromatization with Zn in pyridine and a trace amount of water.[57] The 5-hydroxyindoles were *O*-methylated or *O*-acetylated with dimethyl sulfate or acetic anhydride, respectively. The substituted indolo[2,3-*d*]oxazine-2,4-diones **30** were cyclized in 37–73% yields by treating *tert*-butyl 2-amino-1*H*-indole-3-carboxylate (**29**) with triphosgene.[53,54]



Scheme 9. Syntheses of *N*-substituted pyrrolo[2,3-*d*][1,3]oxazinediones and substituted indolo[2,3-*d*]oxazine-2,4-diones. Reagents and conditions: (a) $COCl_2$, THF, reflux; (b) i. Ethyl propiolate, ethanol, reflux; ii. Zn, pyridine/H_2O, reflux; (c) $(CH_3O)_2SO_2$, NaH, THF, reflux; (d) Ac_2O, r.t.; (e) $(Cl_3CO)_2CO$, DCM, reflux.

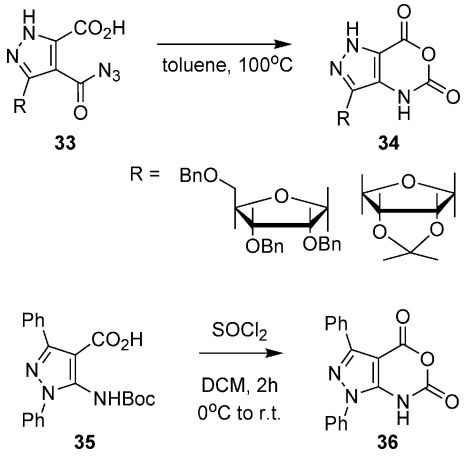
To the best of our knowledge, only one example of isomeric 5-methyl-7-phenylpyrrolo[3,4-*d*][1,3]oxazine-2,4-dione (**32**) has been described. *N*6-Unsubstituted pyrrolo derivative **32** was synthesized in 91% yield under previously mentioned conditions, in which hydrochloride **31** was treated with triphosgene (Scheme 10).[54]



Scheme 10. Synthesis of pyrrolo[3,4-*d*][1,3]oxazine-2,4-dione (**32**).

2.1.2.5 Pyrazole

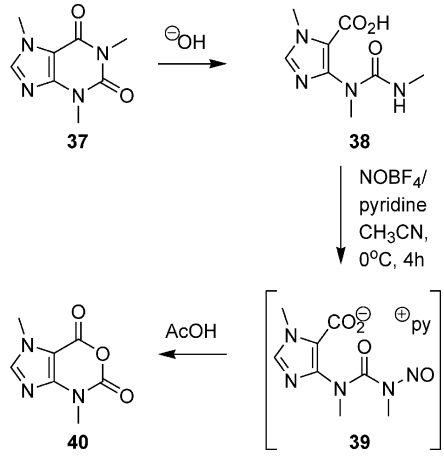
Pyrazolo[4,3-*d*][1,3]oxazine-2,4-dione (**34**) was synthesized in 90% yield by Curtius rearrangement of 4-(azidoformyl)-1*H*-pyrazole-5-carboxylic acid (**33**; Scheme 11). This intermediate was useful for the first synthesis of the nucleoside antibiotic Formycin B.[58] 5,7-Diphenylpyrazolo[3,4-*d*][1,3]oxazine-2,4-dione (**36**) was also synthesized in 96% yield by treatment of its Boc-protected corresponding β-amino acid **35** with thionyl chloride (Scheme 11).[59]



Scheme 11. Syntheses of pyrazolo[4,3-*d*] and [3,4-*d*][1,3]oxazine-2,4-dione.

2.1.2.6 Imidazole

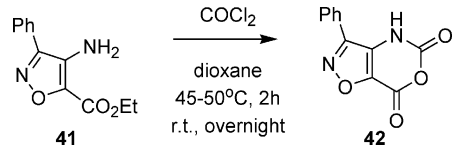
Caffeine (**37**) is known to be hydrolyzed to caffeidine acid (**38**) in alkaline conditions.[60,61] It was showed that caffeine as the main constituent of tea leaves, when treated under conditions of tea preparation, gave rise to **38**. While studying the synthesis and spectral characterization of nitrosation products of **38**, imidazole **40** was obtained in a unique way. Compound **40** can be prepared in 82% yield by nitrosation of **38** by using nitrosyl tetrafluoroborate ($NOBF_4$; Scheme 12).[62]



Scheme 12. Synthesis of imidazo[4,5-*d*][1,3]oxazinedione (**40**).

2.1.2.7 Isoxazole

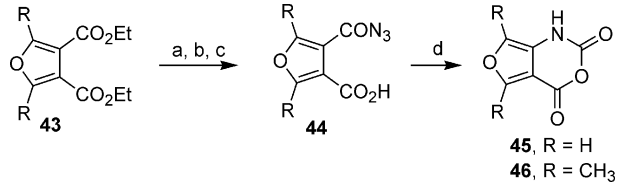
The only example of isoxazolo-fused example **42** was obtained in a straightforward procedure without cleavage of the ethyl ester from **41**. Typical addition of phosgene (solution in toluene) to ethyl 4-amino-3-phenylisoxazole-5-carboxylate (**41**) directly delivered isoxazolo[4,5-*d*]oxazine-2,4-dione (**42**) in 88% yield (Scheme 13).[63]



Scheme 13. Synthesis of isoxazolo[4,5-*d*]oxazine-2,4-dione (**42**).

2.1.2.8 Furan

The furan analogue of isatoic anhydride, 1*H*-furo[3,4-*d*]-[1,3]oxazine-2,4-dione (**45**), and its dimethyl counterpart **46**, were prepared by initial conversion of commercially available diethyl 3,4-furandicarboxylate **43** into its monoacid **44**.[64] Compound **44** was then treated with an excess amount of hydrazine hydrate to afford the corresponding hydrazide. Further treatment with native aqueous nitrous acid followed by standard Curtius rearrangement of the acyl azide gave the corresponding furo[3,4-*d*][1,3]oxazine-2,4-diones **45** and **46** in 75 and 51% yield from **43**, respectively (Scheme 14).[65–67]

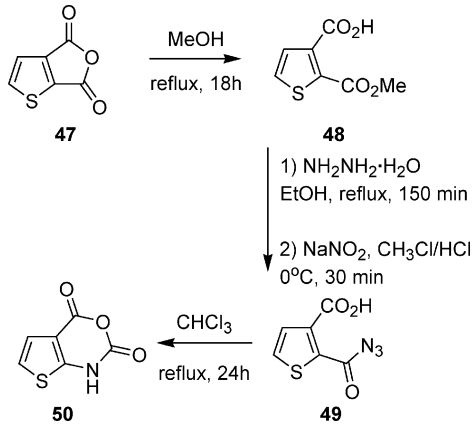


Scheme 14. Syntheses of furo[3,4-*d*][1,3]oxazinedione **45** and **46**. Reagents and conditions: (a) NaOH, 0 °C, H_2O/EtOH; (b) NH_2NH_2, EtOH, reflux; (c) HCl, $NaNO_2$; (d) $CHCl_3$, reflux.

