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Methods for synthesizing hydroxamic acids and their metal complexes

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REVIEW ARTICLE

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ABSTRACT

In previously published works, the antibacterial, antifungal, antimycobacterial and anticancer activities of hydroxamic acids (HA) and their complexes were reported. Our recently published work shows that aliphatic HA with a number of carbon atoms equal to 12 (C_{12}) and its Fe(II), Fe(III), Ni(II), Cu(II) and Zn(II) complexes are significantly active against bacteria (*Staphylococcus aureus*, *Escherichia coli*), fungal (*Candida albicans*) and mycobacteria (*Mycobacterium smegmatis*). Furthermore, the inhibitory activities against biofilms of *Mycobacterium tuberculosis, Mycobacterium bovis* BCG, *Mycobacterium marinum* and *Pseudomonas aeruginosa* were observed with a large number of HA and their complexes. Suberoylanilide HA and resminostat were approved to treat cutaneous T cell lymphoma and in clinical trials to treat advanced hepatocellular carcinoma, respectively. In view of the interesting biological properties of this family of chemical compounds, the synthesis of HA has been reported in numerous research articles in recent years but this is the second review article dedicated to their synthetic methods and the first review for their complexes. The aim of this review is to highlight optimal and rational methods for the synthesis of HA and their complexes. HA are obtained in near-quantitative yields from carboxylic acid, ethyl chloroformate, *N*-methylmorpholine and hydroxylamine. As for their complexes, the synthesis methods described are fairly similar and would all appear to be optimal. The main criteria are the number of equivalents of HA, the type of metal salt or solvent used and the reaction conditions.

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1. Introduction

Hydroxamic acid (HA) are the organic compounds with the general formula R-CO-NH-OH, where R = Alkyl or aryl (Figure 1a and 1b). Oxalohydroxamic (Figure 1c) is the first HA were discovered by Lossen in 1869, this class of organic compounds was only thoroughly studied from the nineteen eighties [1]. Due to the significant applications, the HA are well studied in modern society [2].

HA have many applications in biology and medicine [2,3], particularly against bacteria, cancer cells and fungi [4-6]. HA derivatives are known to be good antimicrobial agents for inhibiting the growth of fungi [7], but also of cancer cells [8]. They are also known to inhibit a number of enzymes [8]. Furthermore, the HA possesses multiple biological activities attributed from to their ability to bidentate chelate metal ions, interacting with a variety of metal-containing enzymes, such as matrix metalloproteases, lipoxygenase, hydrolase, urease, peptide deformylase, histone deacetylase, carbonic anhydrase *etc*. [4]. HA were developed as drugs used in the following diseases: cancer, cardiovascular disease, HIV, Alzheimer's disease, malaria, hypertension, tuberculosis, glaucoma, ulcers and metal poisoning, including iron. They have also been developed as insecticides, antioxidants, anticorrosive agents and siderophores [4].

A number of HA derivatives are different stages of clinical trials to treat a wide range of cancers such as pracinostat (HDAC inhibition activity) [3]. Some HA were approved to treat different types of cancers. Suberoylanilide HA (SAHA) was approved to treat cutaneous T cell lymphoma in 2006. Resminostat is in clinical trials to treat advanced hepatocellular carcinoma in East Asian patients [3]. The hydroxamate group is considered to be a key element in the pharmacophores of many biomolecules and is reported to be responsible for the biological activity of HA [9].

Although HA exhibit a broad spectrum of biological activities, their antimicrobial properties are generally enhanced when they are in metal chelate forms [10-12]. Although metal ions or complexes have been used in medicine since antiquity, the use of structurally well-defined metal complexes in coordination chemistry appeared mainly at the beginning of the 20th century (Pt anticancer agents, for example). Our interest in HA complexes is justified by the advantageous biological properties of the complexes compared with the ligands (HA) and metals of which they are composed.

HA complexes are formed by the interaction of an HA (ligand) and a metal ion. Their structures previously known and published show a mono- which are rarely presented (Figure 2a), bi- (Figure 2b and 2c) or tri- (Figure 2d) hydroxamato

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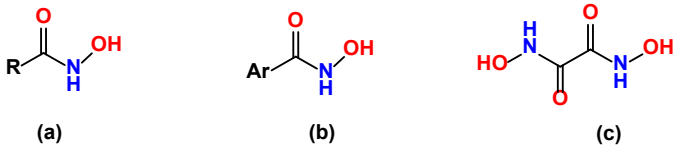


Figure 1. General structures of HA (a and b) and oxalohydroxamic acid (c).

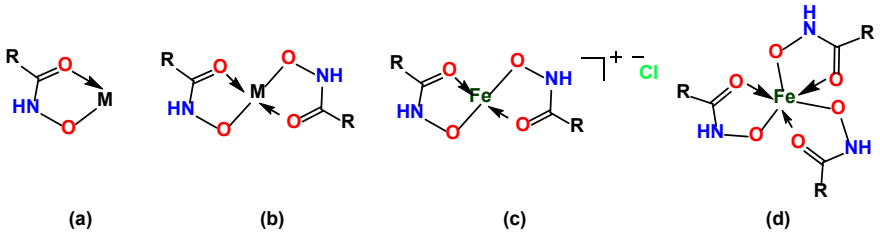
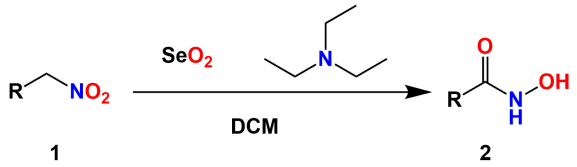


Figure 2. General structures of HA complexes with mono-(a), bi- (b and c) and tri- (d) hydroxamato (*O,O'*) coordination via C=O and deprotonated OH. M = Fe(II), Ni(II), Co(II), Cu(II) or Zn(II).



R= -H, -CH_3, -CH_2CH_3, -$(CH_2)_2CH_3$, -$(CH_2)_4CH_3$, -$(CH_2)_5CH_3$ and -$(CH_2)_6CH_3$

Scheme 1. Synthesis of HA (**2**) from nitroalkanes (**1**), triethylamine and selenium dioxide in dichloromethane.

