A mild alkaline hydrolysis of *N*- and *N,N*-substituted amides and nitriles

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Abstract

A mild protocol for the alkaline hydrolysis of secondary and tertiary amides in non-aqueous conditions, by the use of NaOH in methanol/dichloromethane or methanol/dioxane (1:9) at room temperature or under reflux, has been developed and a plausible reaction mechanism is discussed. Primary amides are hydrolyzed much slower than with the classical procedure, while nitriles are converted selectively to primary amides.

Keywords: Alkaline hydrolysis, amides, *N*-substituted amides, nitriles, imidates, anhydrous conditions, protection

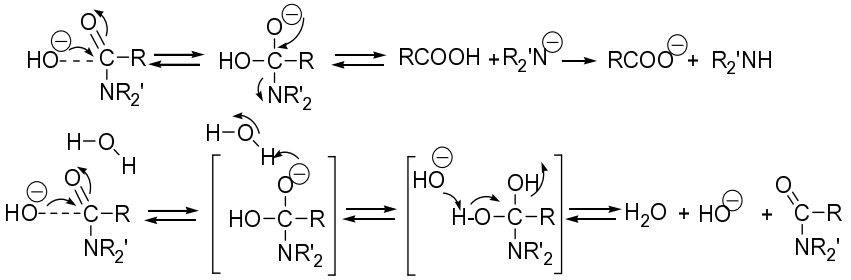
Introduction

Amide derivatives constitute important moieties in many pharmaceutical and biologically active molecules. Hydrolysis of an amide, a nitrile or an ester functional group is a very common transformation in organic synthesis with many applications and a common way to prepare carboxylic acids. In general, nitriles and amides are exceptionally stable to acid and basic hydrolysis and classically they are hydrolyzed under vigorous reaction conditions and long reaction times[1-3] by heating in the presence of mineral acids or concentrated solutions of alkali hydroxides (10-40%), which can sometimes cause undesirable side reactions and low yield. Tertiary amides are very difficult to be cleaved and in most cases stronger conditions are required than for primary and secondary amides. Nitriles are hydrolyzed first to amides and further to carboxylic acids and ammonia with even more strong reaction conditions.

The hydrolysis of amides and nitriles is a well studied reaction and numerous methods have been developed.[4-14] Among them, the use of sodium peroxide[4] and of phthalic anhydride[5] for the amide hydrolysis have been described, while nitriles can also be converted to amides by catalyzed hydration,[6-9] enzymatically[10] and on unactivated alumina.[11] Ames and Islip in their

work,[12] described the use of *N*,*N*-dimethylamide as a protecting group for long-chain ω-acetylenic acids. The amide achieved by the reaction of the appropriate acid chloride and dimethylamine, was hydrolyzed under vigorous alkaline conditions, with KOH/H_2O in refluxing 2-methoxyethanol. Confalone et al., during the total synthesis of biotin[13] in the presence of more active sites, protected the carboxylic group as its piperidide, for the removal of which vigorous hydrolysis conditions were required. Gassman et al. succeeded to hydrolyze tertiary amides using two equivalents of the strong base t-BuOK[14] in diethyl ether and one equivalent of water at room temperature, while primary and secondary amides were extremely resistant under the same conditions.

The mechanism of the alkaline amide hydrolysis has been intensively investigated.[14-21] It is similar to that of the esters, with the exception that the tetrahedral intermediate, formed after the addition of the hydroxide, could regenerate the amide than give the hydrolysis products. The loss of the hydroxide anion is the thermodynamically preferred route and the accompanying oxygen exchange is generally faster than hydrolysis (Scheme 1).[15-19]



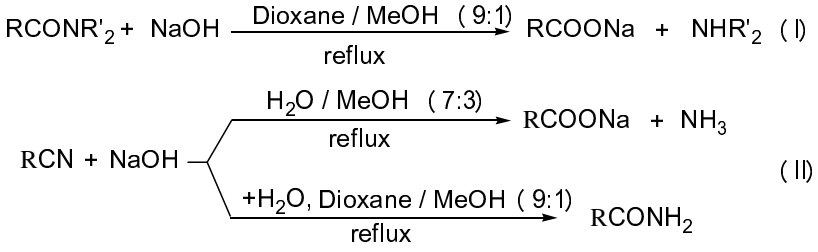
Scheme 1. Alkaline hydrolysis reaction and oxygen exchange (where R' = H, alkyl, aryl).