2.1.2.9 Thiophene and Benzo[*b*]thiophene

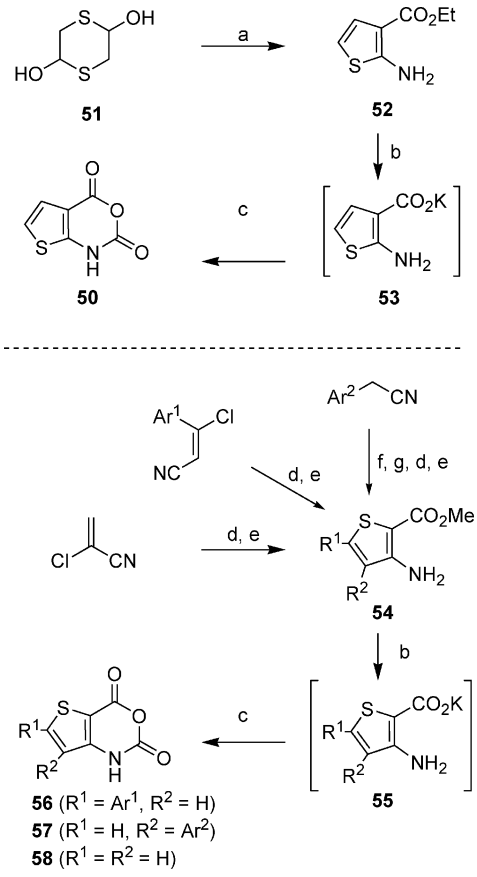
The first synthesis of 1*H*-thieno[2,3-*d*][1,3]oxazine-2,4-dione (**50**; also named 3-thiaisatoic anhydride) was described by B. R. Baker et al. in 1953 (Scheme 15).[68] Starting from thiophene-2,3-dicarboxylic anhydride (**47**), refluxing in methanol for 18 h gave monoester **48** in 37% yield. It was further treated with hydrazine hydrate to deliver the hydrazide in 78% yield. Conversion of the hydrazide by using sodium nitrite formed azide **49**, which was directly cyclized in refluxing chloroform to 3-thiaisatoic anhydride (**50**) in 70% yield.

In 1986, an improved procedure detailed the synthesis of thiaisatoic anhydrides from aminothiophenes **52** and **54**. Ethyl 2-aminothiophene-3-carboxylate (**52**) can be obtained in 80% yield by treating mercaptoacetaldehyde dimer **51** (or 2,5-dihydroxy-1,4-dithiane) with ethyl cyanoacetate in the presence of triethylamine (Scheme 16).[69–72] As for methyl 3-aminothiophene-2-carboxylate (**54**; $R^1 = R^2 = H$), it can be synthesized in 55% yield by reaction of methyl thioglycolate with sodium methoxide followed by treatment with 2-chloroacrylonitrile.[73] With these precursors in hand, hydrolysis of methyl 2-aminothiophene-3-carboxylate (**52**) and methyl 3-aminothiophene-2-carboxylate (**54**), followed by reaction with phosgene (solution in toluene), afforded the isomers 3-thiaisatoic anhydride (**50**) and 2-thiaisatoic anhydride (**58**) in 59 and 69% yield, respectively (Scheme 16, $R^1 = R^2 = H$).[74,75] More recently, a similar synthetic protocol



Scheme 15. Synthesis of 1*H*-thieno[2,3-*d*][1,3]oxazine-2,4-dione (**50**).

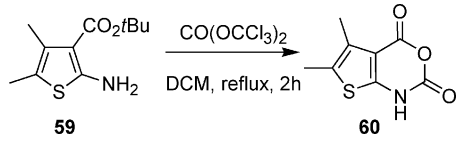
under microwave conditions was reported to shorten the reaction time, limit the formation of byproducts and deliver higher yields (67 and 85%, respectively).[76] Furthermore, substituted aminothiophene esters **54**, obtained from 3-chloro-3-arylacrylonitrile or 2-arylacetonitrile, were treated under the same conditions described above to also form the



Scheme 16. Syntheses of 3-thiaisatoic and 2-thiaisatoic anhydrides (**50** and **58**). Reagents and conditions: (a) EtO_2CCH_2CN, Et_3N, DMF, 45 °C, 30 min; (b) KOH, H_2O or dioxane, reflux, 1–12 h; (c) $COCl_2$, r.t., 1 h; (d) MeONa, MeOH, 1 h, 0 °C; (e) $HSCH_2CO_2Me$, 2 h, r.t.; (f) ethyl formate, MeONa, MeOH; (g) benzenesulfonyl chloride, DMF.

corresponding thiophene-substituted thiaisatoic anhydrides **56** and **57** (Scheme 16).[77,78] An analogous procedure also reported the use of phosgene (solution in carbon tetrachloride) in refluxing dioxane to deliver high yields of anhydrides **50** and **58** (89–90%).[79] Extension of the synthetic strategy used with thiophene derivatives **52** and **54** proved to be as successful with the benzo[*b*]thiophene derivative.[80]

In a more expedient fashion, 5,6-dimethyl-1*H*-thieno[2,3-*d*][1,3]oxazine-2,4-dione (**60**) was reported to directly cyclized in 56% yield from *tert*-butyl precursor **59** by using triphosgene (Scheme 17).[54]



Scheme 17. Synthesis of 5,6-dimethyl-1*H*-thieno[2,3-*d*][1,3]oxazine-2,4-dione (**60**) by using triphosgene.

Overall, it is reported that thiaisatoic anhydrides **50** and **58** are now commercially available from SYNTHEVAL SA.[76]

2.2 Nonaromatic Cycles

Nonaromatic rings fused to the oxazinediones constitute a minor class of such anhydrides in comparison to the aromatic derivatives. Nevertheless, an important series of compounds was synthesized by a few research groups over the past 35 years. Most of the studies surrounding the cycloalkanes fused to the oxazine-2,4-dione were reported by Kricheldorf et al. and include cyclopropane, cyclobutane, cyclopentane and cyclohexane.[81–83] Unsaturated cycles fused to the oxazinedione, such as bridged cycles (isatoic anhydrides containing a carbon bridge from the nitrogen atom of the oxazine ring to the fused benzene ring or analogous pentacycles)[84–87] and cyclohexenes[88–90] have also been reported, but will not be explicitly depicted in this microreview.

3 Reactivity

The reactivity of ring-fused oxazine-2,4-diones has led to the synthesis of a wide range of potentially attractive biological compounds over the last few years. The popular isatoic anhydride is still the leader of this family for the preparation of new biomolecules, as it can be seen in recent examples.[9,91–103] Nevertheless, many heterocycle-fused oxazine-2,4-diones showed their resourcefulness in the generation of novel biologically active scaffolds. For instance, azaisatoic anhydrides **16**, **18**, **20** and **21** were used as starting materials for the synthesis of bronchodilators of type **61**,[42] of in vivo antipsychotic agents of type **62**[47] and of anti-inflammatory agents of type **63**, possessing a broader spectrum of anti-inflammatory activity than the classical nonsteroidal anti-inflammatory drugs (NSAIDs) such as indomethacin and piroxicam (Figure 2).[104] Furthermore, pyrrole-fused oxaz-