(*O,O'*) coordination mode via carbonyl (C=O) and deprotonated hydroxyl (OH) oxygen atoms [13].

Numerous HA complexes are reported, *e.g.* tris-chelate complex of Fe(III) with aceto-HA [14] and similar complex with heptano- and octano-HA [15]. A major study about the biological activity, the structure, the synthesis properties, the relationship of structure and biological properties have been reported recently [16,17]. Therefore, this review is to dedicate the synthesis methods of HA and HA complexes with various ions metals (Fe(II), Fe(III), Ni(II), Co(II), Cu(II), and Zn(II)).

Synthetic methods for HA are not so developed as compared to the biological application of these molecules. Sometimes synthetic chemists are content with as low yields of the HA from its precursors. According to literature reports so far, there is not a particular reagent or condition that can be used for a wide variety of compounds [3]. Several methods for the preparation of HA have been used. An exploratory and descriptive study of methods for the synthesis of HA will help medicinal and therapeutic chemists to choose an optimal and rational method.

Unlike HA, the methods to synthesize their complexes are fairly similar. The number of reagent equivalents, the type of metal salt or solvent used, and the reaction conditions are the key criteria that must be sparingly observed. One of the method for synthesizing HA complexes with Fe(II) and Fe(III) was patented in 1967 [18]. Other HA complexes with Fe(III), Ni(II), Co(II), Cu(II) and Zn(II) have been synthesized, similar protocols with Bayer's [19-21]. The Failes *et al.* developed methods to synthesis HA complexes, differently from the previously described reports [14].

The particularly interesting biological activities of HA and their complexes justify my interest in this family of chemical compounds. In this review, I will therefore present and discuss the methods used to synthesize these chemical compounds.

2. HA synthesis methods

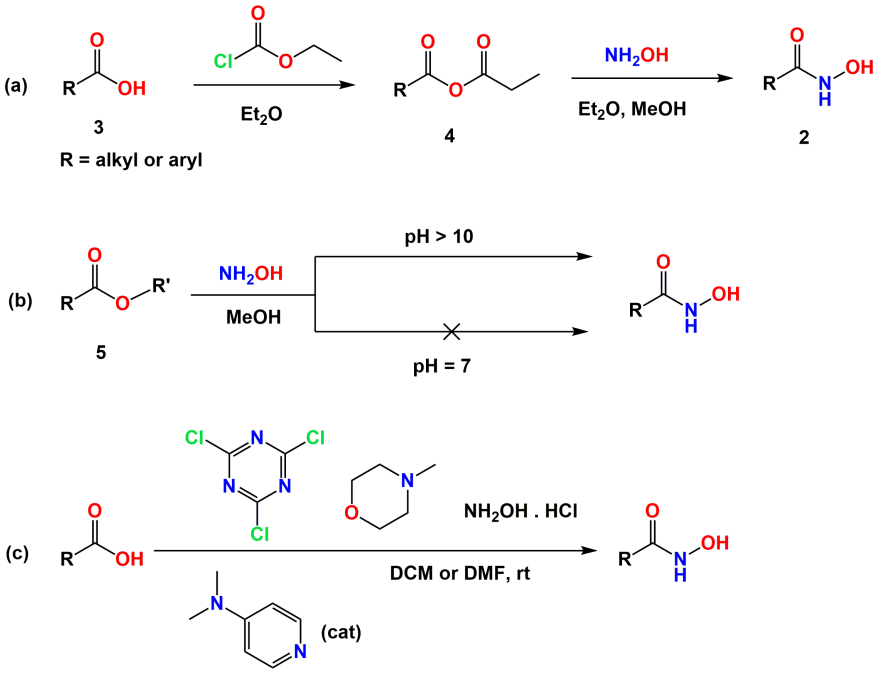
A number of strategies have been developed to synthesize HA, for instance, direct conversion of nitroalkanes to HA [22-24], the reaction of carboxylic acids [25-28], their esters, anhydrides [22,29-32] or chlorides [33-36] with hydroxylamine (or substituted hydroxylamines) or with *N,N,O*-tris (trimethylsilyl)hydroxylamine and finally the transformation of aldehydes or lactones into HA [22,35]. According to the nature of the starting reagents, the reported HA synthesis methods in the literature can be classified into three categories.

2.1. Synthesis of HA from nitroalkanes

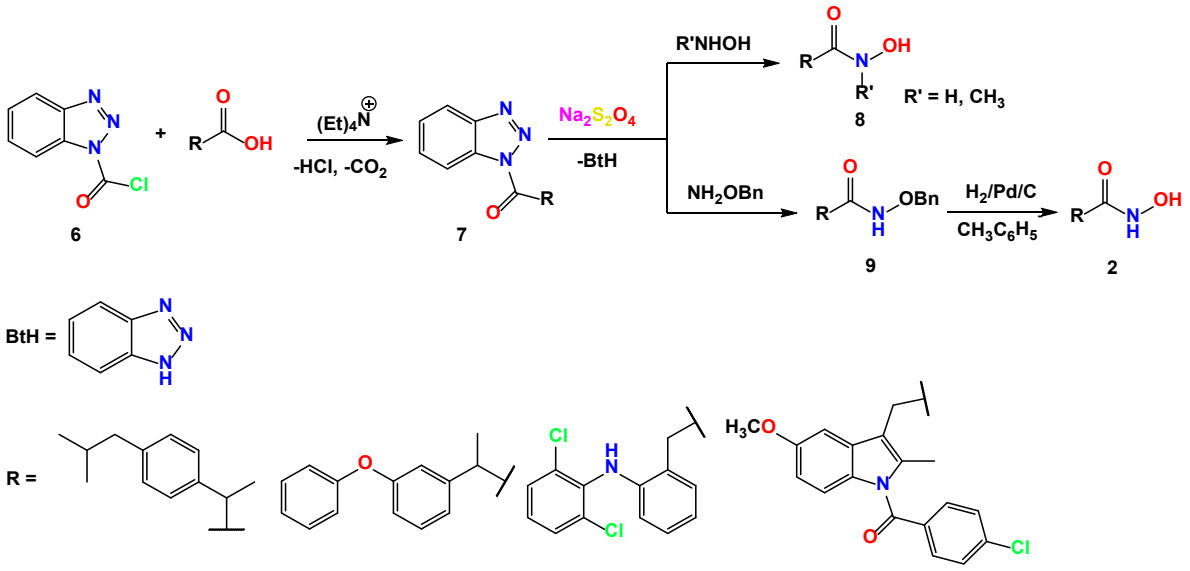
The direct conversion of primary nitroalkanes to HA is carried out with selenium dioxide in the presence of triethylamine in dichloromethane (DCM) with a yield of 63-76% [24]. A 1:1:2 molar ratio of nitroalkane (**1**), selenium dioxide and triethylamine, respectively, was used (Scheme 1). By varying the ratio of reagents to 1:2:2 or 1:1:1, mixtures of HA (**2**) and nitrile activation are formed in variable proportions [24], the latter representing a by-product that will then have to be disposed [23].