We previously developed a very mild and rapid procedure for an efficient alkaline hydrolysis of esters in non aqueous conditions[22] by the use of NaOH in dichloromethane /methanol (9:1) as the solvent. That "anhydrous" hydroxide in aprotic solvent proved to be an excellent reagent for ester hydrolysis. The facility of this process suggested to us that similar reaction conditions might operate also for the basic hydrolysis of similar substrates. Changing the traditional protic solvents, used in hydrolysis reactions, to less polar aprotic solvents, that do not stabilize the reactants, seemed to be a good modification, since the relatively unsolvated hydroxide acts as a stronger nucleophile. Procedures allowing simple and mild reactions, without large excess or high concentrations of the reagents, avoiding undesirable side reactions, are very helpful in organic synthesis. On the basis of these data, we considered to use the same protocol as an efficient and mild hydrolysis process of amides and nitriles in non aqueous conditions.

Results and Discussion

In order to establish our methodology, we performed the alkaline hydrolysis of a range of amides

and nitriles using a methanolic solution of NaOH in a less polar aprotic solvent. As short reaction times are desired and heating reduces the reaction time for the amide hydrolysis, we replaced dichlororomethane (DCM, bp 40 °C) with THF (bp 66 °C, MeOH/THF 1:9), or especially with dioxane (bp 101 °C, MeOH/Diox. 1:9) under reflux in order to speed up. From the results summarized in Table 1, it is obvious that the applied protocol works efficiently with *tert*- amides and *sec*-amides to carboxylates and amines, and with nitriles to primary amides (Scheme 2). This methodology is not successful with primary amides, for which the classical reaction conditions give better results.



Scheme 2. Reactions for the alkaline hydrolysis of amides (I) and nitriles (II).

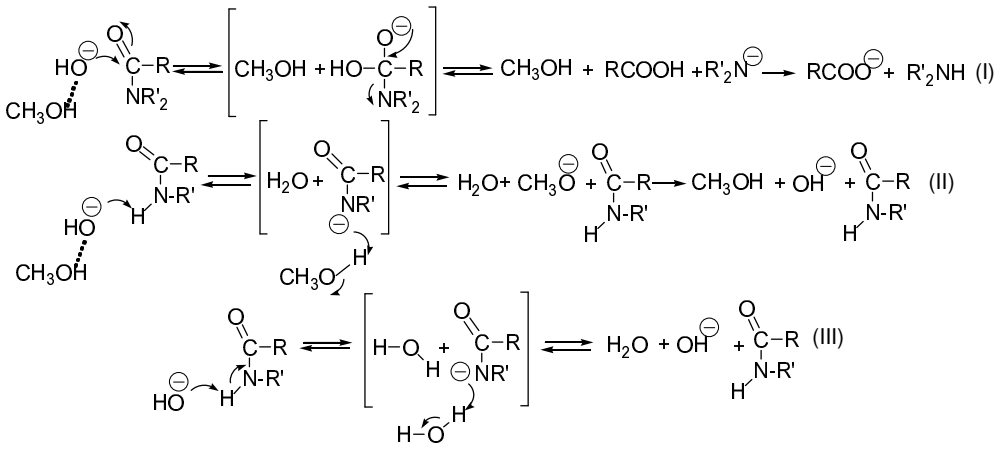
As it is known, the rate of the alkaline hydrolysis depends on both steric and electronic factors. Bulky substituents show steric hindrance and electron donating groups on the acyl moiety decrease the electrophilicity of the carbonyl carbon or of the cyano group and lower the reaction rate, while electron withdrawing groups increase the electrophilicity and the reaction rate. On the other hand, substituents on the amine moiety stabilizing the amide anion NR_2^- leaving group, increase the reaction rate.