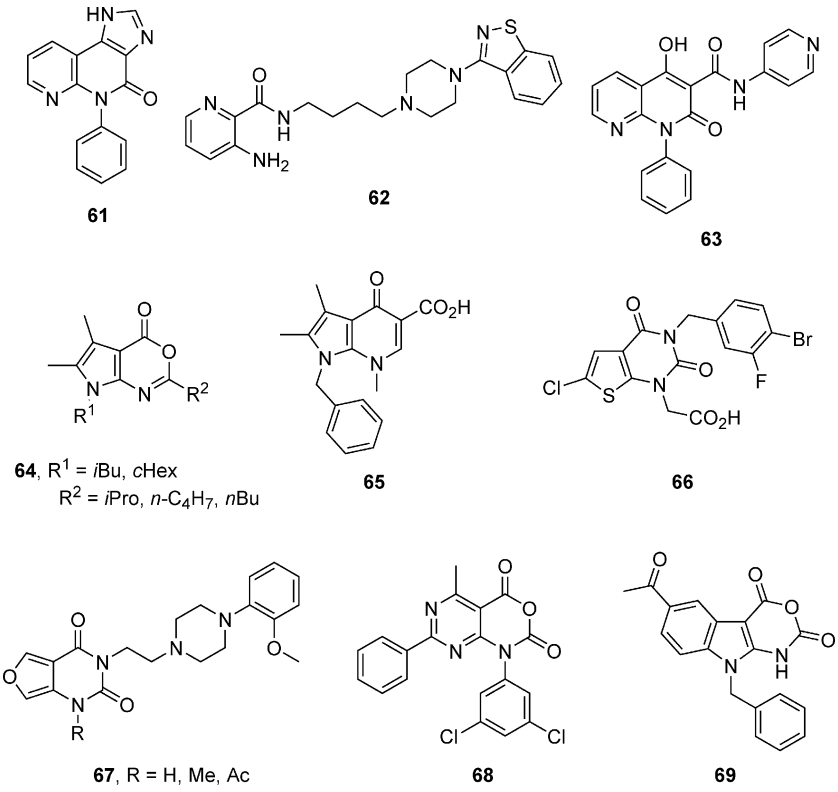


Figure 2. Biologically important structures obtained from ring-fused oxazine-2,4-diones.

ine-2,4-dione **27** served in the elaboration of antimicrobial **64**[55] and antifungal agents **65** with in vitro activity against *Tricophyton* and *Scopulariopsis sp.*[52]

In addition, ring-fused oxazine-2,4-diones containing a thiophene moiety led to in vitro aldose reductase inhibitors **66**[79] and containing a furan ring to antihypertensive agents **67**.[67] Finally, pyrimidine- and indole-fused oxazine-2,4-diones **68** and **69** respectively showed strong antibacterial properties[48,49] and human leukocyte elastase (HLE) inhibition.[53]

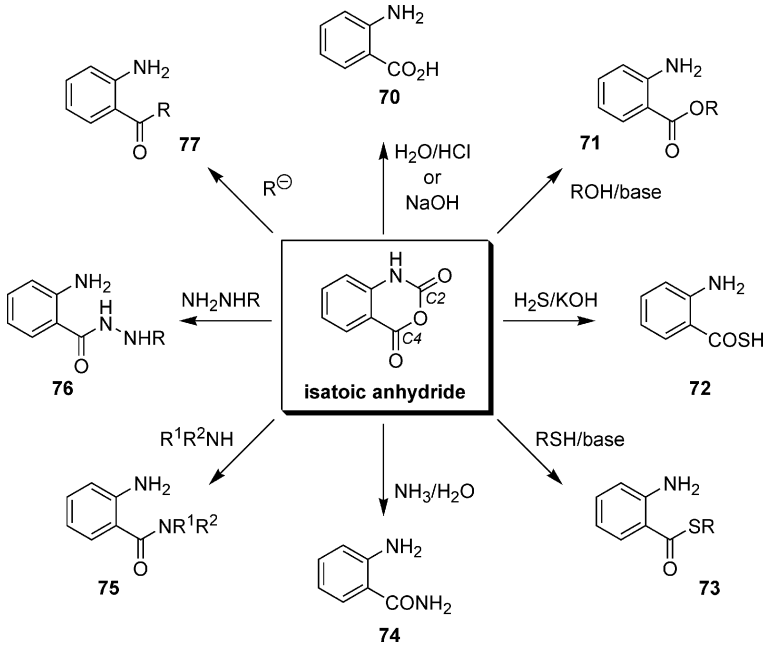
Before analyzing the different types of reactions from heteroaromatic analogues of isatoic anhydride, let us have a look at the reactivity of isatoic anhydride (**1**) itself.

3.1 Isatoic Anhydride

To quote G. M. Coppola, "the most interesting chemistry related to isatoic anhydride is the result of nucleophilic attack on its oxazine ring".[1] In fact, isatoic anhydride (**1**) proposes two carbonyl groups susceptible to attack by nucleophiles, designated as C-2 and C-4. The majority of the attacks occur at C-4 and the transformation is accompanied by carbon dioxide evolution.

Isatoic anhydrides react with warm water to produce anthranilic acid **70**, and the transformation may be catalyzed by the addition of acid or base (Scheme 18).[105] Primary aliphatic alcohols form the corresponding ester **71** with ease under heating conditions (above 80 °C). With phenols, by using dioxane as solvent and NaOH as catalyst, the reaction proceeds similarly.[106] Secondary aliphatic alcohols, such as 2-propanol, react with more difficulty, producing the consequent ester **71** along with byproducts.[106] Tertiary alcohols such as *tert*-butyl alcohol resist reaction with isatoic anhydride.[106] The reaction of **1** with hydrogen sulfide in the presence of potassium hydroxide (H_2S/KOH) produces thioanthranilic acid (**72**) in quantitative yield. However, the product is very unstable and undergoes self-acylation and elimination of two equivalents of hydrogen sulfide.[107] Under base catalysis, primary aliphatic mercaptans and thiophenols react with **1** to yield thioesters of anthranilic acid **73**.[106] Reaction of **1** with ammonium hydroxide produces anthranilamide **74**. Reaction with primary, secondary or aromatic amines also form the corresponding anthranilamide **75**. If the nucleophilic character of aniline **75** approaches or exceeds that of the amine employed, then **75** will preferentially react with another molecule of **1** to produce polymeric material. The use of an excess amount of amine (2–5 equiv.) tends to suppress the formation of polymers and increases the yields of the anthranilamides derivatives.[108] Hydrazines[109] and carbanions (such as salts of nitromethane,[110] methylsulfinylmethide,[111] malonate,[112] β-keto ester,[113] alcyne,[114] triphenylphosphorane[115] and isocyanoacetate)[114] also react in the same way by attack at the C-4 carbonyl of the benzoxazine to form the corresponding anilines **76** and **77** (Scheme 18).

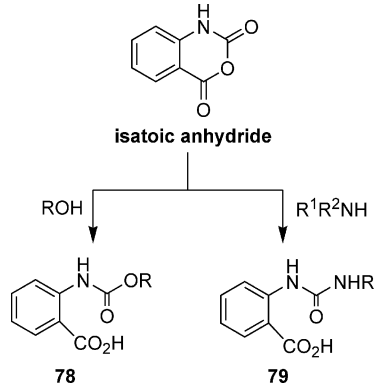
However, important exceptions are worth mentioning. In the absence of a base catalyst, alcohols react with **1** by a different route and produce the corresponding carbamates



Scheme 18. General nucleophilic attacks on isatoic anhydride (**1**).