2.2. Synthesis of HA from carboxylic acids, their esters, anhydrides, chlorides or lactones

A one-step approach to the preparation of HA has been described using ethyl chloroformate as the carboxylic acid (**3**) activator under neutral pH conditions, with a yield of between 81 to 95% (Scheme 2a). Unlike compound **3**, the reaction of hydroxylamine with esters (**5**) take place under alkaline conditions (pH > 10) (Scheme 2b) [27]. Then, the method was applied to a wide range of aliphatic and aromatic carboxylic acid derivatives containing the hydroxyl, halogen, ester and other base-sensitive groups. The advantage of this method is that it is easy and cost-effective (reagents available and inexpensive).



Scheme 2. Synthesis of HA (**2**) from carboxylic acid (**3**), esters (**5**) and ethyl chloroformate or 2,4,6-trichloro-1,3,5-triazine.



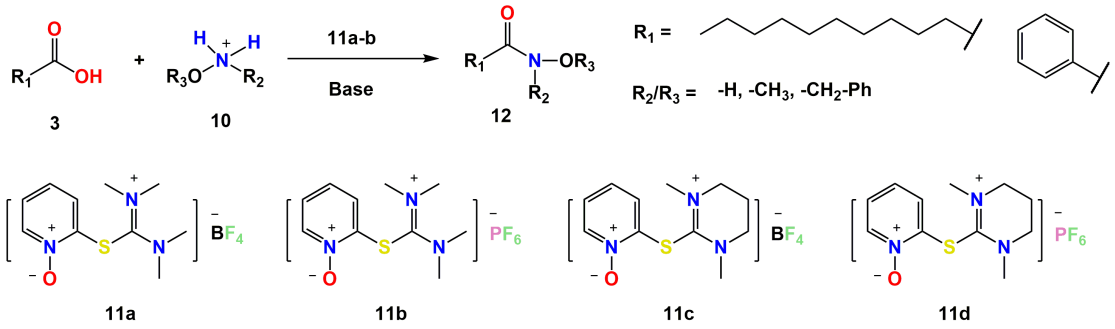
Scheme 3. Synthesis of *N*-substituted (**8**) and unsubstituted (**2**) HA from carboxylic acid with 1-benzotriazole carboxylic acid chloride (**6**).

However, ethyl chloroformate is water-sensitive and very irritating, particularly to the respiratory system and eyes [26]. Another simple, mild and high yield (80-98%) synthesis method is based on compound **3** treated with 2,4,6-trichloro-1,3,5-triazine (TCT), *N*-methylmorpholine, dimethylaminopyridine (DMAP) catalyst and hydroxylamine hydrochloride in dichloromethane (DCM) or dimethylformamide (DMF) (Scheme 2c) [26].

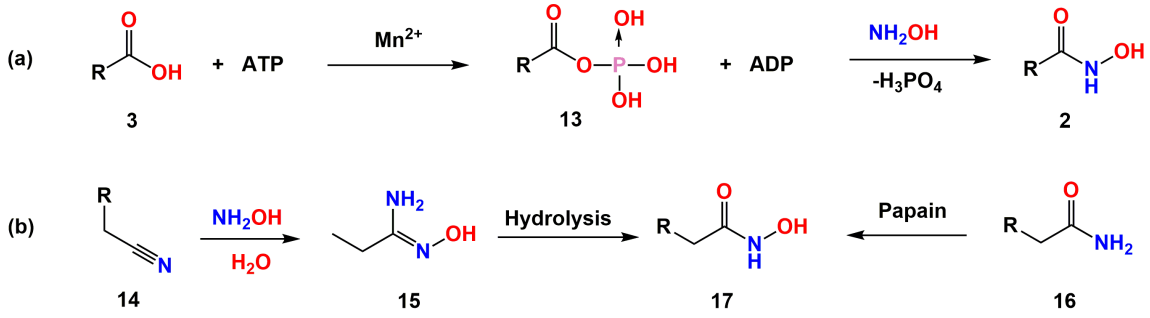
Furthermore, a method of synthesizing HA was also developed by the reaction of 1-benzotriazole carboxylic acid chloride (**6**) with compound **3** by two steps with a yield of between 40 and 90% [28]. The benzotriazolides (**7**) first were converted to *N*-substituted HA (**8**) or *O*-protected derivatives (**9**) reacted with hydroxylamine (NH_2OH), *N*-methylhydroxylamine (CH_3NHOH) or *O*-benzylhydroxylamine (NH_2OBn). A stoichiometric excess (5 equivalents) of hydroxylamine is required to achieve full conversion. Compound **9** were converted to unsubstituted HA by catalytic hydrogenation (Scheme 3).

Thiouronium salts (**11a-d**) based on 2-mercaptopyridone-1-oxide (**10**) are reagents for compound **3** synthesis with the easy, clean and direct preparation of HA and their derivatives in high yields ranging from 60 to 95% (Scheme 4) [25].