We realized, as expected, that the hydrolysis rate of aryl amides is slower than that for aliphatic amides. Moreover, the hydrolysis rate is accelerated with the reaction temperature, the excess and the concentration of NaOH. It is of interest to note that nicotinamide (**2**) is hydrolyzed easier than benzamide (**1**), due to the pyridyl nitrogen, while the amides $CH_3CONHPh$ and CH_3CONMe_2 (**3** and **5**) are hydrolyzed in a shorter time than PhCONHPh and $PhCONMe_2$ (**4** and **6**), respectively, due to the acetyl moiety. The *tert*-amides (**5**-**13**) are hydrolyzed without difficulty comparing with *sec*-amides (**3** and **4**), especially entries **11**-**13**, as expected, depending on the electron withdrawing phenomena of the *o*- and *p*-nitro substituents and the acyl moieties. The most rapid hydrolysis experiment was that of the *N*-phenyl-*N*-2,4-dinitrophenylacetamide $CH_3CON(Ph)\{2,4\text{-}(NO_2)_2C_6H_3\}$ (**11**), where the reaction solution changed immediately its colour from light yellow to bright red, followed by the amides $CH_3CON(Ph)(2\text{-}NO_2\text{-}C_6H_4)$ and $PhCON(Ph)\{2,4\text{-}(NO_2)_2C_6H_3\}$ (**12** and **13**). Importantly, the hydrolysis of *N*-acetyl L-proline (**7**) as a tertiary amide was carried out at room temperature without racemization. In this case one more equivalent of NaOH was required, due to the COOH group of the amino acid.

With our methodology, nitriles (**14-17**) are readily hydrolyzed to amides, but very slowly to the corresponding acid salts. This means that our method may allow the selective hydrolysis of a nitrile to primary amide. From the alkaline hydrolysis of benzonitrile (**14**) pure benzamide can be isolated after refluxing in NaOH/MeOH/Dioxane for about 4-5 h, while under the classical hydrolysis conditions the hydrolysis of the nitrile to amide could not be controlled and exclusive formation of sodium benzoate is completed in ~2 h. *p*-Cyanobenzonitrile (**16**) leads mainly to terephthalamide, but *p*-aminobenzonitrile (**15**) reacts very slowly, due to the electron donating *p*-amino-substituent. Interestingly, hydrolysis of the activated pyrazinecarbonitrile (**17**) after refluxing at a lower temperature with NaOH in MeOH/DCM for 3 hours gave two products, methyl pyrazinimidate (**17a**, ~70%) and pyrazinecarboxamide (**17b**, ~30%), as confirmed from their spectral data. Obviously, the nucleophile methoxide anion, formed in the reaction solution, attacked the nitrile to the corresponding imidate. Hydrolysis of benzonitrile (**14**) after refluxing with NaOH in MeOH/DCM for ~9 h afforded small amounts of methyl benzimidate(**14a**, ~40%) and benzamide (**1**, 10%), with 50% unreacted nitrile, after purification by column chromatography. It is of interest to note that the benzimidate is not isolated when refluxing in dioxane, at ~100 °C, but it has been detected only as an intermediate during the first hour of the reflux.

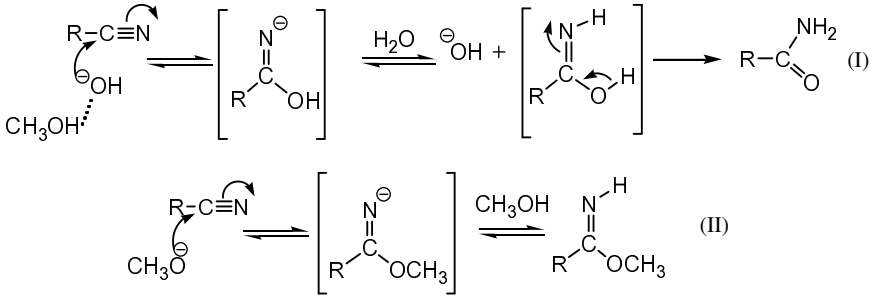
The preparation of imidates from the reaction of nitriles with alcohols in the presence of sodium alkoxide (ROH/RONa) or anhydrous hydrogen chloride (ROH/HCl) has been described several decades ago.[23-24] Recently, the isolation of the benzothiazole imidate was described very well, during the alkaline hydrolysis of 2-cyanobenzothiazole by the use of NaOH in methanol.[25]