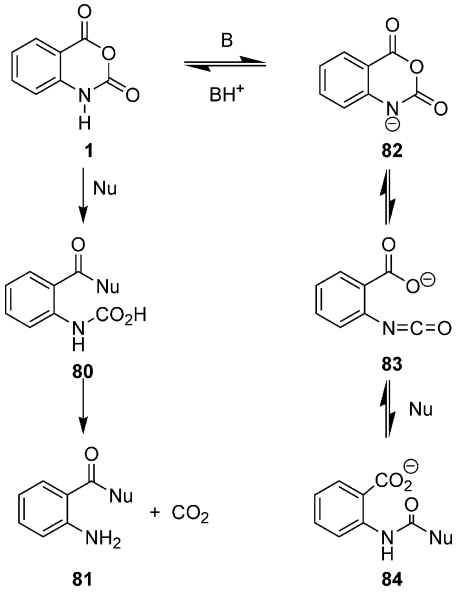
78 in yields ranging from 17 to 98% (Scheme 19).[116] In order for these reactions to occur, temperatures must be above 100 °C. Primary, secondary and tertiary alcohols yielded carbamates **78** along with varying amounts of the corresponding anthranilates **71** as side products. In general, ethanol and 2-propanol produced the least amount of anthranilate byproduct **71** and furnished the highest yields of carbamates **78**. No anthranilate was observed to be formed with *tert*-butyl alcohol, and *tert*-butyl carbamate **78** was isolated in 41% yield. As expected, catalytic amounts of sulfuric acid decreased the yield of carbamate and increased the amount of anthranilate **71**.[1] As in the case with alcohols, some exceptions were also reported in 1953 concerning the nucleophilic attack of amines.[117] When 40 equiv. of 16 M ammonia were used, attack at the C-2 position also occurred (42%) to form urea **79** ($R^1 = R^2 = H$) along with the commonly reported product of attack at the C-4 carbon (55%).[118] The primary amines tested (methylamine, ethylamine, *n*-propylamine, isopropylamine, *n*-butylamine, *sec*-butylamine, *tert*-butylamine, allylamine, *c*-hexylamine, benzylamine and aniline) in excess amount in water were all reported to yield in varying ratios, portions of both amides **75** and ureas **79**. The use of the more sterically hindered *tert*-butylamine in water was reported to favour the formation of C-2 attacked product **79** (R^1 = *tert*-butyl, $R^2 = H$).[117,118] Secondary amines (diethylamine, di-*n*-propylamine, piperidine, morpholine and methylaniline) also yielded similar results.[117] The use of dimethylformamide (DMF), dimethylacetamide (DMA) or dimethyl sulfoxide (DMSO) as solvents suppressed the formation of *o*-ureidobenzoic acids **79** (Scheme 19).[119]

When isatoic anhydride is substituted on its nitrogen, no formation of carbamate products was observed upon reaction with alcohols, and only the corresponding anthranilates were isolated. Similarly, the reaction of *N*-alkylated isatoic anhydride with amines only produces anthranilamides. An interesting explanation was postulated by R. P. Staigner and E. B. Miller[106] and was later supported by a kinetic study.[120] They hypothesized that ionization of isatoic anhydride followed by ring opening of the anhydride may play an important part under conditions of generally lower reactivity and produce isocyanate intermediate **83**, which is attacked by the bulkier groups to yield the ureido or carbamate derivatives **84** (Scheme 20). Although attempts to demonstrate the presence of an –N=C=O band by IR spectroscopy (in dioxane and pyridine solutions of **1** and triethylamine) did not prove its existence to an observable degree, it is believed that isocyanate species **83** is significant because of the complete absence of ureido or carbamate derivatives from *N*-methylisatoic anhydride. This absence may be attributed to the lack of the ability to form the necessary isocyanate species. However, with the most



Scheme 19. Exceptions in the nucleophilic attack at C-2 of isatoic anhydride (**1**).

reactive nucleophiles (i.e., phenoxide and mercaptide), such an equilibrium probably plays a very small role, because the reaction goes so rapidly at the C-4 carbon.



Scheme 20. Ionization of isatoic anhydride (**1**).

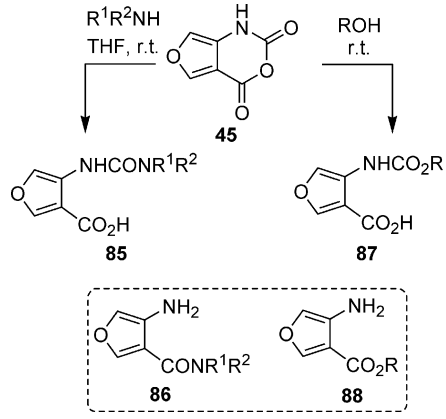
The widespread access to new technologies was utilized to evaluate its reactivity. Isatoic anhydride was used in the microwave-assisted rapid synthesis of luotonin A,[121] benzimidazo[1,2-*c*]quinazolines,[122] 3-(2-benzimidazolyl)-2-alkyl-4-(3*H*)-quinazolinones,[123] 2-methyl-1,4-benzodiazepin-5-ones,[124] as well as pyrrolo[2,1-*c*][1,4]benzodiazepines-5,11-diones under solvent-free conditions.[125] Since Coppola reported the preparation of polymer-supported isatoic anhydride for its use as a scavenger of amines,[126] it also allowed the preparation of many heterocycles on solid phase.[127,128] Moreover, 2-(*o*-aminophenyl)oxazolines were produced by a clay-catalyzed conversion of isatoic anhydride in solution and on solid support.[129]

In sum, nucleophiles always attack isatoic anhydrides at the C-4 carbonyl group, liberating carbon dioxide, with the rare exceptions of specific substrates in particular conditions, as described above. The reactivity of cyclo[*d*]oxazine-2,4-diones was regrouped in five sections depicting the nucleophilic attack at the C-2 or C-4 carbonyl groups of oxazines, the electrophilic substitution of the nitrogen atom of the oxazines and finally the nucleophilic attack at the C-2 and C-4 carbonyl groups of *N*-substituted oxazines.

3.2 Attack at the C-2 Carbonyl Group of Ring-Fused *N*-Unsubstituted Oxazine-2,4-diones

A slight amount of ring-fused *N*-unsubstituted oxazine-2,4-diones was submitted to multiple reagents. Those reactions that were reported are depicted below.

Reaction of 1*H*-furo[3,4-*d*][1,3]oxazine-2,4-dione (**45**) with a variety of aliphatic and aromatic amines at room temperature led to the exclusive formation of ureido acid derivatives **85** (Scheme 21).[66] The exclusivity of the reaction was unaffected by elevated temperature, amine basicity, ionizing properties of various solvents, amine concentration or stoichiometry or by other basic catalysts. Amide **86**, the result of amine attack at the C-4 carbonyl adjacent to the furan ring of **45**, was not detected in the crude reaction mixtures. The fact that **85** is the only reaction product of **45** with amines is in contrast to the results reported for **1**.[1] In these cases, concentration, molar ratio, solvent and basicity of the reactant amines affected the product ratio of anthranilamide **75** and *o*-ureidobenzoic acid **79**. The reactivity of **45** was similar to that reported for isatoic anhydride only in regard to the reaction time and temperature.[66]



Scheme 21. Reactivity of furan anhydride **45**.