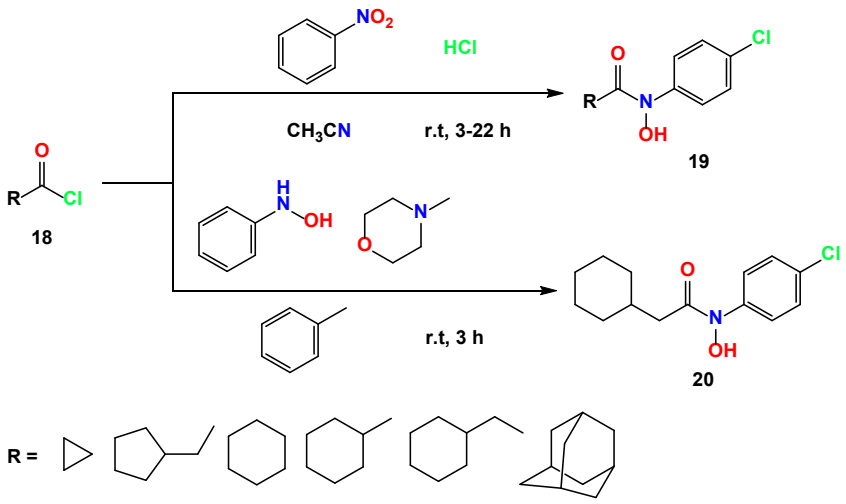
HA is also enzymatically synthesized using compound **3** in the presence of adenosine triphosphate (ATP) [37]. Enzymatic trans-amidations (proteinases such as papain) were also reported, transforming an amide (**16**) into HA [38,39]. The reaction of HA formation from compound **3** in the presence of ATP was took place even in the absence of enzyme, in the presence of manganous ions (Scheme 5a) [40,41].



Scheme 4. Synthesis of HA (**12**) from carboxylic acid (**3**) and thiouronium salts (**11a-d**) based on 2-mercaptopyridone-1-oxide (**10**).



Scheme 5. Synthesis of HA (**2** and **17**) from carboxylic acid (**3**), nitrile (**14**) or amide (**16**), enzymatically or in the presence of Mn^{2+} ions.



Scheme 6. Synthesis of cycloalkyl-*N*-aryl-hydroxamic acids (**19** and **20**) from acid chlorides (**18**) and nitrobenzene.

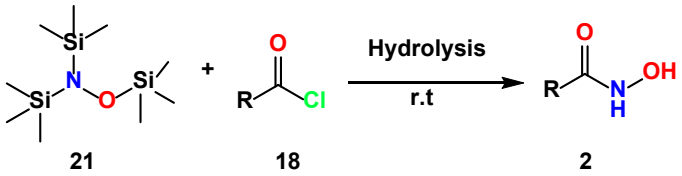
The formation of HA can be produced by the action of hydroxylamine on: diacylamides or polyacrylonitrile in aqueous medium, which transforms the CN groups (**14**) into amidoxime groups -C(NH_2)=NOH (**15**); these are transformed by hydrolysis into HA (**17**) (Scheme 5b) [42,43].

A more selective synthetic approach using acyl chlorides (**18**) and nitrobenzene as starting reagents was applied for the synthesis of cycloalkyl-*N*-aryl hydroxamic acids (**19** and **20**) (Scheme 6) [34] with a low yield (1-9%). This could be explained by decomposition of the nitrobenzene and formation of the corresponding non-halogenated HA analogues. Changing the synthesis conditions replaced with other solvents such as methylene chloride or anhydrous toluene, or changing the temperature (0 °C) did not improve the reaction yields [34].

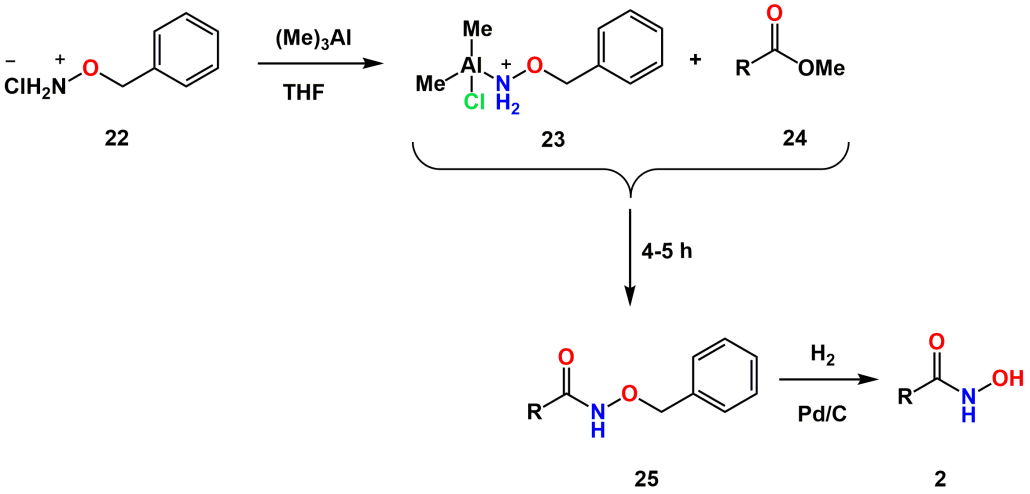
Acrylo-, propiono- and valero-hydroxamic acids were synthesized from their corresponding compound **18** and *N,N,O-tris*(trimethylsilyl)hydroxylamine (**21**) under nitrogen reaction condition in 76% yield (Scheme 7) [36]. However, this method of synthesizing HA is intended for analytical rather than preparative purposes.

The method using *o*-benzylhydroxylamine hydrochloride (**22**) treated by trimethylaluminium in THF to obtain the compound **23**. The latter is refluxed with an ester (**24**) previously dissolved in benzene *in situ* to give *o*-benzylhydroxamate (**25**), which is then deprotected with hydrogen over palladium charcoal (Pd/C) to give HA (**2**) (Scheme 8) [31]. The yields of the products obtained are between 65 and 99%.