A plausible mechanistic process, analogous to that proposed for the saponification of esters and consistent with our results and our experimental observations could be proposed for the alkaline hydrolysis of amides (Scheme 3). Nucleophilic attack on the carbonyl carbon of the tertiary amide by the hydroxide ion with the assistance of a methanol molecule and the aprotic solvent molecules crowded round the methanol, could be favored in the less polar solvent. On the contrary, the water solvated hydroxides OH^-/H_2O of the classical method are repulsed from the lipophilic *tert*-amide. Primary amides can be involved in strong intermolecular hydrogen bonding interactions, resulting in strong attractions, especially in the non polar aprotic solvents dichloromethane and dioxane, used in our methodology. As a result in these solvents the hydroxide anions are hindered and impeded to attack the carbonyls. Moreover, the hydroxides instead of attack the carbonyl can act as a base and abstract a proton from the primary or secondary amide, leading to regeneration of the amide (Scheme 3). With secondary amides, the explanation lies between the behavior of primary and tertiary amides, depending on the lipophilicity and the steric hindrance of the substrate.



Scheme 3. Suggested reaction mechanism for the alkaline hydrolysis of amides (I) and proton abstraction possibility leading back to the reactants in NaOH/MeOH/diox. (1:9) (II) or in NaOH/H_2O (III) (where R'= H, alkyl, aryl).

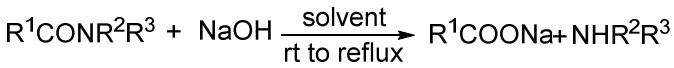
The desolvated hydroxide can also approach and attack without difficulty the nitrile carbon of a lipophilic substrate, but not easily the initially formed primary amide (Scheme 4). That way, one should be able to selectively hydrolyze nitriles to amides and avoid hydrolysis to carboxylic acids, provided that one water equivalent needed for the hydrolysis is added.



Scheme 4. Suggested reactions for the alkaline hydrolysis of nitriles to amides in NaOH/MeOH/diox. (I) and for the conversion of nitriles to methyl imidates (II).

By the addition of the methanolic solution of NaOH to the amide dissolved in dichloromethane or dioxane, a white finely dispersed precipitate of sodium salt begins to form slowly and increases with time (Table 1). The relative amounts of the reactants and the products in the reaction mixtures were estimated by thin layer chromatography, comparing with authentic samples derived from the pure products suppliers. To ensure complete hydrolysis, the reaction mixture is heated in the most cases, as indicated in Table 1. Conversion reactions were nearly quantitative, as revealed by the TLC analysis, unless otherwise noted. After the hydrolysis, the amine or the acid or both of them can be recovered.