Reaction of **45** with alcohols also gave rise to a single product, namely carbamate **87** (Scheme 21).[66] The quantitative formation of **87** was unaffected by base catalysts (such as sodium hydroxide or sodium ethoxide). Anhydride **51** reacted readily with alcohols at room temperature, in contrast to **1**, which may be crystallized from alcohols and which reacts only at elevated temperatures to give both anthranilate and carbamate products, with ratios dependent on reaction conditions. Attempts to thermally rearrange **87** into **88** caused decomposition of the furan ring, although such rearrangements for the analogous benzene system have been reported.[116]

Reactions of **45** with other reagents did not give useful results. Attempts to react **45** with water in tetrahydrofuran, dioxane or dimethyl sulfoxide led to complete decomposition of the system. When **45** was treated with thiols, with or without base catalysis, no characterizable product could be isolated. Attempts to *N*-alkylate **45** by using standard conditions, including those used to prepare *N*-substituted isatoic anhydrides,[1] also resulted in extensive decomposition without formation of the desired products. Reaction of **45** with electrophiles (such as SO_2Cl_2 or Br_2) in a variety of solvents also gave intractable mixtures.[66]

The increased reactivity of **45** toward alcohols, as compared to **1**, is probably a result of the increased ring strain of the [6.5] ring system of **45** in comparison to the [6.6] ring system of **1**. This increased strain is revealed in the infrared spectra by the carbonyl absorption frequencies of **45** (1786 and 1754 cm^{-1}), which are higher than those of isatoic an-

hydride (1760 and 1720 cm^{-1}). A possible cause for the exclusive formation of ureas **85** and carbamates **87** as products of reaction of **45** might be resonance deactivation of the carbonyl adjacent to the furan ring of **45** (i.e., **45b**). This effect would enhance the relative reactivity of the C-2 carbonyl towards nucleophiles (Figure 3).[66] The lack of reactivity of the C-4 carboxylic carbonyl of other five-membered ring-fused oxazine-2,4-diones such as isoxazole[63] and thiophene[76] was also rationalized by a mesomeric effect implying the lone pair of electrons of the heteroatom, strongly deactivating the C-4 carbonyl group towards nucleophilic attack.

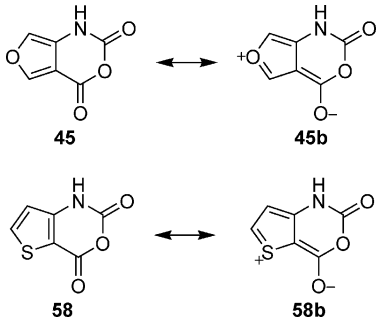
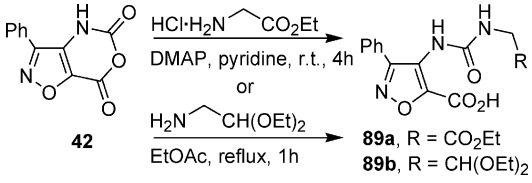


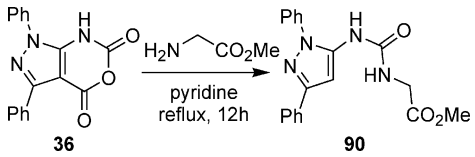
Figure 3. Possible resonance deactivation of the C-4 carbonyl.

Treatment of 3-phenyl-4*H*-isoxazolo[4,5-*d*][1,3]oxazine-5,7-dione (**42**) with glycine ethyl ester hydrochloride in anhydrous pyridine at room temperature in the presence of 4-dimethylaminopyridine (DMAP) as catalyst afforded ureido acid **89a** in 68% yield. Analogously, reaction with aminoacetaldehyde diethylacetal in boiling ethyl acetate (EtOAc) led to ureido acid **89b** in 96% yield (Scheme 22).[63]



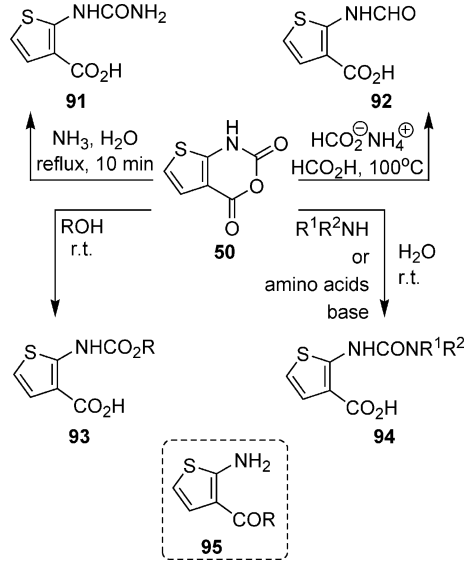
Scheme 22. Reaction of isoxazolo-containing anhydride **42** with primary amines.

In the same manner, nucleophilic attack of glycine methyl ester occurred solely at the C-2 carbonyl of nonalkylated pyrazolo anhydride **36** along with decarboxylation to form urea **90** in 64% conversion (Scheme 23).[59]



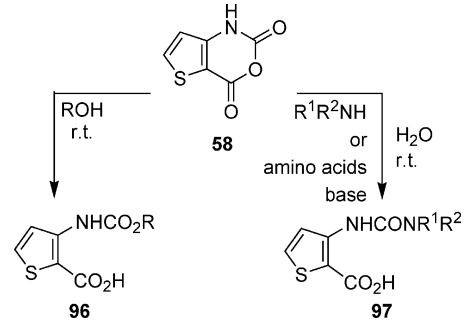
Scheme 23. Reaction of pyrazolo-containing anhydride **36** with an α-amino ester.

Even though the reactivity of thiaisatoic anhydrides has not been as exhaustively explored as that of **1** and its pyridine derivative, thiophene is the most studied five-membered ring fused to an oxazine-2,4-dione. When 3-thiaisatoic anhydride (**50**) was treated with ammonia in boiling water for 10 min, urea **91** was formed in 56% yield (Scheme 24).[68] It was later supplemented that simple standing at room temperature with ammonia for 15 min gave urea **91** in 65% yield, without formation of *o*-aminocarboxamide **95**.[76] When anhydride **50** was treated with ammonium formate in 89% formic acid at 100 °C, ring opening and formylation to acid **92** occurred in poor yields.[68]



Scheme 24. Reactivity of 3-thiaisatoic anhydride (**50**).

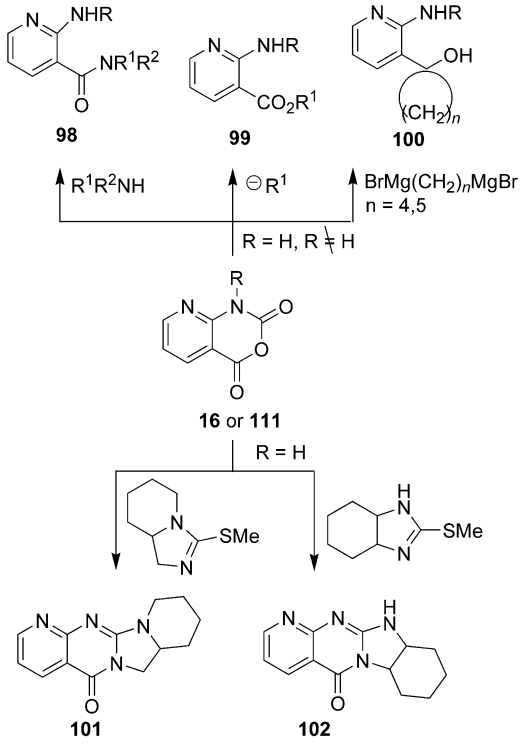
Both 3-thiaisatoic anhydride (**50**; Scheme 24) and 2-thiaisatoic anhydride (**58**; Scheme 25) react at their C-2 carbamate carbonyl at room temperature when attacked by primary amines (aliphatic and aromatic), secondary amines, hydrazines, urea, thiols, alcohols, alkoxides and amino acids.[76–78,130] Heating shortened the reaction times in some cases, but was mandatory for the reaction with methyl thioglycolate.[76] In the same way, reaction of benzo[*b*]thiophene-containing anhydride with a catalytic amount of sodium methoxide or methylamine afforded the corresponding carbamate or ureido acid, respectively, as the sole product.[80]



Scheme 25. Reactivity of 2-thiaisatoic anhydride (**58**).