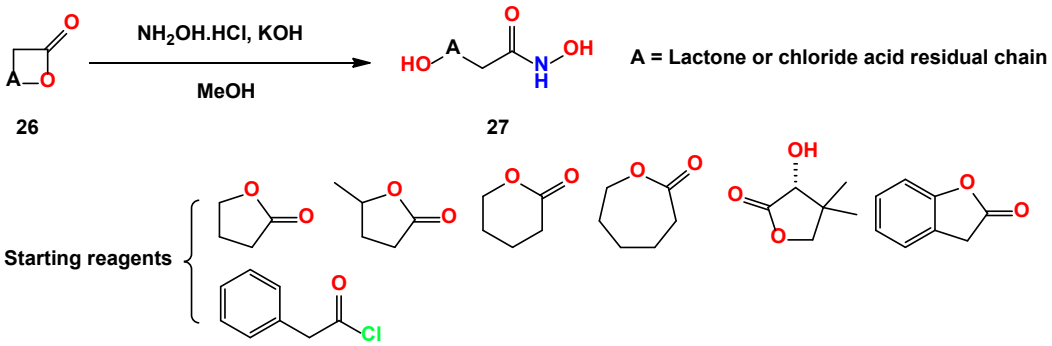
A method for preparing HA (**27**) using hydroxylamine by opening a lactone (**26**) or acyl chloride has also been described [44-46]. This synthesis was explored for a compound obtained from γ-valerolactone (starting reagents) (Scheme 9) in yields of 35% [35].



Scheme 7. Synthesis of acrylo-, propiono- and valero-hydroxamic acids from acid chlorides (**18**) and *N,N,O*-tris(trimethylsilyl)hydroxylamine (**21**).



Scheme 8. Synthesis of HA (**2**) from *O*-benzylhydroxylamine hydrochloride (**22**) and esters (**24**).



Scheme 9. Synthesis of HA (**27**) by opening lactones (**26**) or acyl chloride.

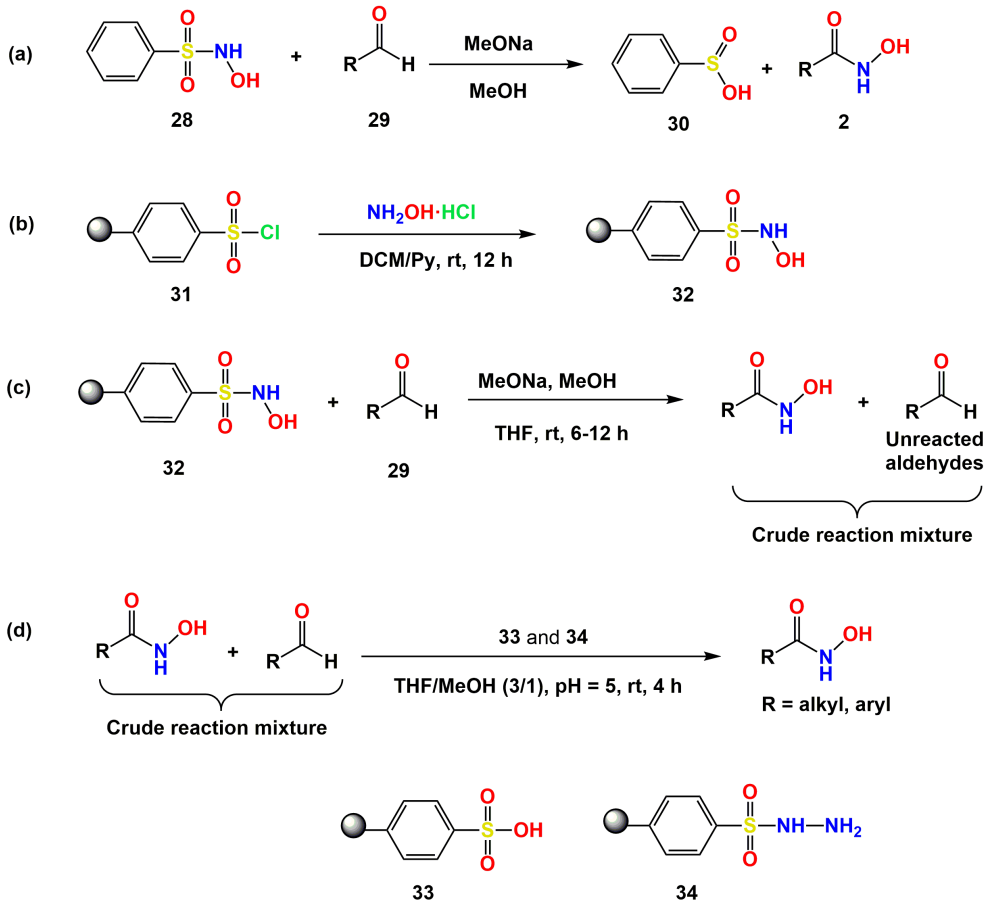
2.3. Synthesis of HA from aldehydes

In 1896, Angeli and Rimini discovered that *N*-hydroxybenzenesulphonamide (**28**) was used form HA in low yields treated with aldehydes (**29**) in the presence of a strong base in MeOH (Scheme 10a). The disadvantage of the reaction is that it gives a by-product: benzenesulfinic acid (**30**). Due to the by-product **30** formation resulted to the impurity, the Angeli-Rimini reaction was limited. It can be overcame by using the compound **28** in the solid phase (**31**), facilitated the purification of HA [47]. The *para*-toluenesulphonyl polystyrene chloride (**31**) (Scheme 10b) [48] contacts with a solution of $NH_2OH{\cdot}HCl$ in a DCM/pyridine mixture for 12 h to synthesis compound **32.** The latter reacted with aldehyde **29** to produce a crude mixture (HA and unreacted aldehyde **29**). Compounds **33** and **34** treated with the crude mixture allow the HA formed to be purified by eliminating the excess of compound **29** (Scheme 10c and 10d) in almost quantitative yields [47]. Considering the expensive reagents, some methods for solid-phase syntheses of HA and their derivatives are not well commercially available [49-55].