Table 1. Alkaline hydrolysis of amides



Entry	Amide	Amide/ NaOH (N)	Solvent	Temp.	Time (% products[a])
1	$PhCONH_2$	1:4 (0.4)	MeOH/Diox. (1:9)	80 °C	~20 h
	$PhCONH_2$	1:4 (0.4)	MeOH/THF (1:9)	reflux	~30 h
	$PhCONH_2$	**1:4** (0.4)	**MeOH/water (3:7)**	**80 °C**	**~4 h[b]**
2	nicotinamide	1:4 (0.4)	MeOH/Diox. (1:9)	80 °C	~8 h (~60%)[c]
	nicotinamide	**1:4** (0.4)	**MeOH/water (3:7)**	**80 °C**	**~4 h**
3	$CH_3CONHPh$	1:4 (0.4)	MeOH/ H_2O (3:7)	80 °C	8 h (20%)
	$CH_3CONHPh$	**1:4** (0.4)	**MeOH/Diox. (1:9)**	**80 °C**	**8 h (80%)**
4	PhCONHPh	1:4 (0.4)	MeOH/ H_2O (3:7)	80 °C	24 h (~10%)
	PhCONHPh	**1:4** (0.4)	**MeOH/Diox. (1:9)**	**80 °C**	**24 h (~90%)**
5	CH_3CONMe_2	1:3 (0.3)	MeOH/DCM (1:9)	rt	~20 h
	CH_3CONMe_2	1:6 (0.3)	MeOH/ DCM (1:9)	rt	~5 h
	CH_3CONMe_2	**1:4** (0.4)	**MeOH/ DCM (1:9)**	**reflux**	**~2 h**
	CH_3CONMe_2	1:4 (0.4)	MeOH/ H_2O (1:9)	reflux	>48 h
6	$PhCONMe_2$	1:4 (0.4)	MeOH/DCM (3:7)	reflux	~30 h
	$PhCONMe_2$	**1:4** (0.4)	**MeOH/Diox. (1:9)**	**80 °C**	**7 h**
	$PhCONMe_2$	1:8 (0.4)	MeOH/H_2O (3:7)	90 °C	>24 h
7	Ac-Pro-OH	1:3 (0.4)	MeOH/ DCM (1:9)	rt	~5 h
8	PhCON(Me)Bn	1:8 (0.4)	MeOH/Diox. (1:9)	80 °C	~9 h
9	**[d]$PhCONC_4H_8$**	**1:8** (0.4)	**MeOH/Diox. (1:9)**	**80 °C**	**~7 h**
	$PhCONC_4H_8$	1:8 (0.4)	MeOH/ H_2O (3:7)	80 °C	>20 h
10	CH_3CONPh_2	1:8 (0.4)	MeOH/DCM (1:9)	rt	~20 h
	CH_3CONPh_2	**1:8** (0.4)	**MeOH/Diox. (1:9)**	**80 °C**	**30 min**
	CH_3CONPh_2	1:8 (0.4)	MeOH/ H_2O (3:7)	80 °C	~48 h

Table 1. Continued

Entry	Amide	Amide/ NaOH (N)	Solvent	Temp.	Time (% products[a])
11	**$CH_3CON(Ph)C_6H_3(NO_2)_2$**	**1:4** (0.4)	**MeOH/DCM (1:9)**	**rt**	**1-3 min**
	$CH_3CON(Ph)C_6H_3(NO_2)_2$	1:4 (0.4)	MeOH/ H_2O (3:7)	rt	15-20 min
12	**$PhCON(Ph)C_6H_3(NO_2)_2$**	**1:4** (0.4)	**MeOH/DCM (1:9)**	**rt**	**~35 min**
	$PhCON(Ph)C_6H_3(NO_2)_2$	1:4 (0.4)	MeOH/ H_2O (3:7)	rt	~2 h
13	**$CH_3CON(Ph)C_6H_4$(o-NO_2)**	**1:4** (0.4)	**MeOH/DCM (1:9)**	**rt**	**40 min**
	$CH_3CON(Ph)C_6H_4$(o-NO_2)	1:4 (0.4)	MeOH/ H_2O (3:7)	rt	1 h 50 min
14	**PhCN**	**1:10 (1.0)**	**H_2O**	**reflux**	**~2 h**
	PhCN	1:4 (0.4)	MeOH/DCM (1:9)	reflux	9 h (~40% imidate + ~10% amide)
	PhCN	1:4 (0.4)	MeOH/THF (1:9)	reflux	~6 h ($PhCONH_2$)
	PhCN	1:4 (0.4)	MeOH/Diox. (1:9)	reflux	~3 h ($PhCONH_2$)
	PhCN	**1:4 (0.6)**	**MeOH/Diox. (1:9)**	**reflux**	**55 min ($PhCONH_2$)**
	PhCN	1:4 (0.4)	MeOH/H_2O (3:7)	reflux	~4 h
15	***p*-NH_2-C_6H_4-CN**	**1:4** (0.4)	**MeOH/H_2O (3:7)**	**reflux**	**~ 8 h (~90% amide)**
	p-NH_2-C_6H_4-CN	1:4 (0.4)	MeOH/Diox. (1:9)	reflux	~ 8 h (~5% amide)
16	***p*-$C_6H_4(CN)_2$**	**1:4** (0.4)	**MeOH/H_2O (3:7)**	**reflux**	**~ 3 h { *p*-$C_6H_4(COONa)_2$}**
	p-$C_6H_4(CN)_2$	1:4 (0.4)	MeOH/Diox. (1:9)	reflux	~6 h {*p*-$C_6H_4(CONH_2)_2$}
17	pyrazinecarbonitrile	1:4 (0.4)	MeOH/DCM (1:9)	reflux	~3 h (~70% imidate + ~30% amide)
	pyrazinecarbonitrile	**1:4** (0.4)	**MeOH/H_2O (3:7)**	**reflux**	**~2 h**