3.3 Attack at the C-4 Carbonyl Group of Ring-Fused *N*-Unsubstituted Oxazine-2,4-diones

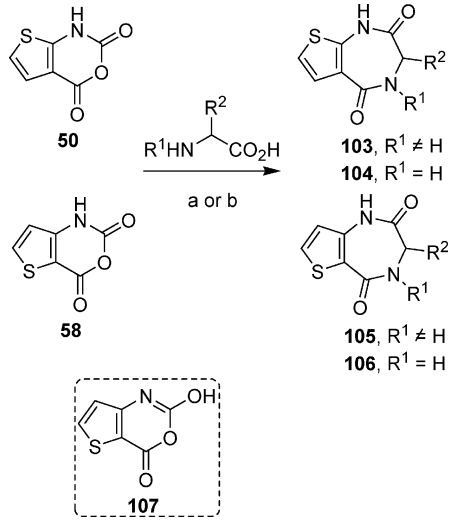
1*H*-Pyrido[2,3-*d*][1,3]oxazine-2,4-dione (**16**) is the most cited of the four azaisatoic anhydrides. *N*-Unsubstituted 3-azaisatoic anhydride **16** was reported to react at its C-4 carbonyl with primary[47] or secondary[131] amines (to form amides **98** in 85–91% yield), with methanol[39] (to form ester **99**) and with alkylmagnesium bromides[132] (to form alcohols **100** in 42–50% yield) as summarized in Scheme 26. Anhydride **16** was also attacked at its C-4 carbonyl by *S*-methylthioureas in the presence of a catalytic amount of sodium hydroxide at reflux and underwent subsequent cyclization to afford the corresponding tetracycles **101** and **102** in 12–60% yields (Scheme 26).[40] The other azaisatoic anhydride isomers were reported to follow the same reaction pattern with primary amines in 24–66% yield.[47] For the four types of azaisatoic anhydrides, alcoholysis and hydrolysis occurred much more rapidly than with **1**, which, as previously mentioned, can be recrystallized from alcohol.[39]



Scheme 26. Reactivity at the C-4 carbonyl of 3-azaisatoic anhydride **16**.

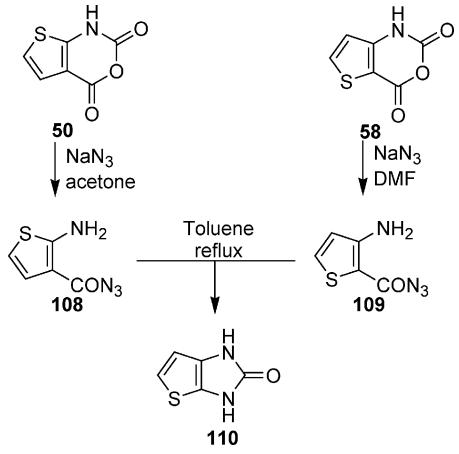
Hydrolysis of heterocyclic-fused anhydrides, with the exception of the furan analogue, occurs in refluxing water, in a quicker manner than with **1**. We took the liberty of describing hydrolysis in the section entitled "Attack at the C-4 Carbonyl Group of *N*-Unsubstituted Oxazine-2,4-diones", but it could be argued that it could be placed elsewhere, as no proof discarding a possible preliminary attack at the C-2 was advanced.

An interesting exception to the general reactivity of ring-fused anhydrides was reported with the case of thiophene derivatives. In a mixture of dioxane/water (1:1) at reflux, thiaisatoic anhydrides **50** and **58** were attacked at their C-4 carboxylic carbonyl by proline and hydroxyproline ($R^1 \neq H$), thus adopting a character similar to isatoic anhydride (Scheme 27).[133] Cyclocondensation led directly to tricyclic thienodiazepines **103** and **105** in 35–70% yield. The authors suggested that this reverse reactivity could be due to the nature of the solvent. In protic solvents (alcohol or water) mesomeric form **107** (Scheme 27) would be favoured, directing a privileged attack at the C-4 carbonyl, whereas in aprotic solvents (dioxane), canonical forms **58b** discussed earlier (Figure 3) would prevail.[133] More recently, our group reported the synthesis of a series of 10 optically pure bicyclic thieno[3,2-*e*][1,4]diazepine-2,5-dione derivatives **106** in 41–75% yield by a two-step process by attack of different natural α-amino acids ($R^1 = H$) on anhydride **58** in H_2O at 40 °C.[134] Even though 3-thiaisatoic anhydride (**50**) was found to be more stable than its isomer **58**, ring opening of its oxazine at the C-4 carbonyl still proved itself feasible with acyclic *N*-substituted α-amino acids under neutral conditions. Consequently, a series of thieno[2,3-*e*][1,4]diazepine-2,5-dione analogues **103** was synthesized in 35–81% yield in our laboratory.[135]



Scheme 27. Attacks of thiaisatoic anhydrides **50** and **58** at their C-4 carboxylic carbonyl by *N*-substituted and *N*-unsubstituted α-amino acids. Reagents and conditions: (a) for $R^1 \neq H$, dioxane/H_2O, reflux; (b) for $R^1 = H$, i. H_2O, 40 °C; ii. AcOH, reflux.

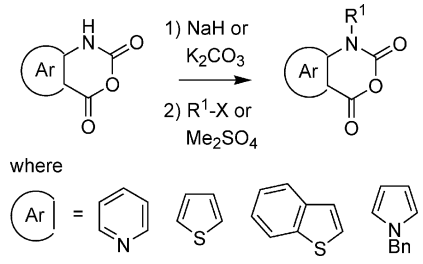
It was also reported that treatment of thiaisatoic anhydride **50** (in acetone at room temperature) and **58** (in DMF at 50 °C) with sodium azide led to the formation of 2-aminothiophene-3-carbonyl azide (**108**) and 3-aminothiophene-2-carbonyl azide (**109**) in 85 and 90% yield, respectively. These two compounds were then subjected to a Curtius rearrangement in refluxing toluene to give identical product **110** in 96 and 80% yield, respectively (Scheme 28).[136] So far, the thiophene ring is the only five-membered heterocycle that showed reactivity at its C-4 carbonyl when the nitrogen of the oxazine was unsubstituted.



Scheme 28. Azide attack on the carboxylic carbonyl of *N*-unsubstituted thiaisatoic anhydrides **50** and **58**.