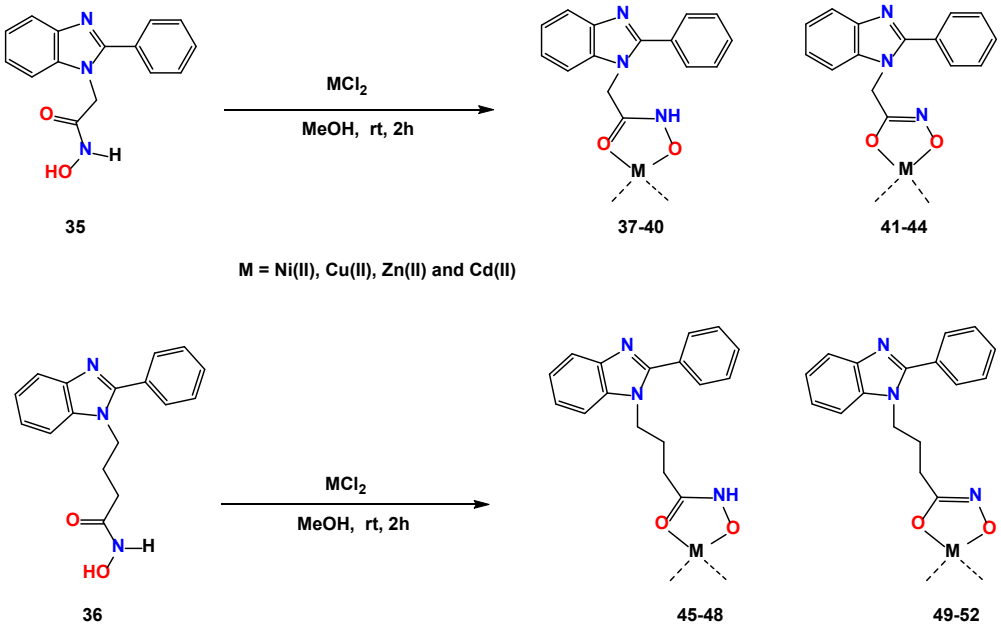
3. HA complexes synthesis methods

Similar with the HA synthesis, the HA complexes were also obtained. The main differences for these two group compounds are the reagent equivalents number, the metal salt types or the solvent, or the reaction conditions [14,18-21]. In the literature, for the most of the HA metal complexes, their ligands are keto form and coordination occurs through carbonyl oxygen and deprotonated OH group (*O,O*). Complexes of HA including enol form can be prepared under custom conditions (Scheme 11) [56], metal-ligand (M:L) ratio of M^{2+} complexes is 1:2 generally ($(R\text{-}CO\text{-}NHO)_2M$) (Scheme 11). When M:L ratio is 1:1, the coordination is completed by hydroxyl group and water molecules ((R-CO-NHO)M(OH)) [56]. Although the works of Adiguzel *et al*. report the existence of complexes with M:L ratios of 1:1, it should be emphasized that their structures are not indicated, unlike other complexes of the 1:2 or 1:3 type [56].

Rarely, some 1:1 complexes form by using enol configuration of the ligands and the product's formula is probably (R-CO-NO)M. Ni(II), Cu(II), Zn(II) and Cd(II) complexes of 2-phenylbenzimidazole-*N*-acetohydroxamic acid (**35**) and 2-phenylbenzimidazole-*N*-butanohydroxamic acid

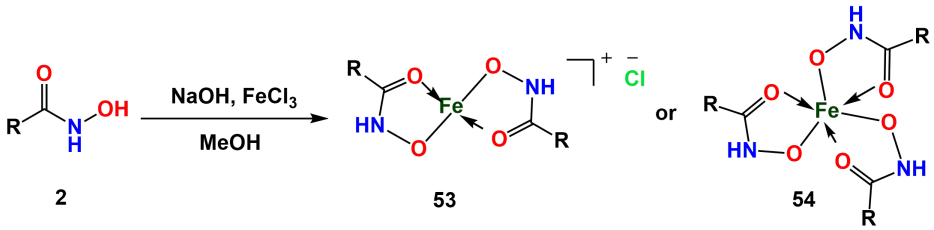


Schema 10. Synthesis of HA (**2**) in the solid phase from *N*-hydroxybenzenesulfonamide (**28**) and aldehyde (**29**).