[a]The hydrolysis products are the corresponding sodium carboxylate and amine or ammonia, unless otherwise noted.
[b]Bold indicates the most effective reaction conditions.
[c]Conversion reactions were quantitative, except of some samples partionally hydrolyzed under the indicated hydrolysis conditions, where the yield is shown in parentheses. All the hydrolysis products and their relative amounts in the reaction mixtures were estimated by TLC and identified by comparison with authentic samples from the pure products suppliers.
[d]$PhCONC_4H_8$ means the *N*-benzoyl pyrrolidine.

Conclusions

Amides and nitriles are very stable to basic hydrolysis in aqueous solutions and forcing reaction conditions are often needed. Primary amides are hydrolyzed more easily than secondary, tertiary amides are very difficult to be cleaved, while nitriles are hydrolyzed first to amides and further to carboxylates and amines with even more strong reaction conditions. With our methodology, in non aqueous conditions, the rank is reversed. As the lipophilicity of the amide increases, going from the primary to the tertiary amides, the rate of the alkaline hydrolysis increases, depending also on the acyl group and the amide leaving anion. This simple methodology offers an attractive alternative, available for the alkaline hydrolysis of *sec*- and *tert*-amides and for the selective hydrolysis of nitriles to primary amides. Furthermore, it may allow the protection of both, secondary amines and carboxylic acids, *via* their conversion to *tert*-amides.

Experimental Section

General. ^{1}H NMR spectra were recorded on a 250 MHz spectrometer (Bruker AMX 250) at ambient temperature using tetramethylsilane (TMS) as an internal standard. The high resolution ESI mass spectra were obtained using a Thermo Fischer Scientific Orbitrap XL spectrometer. Column chromatography was performed either on silica gel (230–400 mesh, Fluka). Melting points were measured on an Büchi 510 apparatus. IR spectra were obtained in KBr discs on a Shimadzu FTIR-84005 spectrophotometer. Elemental analyses were performed on a Heraeus CHN-Rapid Analyzer. All chemicals were used as purchased from commercial sources without further purification. Most of the hydrolysis products are known compounds and were identified by comparison with authentic samples, derived from the pure products suppliers.

Amide synthesis. The amides **11-13** had been prepared by reaction of the *sec*-amine (2 mmol) in dry THF (10 mL) with the appropriate acid chloride, CH_3COCl or PhCOCl, (1 mmol) in dry THF or dry CH_2Cl_2 at 0 °C under argon[26]. After addition was complete, the mixture was stirred for a further 1-2 h at room temperature, then refluxed for about 1 h until completion. At the end of the reaction, as inspected by TLC, the reaction mixture was cooled, evaporated to dryness and the residue was diluted with CH_2Cl_2 and extracted with H_2O, 5% $NaHCO_3$ and 5% solution of $KHSO_4$. The organic layer was dried over Na_2SO_4, concentrated in vacuo and purified by column chromatography on silica gel (CH_2Cl_2-MeOH, 9:1) to afford the desired products (overall yield 60-70%). Their identity was confirmed by NMR spectroscopy.