3.4 Electrophilic Substitution at the Nitrogen Atom of Oxazine-2,4-diones

So far, substitution of the nitrogen in heterocycle-fused oxazine-2,4-diones was described in the pyridine,[40,45] thiophene,[75,79,136,137] benzo[*b*]thiophene[80] and pyrrole[51] series. Briefly, this diversification was mainly achieved in a two-step process by using an inorganic base (such as sodium hydride or potassium carbonate) followed by treatment with dimethyl sulfate or an alkyl halide (Scheme 29). Even though *N*-alkylation of other ring-fused anhydrides has not been reported, in some cases, *N*-substitution was accessible by the cyclization of the corresponding *N*-alkylated precursor, as previously discussed.



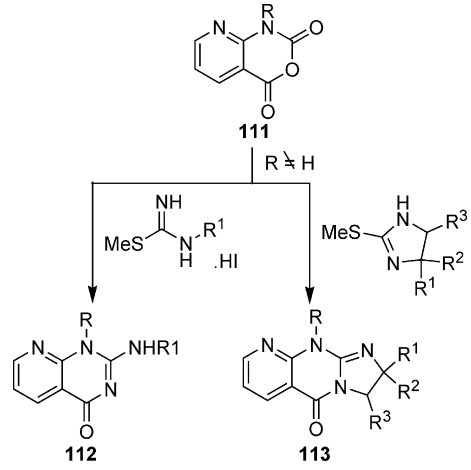
Scheme 29. *N*-Alkylation of ring-fused anhydrides.

3.5 Attack at the C-2 Carbonyl Group of Ring-Fused *N*-Substituted Oxazine-2,4-diones

To the best of our knowledge, no reports of attack on the C-2 carbonyl of any *N*-substituted ring-fused oxazine-2,4-dione has been reported. Experimental results so far seem to be in accordance with the isocyanate postulate, justifying the *N*-substituted anhydrides lack of ability to form the necessary isocyanate species.

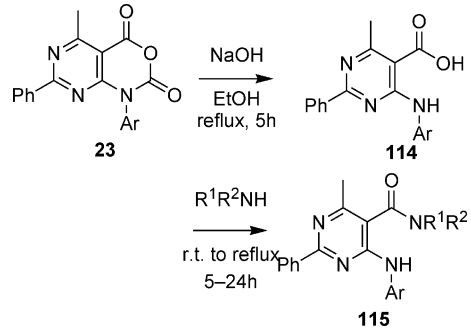
3.6 Attack at the C-4 Carbonyl Group of Ring-Fused *N*-Substituted Oxazine-2,4-diones

To the best of our knowledge, reactivity of only *N*-alkylated 3-azaisatoic anhydride **111** was reported at the C-4 carbonyl of its oxazine with amines,[40,44,45,47,138] carbanions (generated for example from nitromethane, diethylmalonate, ethyl nitroacetate and ethyl *o*-fluorobenzoylacetate)[40–43,104,139,140] and alkylmagnesium bromides[132] (Scheme 26). Anhydride **111** was also cited to be attacked at the C-4 carbonyl by the free base of *S*-methylthioureas in the presence of a catalytic amount of base at reflux and undergoes subsequent cyclization to afford the corresponding bi-, tri- or tetracycles (Scheme 30).[40] From the collected results, *N*-alkylation of the azaisatoic anhydride does not seem to influence its reactivity towards nucleophiles; attacks only proceed at the C-4 carbonyl, whether the nitrogen of the oxazine is alkylated or not.



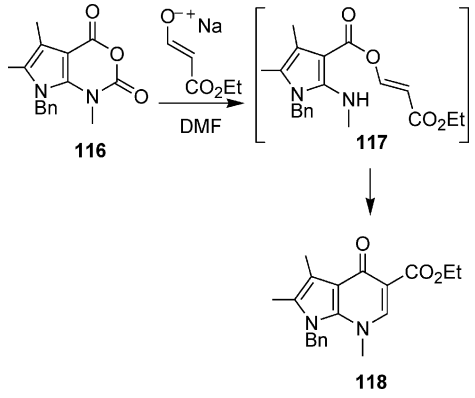
Scheme 30. General reactivity of *N*-methyl 3-azaisatoic anhydride (**111**).

Similarly, heating pyrimidine[1,3]oxazines **23** with alcoholic NaOH produces acids of type **114**, whereas heating with amines yielded amides **115** (Scheme 31).[48,49] The amidation with aromatic amines and primary aliphatic amines proceeds smoothly, whereas the reaction involving the secondary aliphatic amines requires prolonged heating.



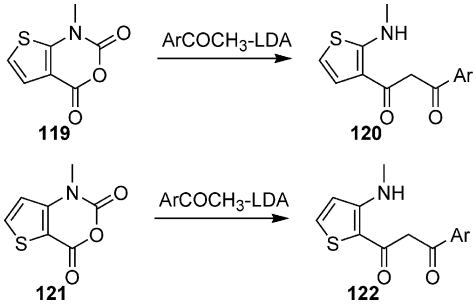
Scheme 31. Nucleophilic attack on *N*-arylpyrimidinoxazines **23**.

Likewise, condensation of *N*-alkylated pyrrole anhydride **116** with sodium ethylformyl acetate in dimethylformamide afforded cyclized product **118** in 40% yield (Scheme 32).[55]



Scheme 32. Attack at the C-4 of *N*-alkylated pyrrolo[2,3-*d*][1,3]-oxazine-2,4-dione **116**.

Similarly, once *N*-methylated, thiaisatoic anhydrides **119** and **121** react at their carboxylic carbonyl with acetophenones in the presence of lithium diisopropylamine (LDA), leading to diketones **120** and **122** (Scheme 33).[75]

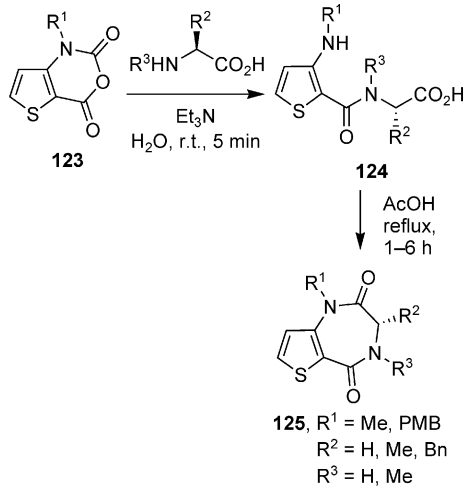


Scheme 33. Reaction of thiaisatoic anhydrides **119** and **121** with acetophenones.