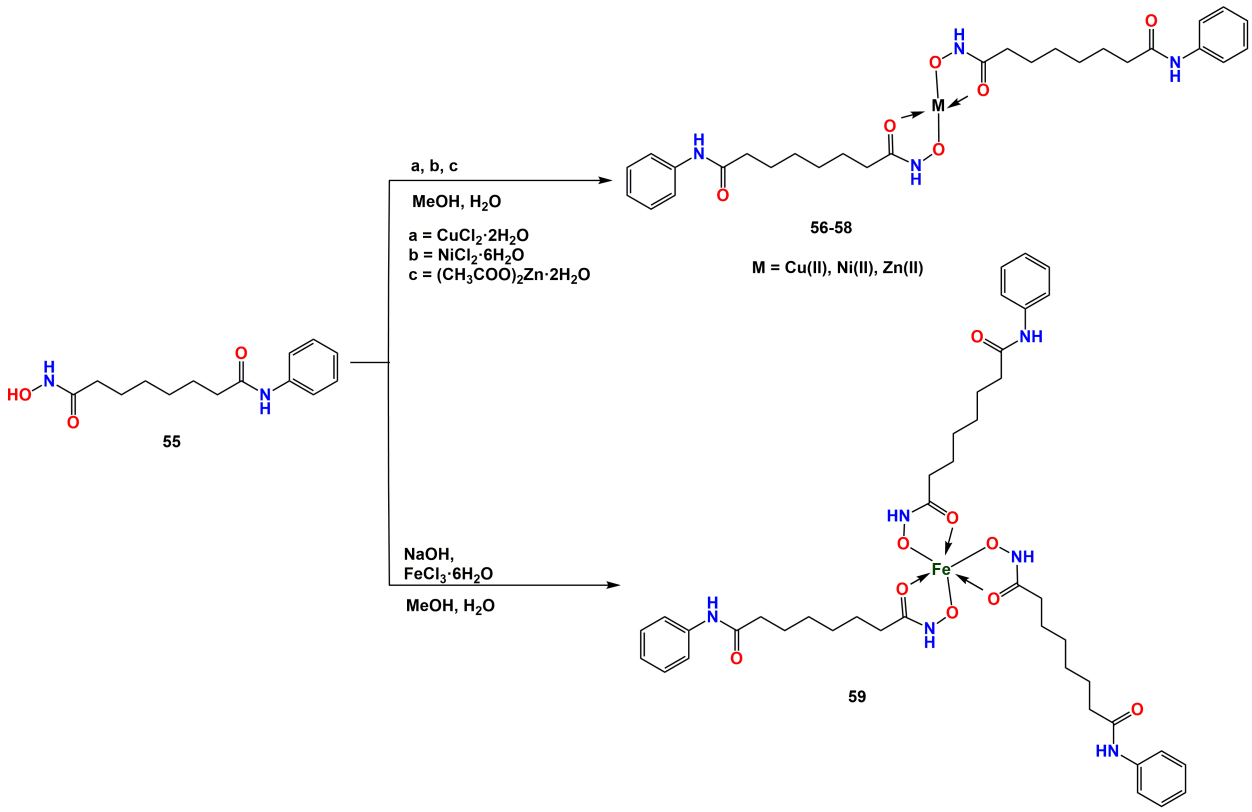


Scheme 11. General structures of complexes of Ni(II), Cu(II), Zn(II) and Cd(II) (**37-52**) from 2-phenylbenzimidazole-*N*-acetohydroxamic acid (**35**) and 2-phenylbenzimidazole-*N*-butanohydroxamic acid (**36**).

(**36**) were synthesized. One equivalent of compound **35** or **36** were dissolved at MeOH solution and mixed with one equivalent KOH. Then the solutions were stirred at room temperature. After 15 min, MCl_2 salts (M = Cu, Ni, Zn and Cd) that dissolved in water were added and stirred for 2 h. The products were filtered off, washed with H_2O, MeOH, and Et_2O and dried over P_4O_{10} [56].



Scheme 12. Synthesis of Fe(III) complexes (**53** and **54**) from aceto-, capro-, benzo-, alanino- and glutamino-hydroxamic acids (**2**).



Scheme 13. Synthesis of Cu(II), Ni(II), Zn(II) and Fe(III) complexes (**56**-**59**) from vorinostat (**55**).

The particularity of this synthesis of complexes **37**-**52** (yield 65-67%) is the formation of complexes in which the hydroxamate forms (**37**-**40** and **45**-**48**) and hydroximic forms (**41**-**44** and **49**-**52**) are observed. However, the authors showed from this study that bound HA preferred the enol form in the complexes in most cases (**41**-**44** and **49**-**52**) [56].

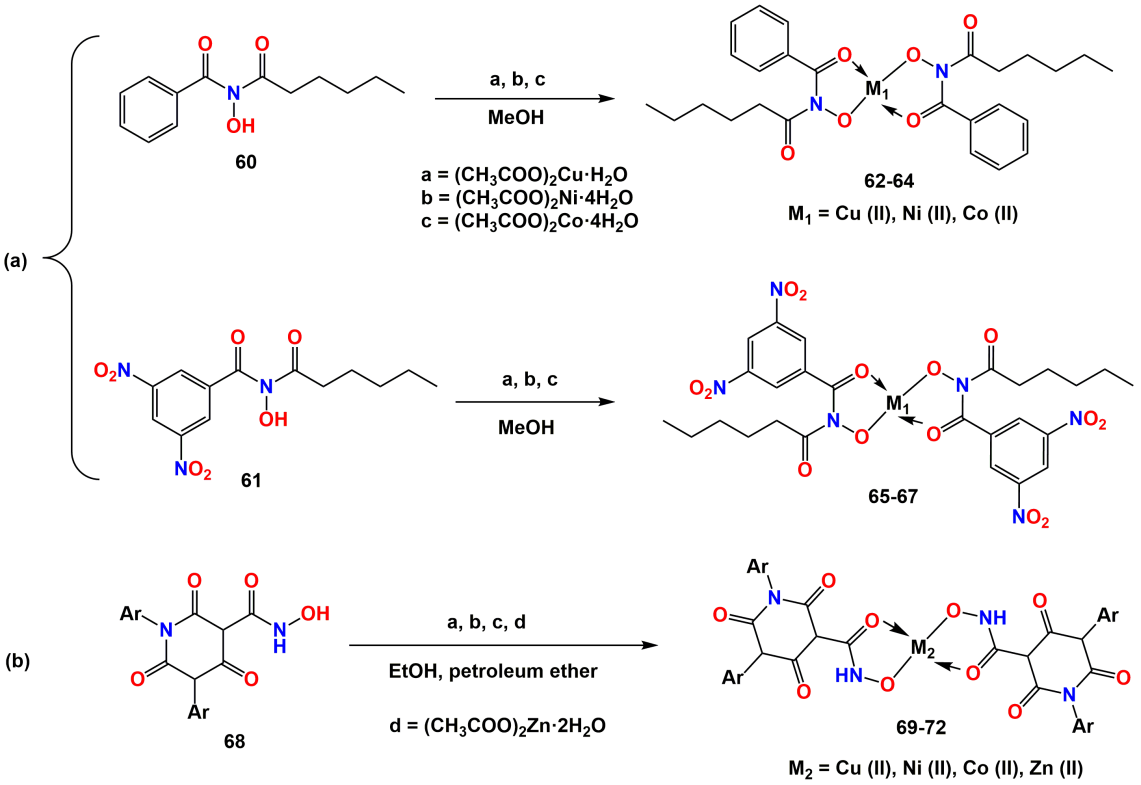
One patented method involves the treating 2 or 3 equivalents of compound **2** with a formula R-CO-NH-OH (R = CH_3, $CH_3(CH_2)_4$, $MeCH(NH_2)$ or $HO_2CH_2CH_2CH(NH_2)$) with one equivalent of $FeCl_3$ in the presence of two equivalents of NaOH (1 M) in MeOH solution (Scheme 12). Recrystallisation must be performed in a MeOH-Et_2O mixture, followed by washing with Et_2O and drying at 60 °C/12 mmHg over P_2O_5 to give fine dark brown crystals (**53** and **54**) in 50% yield [18].