Amide and nitrile hydrolysis. In a typical procedure, a solution of 4N NaOH in methanol (1 mL, 4 mmol) was mixed with a solution of the amide or the nitrile (1 mmol) in dioxane or dichloromethane (9 mL) and the mixture ([NaOH]= 0.4 N) was stirred at the indicated temperature. The course of the reaction was followed by TLC analysis (SiO_2, EtOAc/hexane,

1:2) until the starting material was consumed. When the reaction was complete, the reaction mixture was cooled and evaporated to dryness, diluted with diethyl ether or CH_2Cl_2, to get the amine, and extracted with water. The aqueous layer was acidified with aqueous 1 N HCl and extracted with ethyl acetate or CH_2Cl_2 to get the acid. The organic phase was concentrated and purified by column chromatography. In the most cases the conversion was quantitative, with the relative amounts of products estimated by TLC. As indicated in Table 1, some samples were partionally hydrolyzed in the indicated time and reaction conditions (the yields determined by TLC are given in parentheses).

The classical hydrolysis process was the same, except of using water as the solvent instead of dioxane, usually methanol/water 3:7, due to the low solubility of the amide or nitrile in water.

In order to isolate the primary amide formed by the selective hydrolysis of a nitrile following the same procedure, except of adding 1-2 equiv of water, an additional step is required. After cooling, the reaction mixture was evaporated to dryness, the residue was acidified with 1N HCl and extracted with ethyl acetate. The organic phase was extracted with 5% $NaHCO_3$ to remove the acid and then dried, concentrated and purified by column chromatography.

***N*-Benzoyl pyrrolidine (9).**[27] Viscous liquid (86%, 0.15 g). ^{1}H NMR ($CDCl_3$, 250 MHz) δ 1.84-1.99 (m, 4H), 3.42 (t, 2H, *J* 6.5 Hz), 3.65 (t, 2H, *J* 6.5 Hz), 7.40 (m, 3H), 7.49−7.52 (m, 2H); ^{13}C NMR ($CDCl_3$, 63 MHz) δ 19.63, 21.58, 41.39, 44.80, 122.27, 123.44, 124.98, 132.41, 164.87; IR (KBr): ν_{max} (cm^{-1}) 1630; Anal. Calcd. for $C_{11}H_{13}NO$: C, 75.40; H, 7.48; N, 7.99; found: C, 75.28; H, 7.54; N, 7.76%.

***N*-Phenyl-*N*-2,4-dinitrophenyl-acetamide** (**11**).[28] Pale yellow solid (62%, 0.19 g), mp 148-150 °C [Lit.[27] mp 151-152 °C]; ^{1}H NMR (250 MHz, DMSO-d_6) δ 1.98 (s, 3H, Me), 7.40-7.62 (m, 6H), 8.47 (d, 1H, *J* 7.75 Hz), 8.73 (s, 1H); ^{13}C NMR ($CDCl_3$, 63 MHz) δ 23.28, 120.82, 127.69, 128.68, 129.50, 129.71, 130.58, 140.62, 141.18, 144.87, 145.62, 170.89; IR (KBr): ν_{max} (cm^{-1}) 1678, 1579, 1521, 1377, Anal. Calcd. for $C_{14}H_{11}N_3O_5$: C, 55.82; H, 3.68; N, 13.95; found: C, 55.44; H, 3.82; N, 13.79%.