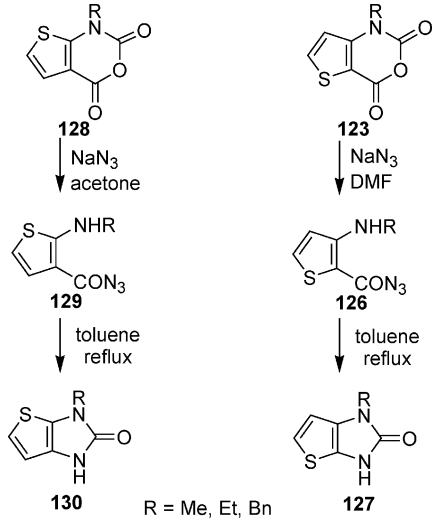
Recently, we demonstrated that thiaisatoic anhydride **58** and its *N*-alkylated derivatives **123** react in an opposite manner with α-amino acids under basic conditions. Our group used this finding to prepare a library of 10 *N*-substituted thieno[3,2-*e*][1,4]diazepine-2,5-dione analogues **125** in 55–98% yield (Scheme 34). These observations were further extended and led us to transpose our protocol to the solid phase, allowing the initial synthesis of a series of eight 1*H*-thieno[3,2-*e*][1,4]diazepine-2,5-dione analogues in 83–99% purity and 71–95% yield in a three-step process.[137]

Interestingly, treatment of both *N*-alkylated thiaisatoic anhydrides **123** and **128** with sodium azide led to the same regioselective C-4 attack to that reported for the *N*-unsubstituted thiaisatoic anhydrides **58** and **50** (Scheme 28).[136] Subsequent Curtius rearrangement of azides **126** and **129** led to monosubstituted thienoimidazolones **127** and **130** in 95 and 73% yield, respectively (Scheme 35).

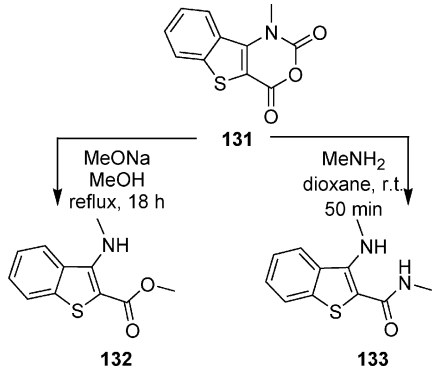
In the same manner, *N*-methylbenzothieno[3,2-*d*][1,3]oxazine-2,4-dione (**131**) reacts under the same conditions to those of its unsubstituted derivative with sodium methoxide to give this time only amino ester **132**, resulting from C-4 attack in 86% yield.[80] *N*-Methylamine reacted in a similar fashion to give only amino amide **133** in 63% yield (Scheme 36).[80]



Scheme 34. Reverse reactivity of *N*-substituted thiaisatoic anhydride with α-amino acids.



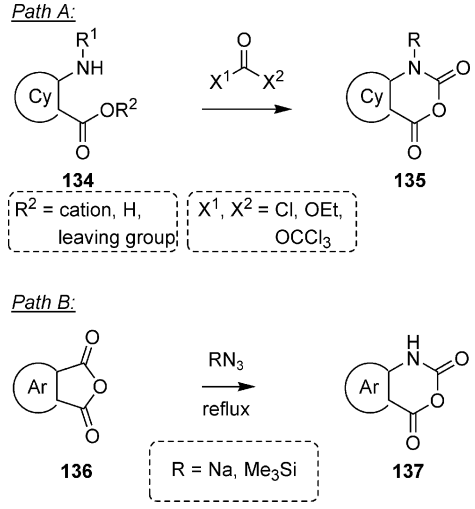
Scheme 35. Azide attack at the C-4 carboxylic carbonyl of *N*-alkylated thiaisatoic anhydrides.



Scheme 36. Nucleophilic attack at the C-4 carboxylic carbonyl of *N*-methyl benzothiaisatoic anhydride.

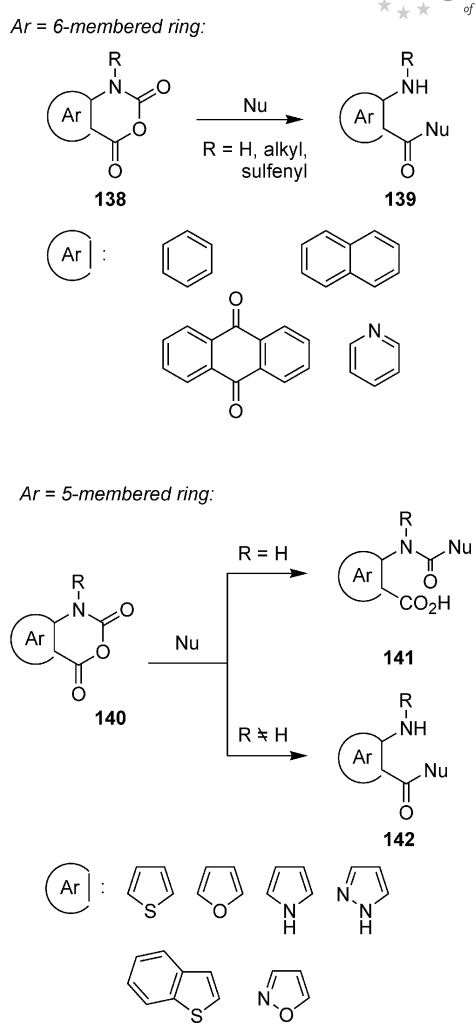
4 Conclusions

Two methods mainly cover the synthetic pathways to access ring-fused oxazine-2,4-diones **4**. The most commonly used strategy implicates the treatment of phosgene (or its derivatives) on the corresponding amino acid **134** (Scheme 37, Path A). The second widely adopted methodology involves ring opening of cyclic anhydride **136** and subsequent Curtius rearrangement with an azide reagent (Scheme 37, Path B). The other methods applied to specific cases included the use of PCl_5 or $SOCl_2$ on amino acids, oxidation of a urea with $NOBF_4$, oxidation of a ketoamide with *m*-CPBA and acidification of an aminooxazinone.



Scheme 37. Principal synthetic routes to ring-fused oxazine-2,4-diones **135** and **137**.

Concerning the reactivity of ring-fused oxazine-2,4-diones toward nucleophiles, a clear distinction can be made between the six-membered rings and the five-membered rings. Six-membered ring-fused oxazine-2,4-diones **138** react solely at their C-4 carbonyl groups (Scheme 38), with rare exceptions noted with isatoic anhydride (**1**) and certain alcohols in specific conditions. Five-membered ring-fused oxazine-2,4-diones **140** react, in an opposite way to that of the six-membered ring, at their C-2 carbonyl group, when the nitrogen atom of the oxazine is unsubstituted. Once it is *N*-substituted (such as by an alkyl or acyl group), the five-membered ring-fused oxazine-2,4-diones regain a behaviour similar to that of their six-membered analogues, where nucleophilic attacks unvaryingly proceed at their C-4 carbonyl groups (Scheme 38). Hypothesis of an intermediate isocyanate could justify the behaviour of *N*-unsubstituted oxazine-2,4-diones. Delocalization engaged by heteroatoms might help to rationalize the accessibility between the carbonyl groups. Additional strain exerted on the oxazine ring by the fused five-membered ring may favour the molecule into the ionized isocyanate state. An important exception to these behaviours was observed with the thiophene derivative, where attack at the C-4 carbonyl was observed with α-amino acids and NaN_3 on *N*-unsubstituted thiaisatoic anhydrides **50** and **58**.



Scheme 38. General reactivity of ring-fused oxazine-2,4-diones regarding nucleophiles.

Over the last few years, the simple synthetic access to numerous ring-fused oxazine-2,4-diones has made them an emergent class of worthy starting materials, as seen with the multitude of examples illustrated in the literature. The different chemical transformations envisaged with this family of reagents as a result of their two possible regio-controlled ring openings have made them useful and flexible intermediates for the diversification of a wide range of known heterocycles and for access to new interesting scaffolds. Transposition of this chemistry is now being developed in certain series on solid support and promises the rapid formation of large libraries of potentially valuable compounds.

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