Unlike the work of Adiguzel *et al*. where the yields are higher [56], Bayer's synthesis does not report the formation of complexes where the enol form of the HA is bound to the coordinating metal. In addition, the formation of complexes with a 1:1 M:L ratio is not reported in this study.

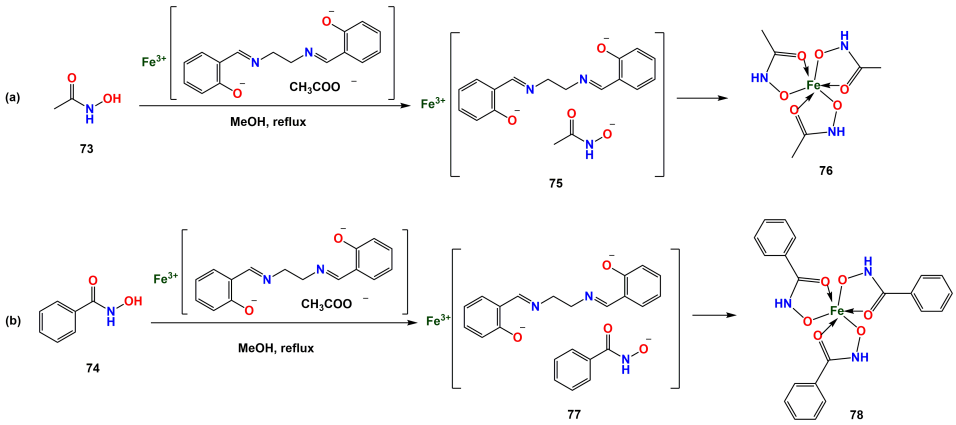
Vorinostat metal complexes were synthesized by dissolving the vorinostat (**55**) in water or in MeOH/water mixture (1:1, *v*/*v*) by adding to an aqueous solution with metal salts ($FeCl_3·6H_2O$, $CuCl_2·2H_2O$, $NiCl_2·6H_2O$ or $(CH_3COO)_2Zn·6H_2O$) and a 10% aqueous KOH solution to bring the pH to between 3.5 and 6.5. This method gave *bis*-hydroxamato Cu(II), Ni(II), Zn(II) and *tris*-hydroxamato Fe(III) complexes, respectively (**56**-**59**) in yields of 36, 86, 60 and 32%, respectively (Scheme 13) [20].

We can see from this synthesis that the types of complex synthesized using the same method have different yields. Complex **59** (Fe(III)) has the lowest reaction yield. The complexes **57** (Ni(II)) and **58** (Zn(II)) formed have almost quantitative yields. In our opinion, this difference in yields obtained with this method may not be related to the starting reagents, but rather to the protocol used during the synthesis. In this synthesis, complexes with M:L molar ratio of 1:1 were not synthesized.

The HA complexes with six chelates Cu(II), Ni(II) or Co(II) (**62**-**67**) were synthesized using HA **60** or **61** and the Cu(II), Ni(II) and Co(II) acetate salts (Scheme 14a). In addition, these metal salts and Zn(II) acetate were used with compound **68** for the preparation new four complexes **69**-**62** (Scheme 14b) [21]. Unlike previous methods where the starting reagents were



Scheme 14. Synthesis of Cu(II), Ni(II) and Co(II) complexes (**62-67**) from *N*-caproyl-(**60**) and 3,5-dinitro-*N*-caproylbenzohydroxamic acid (**61**) and Cu(II), Ni(II), Co(II) and Zn(II) complexes (**69-72**) from 2,4,6-trioxo-1,3-di-p-tolyl-1,2,3,4,5,6-hexahydropyrimidine-5-hydroxamic acid (**68**).



Scheme 15. Synthesis of Fe(III) complexes (**76** and **78**) from HA and a solution of Fe(III) *N,N′*-bis(salicylidene)-ethylenediamine) acetate.

metal chlorides (Schemes 11-13), in this case metal acetates were used to synthesize the complexes **62-72** (Scheme 14).

The way for Fe(III) complexes were synthesized by another method different from those described previously from the following HA: *N*-hydroxyacetamide (**73**) and *N*-hydroxybenzamide (**74**). The solution of Fe(III) *N,N′*-bis(salicylidene)-ethylenediamine) acetate in MeOH was added a solution of compound **73** in MeOH. The dark purple solution turned red and after several minutes a dark precipitate was formed (**75**, yield: 70%). The filtrate was left to evaporate slowly [14]. Red crystals were formed after several days (**76**, Scheme 15a). The synthesis of complex **78** from compound **74** (Scheme 15b) proceeded in a similar manner to that used for complex **76** in 89% yield. The special feature of this method is that the acetate ligand in the starting material acts as a suitable base to promote the deprotonation of HA.

4. Conclusion

In the present review, various methods to synthesis HA and their complexes were summarized and discussed to select the most optimal and rational for compounds synthesis. Multi-step synthesis strategies requiring a high purification can reduce reaction yields. A one- or two-step synthesis approach with virtually quantitative yields and selectively pure products is to be preferred. The methods described by Reddy *et al.* (synthesis of HA) [27] and those patented by Bayer (synthesis of HA complexes) [18] used in our previous work were the optimal and rational approaches.

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