***N*-Phenyl-*N*-2,4-dinitrophenyl-benzamide** (**12**). Pale yellow solid (61%, 0.22 g), mp 103-105 °C; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 7.08-7.42 (m, 11H), 8.29 (dd, 1H, *J* 2.5 and 8.75 Hz), 8.80 (d, 1H, *J* 2.5 Hz); ^{13}C NMR $CDCl_3$, 63 MHz) δ 121.15, 127.90, 128.16, 128.22, 129.34, 129.99, 130.01, 131.44, 134.02, 142.00, 142.34, 144.88, 145.46, 170.53; IR (KBr): ν_{max} (cm^{-1}), 1662, 1581, 1525, 1350; Anal. Calcd. for $C_{19}H_{13}N_3O_5$: C, 62.81; H, 3.61; N, 11.57; found: C, 62.75; H, 3.54; N, 11.68%.

***N*-Phenyl-*N*-2-nitrophenyl-acetamide** (**13**).[29] Pale yellow hemisolid (67%, 0.17 g); ^{1}H NMR ($CDCl_3$, 250 MHz) δ 2.05 (s, 3H, Me), 7.15 (d, 1H, *J* 8.0 Hz), 7.28-7.58 (m, 7H), 7.94 (d, 1H, 8.0 Hz); ^{13}C NMR ($CDCl_3$, 63 MHz) δ 23.17, 125.06, 127.24, 128.50, 128.58, 129.38, 130.04, 133.58, 135.66, 142.42, 146.28, 170.82; IR (KBr): ν_{max} (cm^{-1}) 1682, 1576, 1347; Anal. Calcd. for $C_{14}H_{12}N_2O_3$: C, 65.62; H, 4.72; N, 10.93; found: C, 65.38; H, 4.84; N, 11.06%.

Methyl benzimidate (14a).[30] White liquid (37%, 0.05 g); ^{1}H NMR ($CDCl_3$, 250 MHz) δ 3.94 (s, 3H, OMe), 7.31 (s, 1H, NH), 7.44 (m, 3H), 7.74 (dd, 2H, *J* 1.50 and 7.75 Hz); ^{13}C NMR $CDCl_3$, 63 MHz) δ 55.71, 126.69, 128.22, 130.81, 132.94, 167.83; IR (KBr): ν_{max} (cm^{-1}) 3345, 1640; Anal. Calcd. for C_8H_9NO: C, 71.09; H, 6.71; N, 10.36; found: C, 70.88; H, 6.74; N, 10.46%.

Methyl pyrazinimidate (17a). White solid (66%, 0.09 g), mp 116-118 °C; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 4.03 (s, 3H, OMe), 8.61 (dd, 1H, *J* 1.0 and 2.5 Hz), 8.66 (d, 1H, *J* 2.5 Hz), 9.07 (d, 1H, *J* 1.0 Hz), 9.19 (s, 1H, NH); ^{13}C NMR ($CDCl_3$, 63 MHz) δ 54.34, 142.92, 143.12, 144.16, 146.69, 165.73; IR (KBr): ν_{max} (cm^{-1}) 3310, 1638; Positive-ion MS**:** m/z 138.0650 $[M+H]^+$ (calcd for $C_6H_8N_3O^+$, 138.0662); Anal. Calcd. for $C_6H_7N_3O$: C, 52.55; H, 5.14; N, 30.64; found: C, 52.67; H, 5.20; N, 30.45%.

Pyrazinecarboxamide (17b). White solid (32%, 0.04 g), mp 187-190 °C [in agreement with literature data, mp 189-191 °C, see: Aldrich Catalog of Fine Chemicals, Sigma-Aldrich Chemical Company]; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 5.96 (w, 1H, NH), 7.65 (w, 1H, NH), 8.56 (dd, 1H, *J* 1.0 and 2.5 Hz), 8.78 (d, 1H, *J* 2.5 Hz), 9.42 (d, 1H, *J* 1.0 Hz); ^{13}C NMR ($CDCl_3$, 63 MHz) δ 143.30, 143.69, 145.12, 165.52; IR (KBr): ν_{max} (cm^{-1}) 3412, 3303, 1708; Anal. Calcd. for $C_5H_5N_3O$: C, 48.78; H, 4.09; N, 34.13; found: C, 48.46; H, 4.04; N, 34.26%.

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