Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Ionic hydrogenation of azines: an efficient synthesis of 1,2-dialkylhydrazines.

Dario Perdicchia[a,*]

[a]Dipartimento di Chimica, Università degli Studi di Milano, Via Golgi 19, 20133 Milan, Italy.

ARTICLE INFO

Article history:
Received
Received in revised form
Accepted

Available online

Keywords:
Azines
1,2-Dialkylhydrazines
Ionic hydrogenation
Amine boranes
Hydrazides

ABSTRACT

An efficient synthetic method of ionic hydrogenation of azine to the corresponding 1,2-dialkylhydrazines was accomplished. Reaction time was fast and isolation and purification of the 1,2-dialkylhydrazines were operationally simple. Yields were almost quantitative for most of the products with good functional group tolerance. Moreover, the byproduct of reduction gave the opportunity for the selective synthesis, *in situ*, of the mono hydrazide extending the potentiality of the synthetic method described.

1. Introduction

Hydrazine derivatives play a significant role in various applications in organic synthesis and they are the starting material for many compounds, such us heterocycles, pharmaceuticals, agrochemicals, polymers, dyestuffs, and antioxidants.[1] Although they are recognized as hazardous compounds[2] not all of them share this feature. Procarbazine (a chemotherapy medication), Hydralazine (to treat high blood pressure) and Carbidopa (management of Parkinson's disease) are some examples of hydrazines that are on the World Health Organization's List of Essential Medicines[3], the safest and most effective medicines needed in a health system. Furthermore, over 200 natural products containing a N-N bond with a vast degree of structural diversity have been reported to date showing a wide range of biological activity for these compounds.[4]

Substituted alkyl hydrazines are an important subclass that have found applications in medicinal chemistry and as intermediates in the synthesis of heterocyclic compounds but still difficult to access.[5] As mimicry of the amino group, they found application in the synthesis of peptidomimetics in which the α-carbon of one or more amino acid residues are substituted by nitrogen.[6]

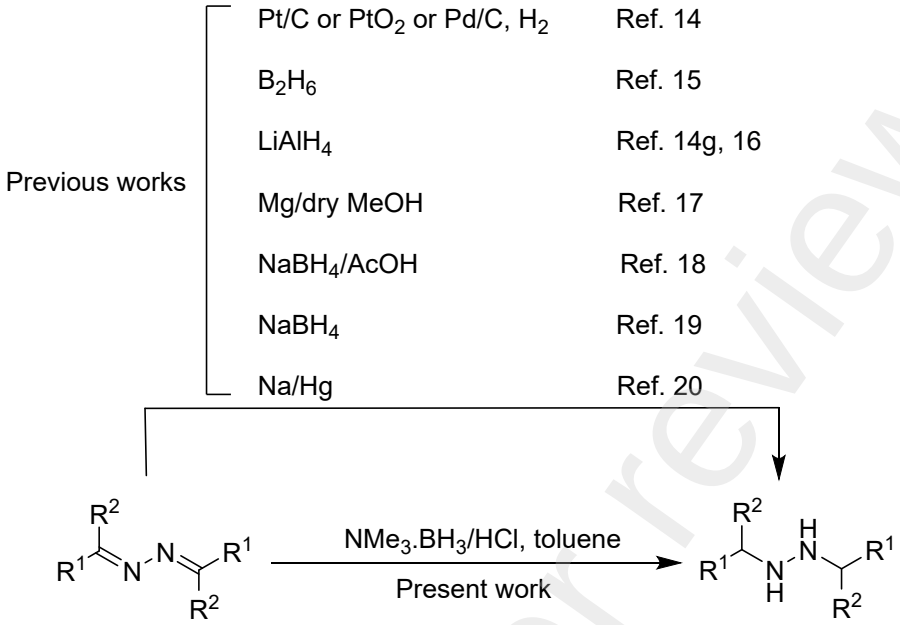
It is hardly surprising that considerable effort has been addressed to the development of efficient synthetic methods for the production of alkyl hydrazine derivatives, but some features of these compounds make demanding the task. Having four replaceable hydrogens, hydrazine can generate a huge diversity of compounds and generally a specific synthetic strategy is required for each typology. The two active nucleophilic nitrogen atoms are the source of over reactivity and worsening of the regioselectivity: for example, direct alkylation of hydrazines is a poor strategy and an extensive use of protective groups is essential.[5, 7] The weak N-N bond is susceptible of breaking under reductive conditions, for example by ammonia–borane,[8] catalytic hydrogenation,[9] diborane[10] or titanium(III) trichloride.[11]

A further difficulty is constituted by the reaction work-up since free hydrazines are quickly oxidized and even a small amount of air changes the purity remarkably:[1] usually an inert atmosphere is used during the reaction and work-up. Moreover, the hydrazine derivative has to be converted in a more stable compound such as a salt or a hydrazide[12] and the isolation of the free hydrazine gives rise to a consequent health and safety hazard.[2] Finally, hydrazines have the peculiar property to form mono and di salts using acid in excess, where both the two basic nitrogen atoms are protonated, giving an analytical result that does not correspond to a definite compound (a mixture of two salts).[13]

Azines are strategic starting compounds for the synthesis of 1,2-dialkylhydrazines as they are easily prepared from hydrazine through its reaction with aldehydes and ketones and are very stable. Furthermore, they are intermediates, on industrial scale of thousands tons, for the production of hydrazine by the Bayer ketazine process and peroxide–ketazine process, both of them oxidizing ammonia in the presence of a ketone.[1] The most widely used methods for the reduction of azines to hydrazines are: 1) by hydrogenation under metal catalysis,[14] 2) by diborane,[15] 3) by $LiAlH_4$,[14g, 16] 4) by Mg/dry MeOH,[17] 5) by $NaBH_4$/AcOH,[18] 6) by $NaBH_4$[19] and 7) by Na/Hg amalgam[20] (Scheme 1). Each method is afflicted with drawbacks described above and with a narrow scope with only a single example in mostly references.

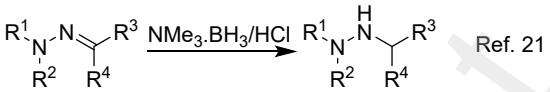
We have previously reported a synthetic method of ionic hydrogenation of hydrazones to the corresponding hydrazines (Scheme 2)[21] that addressed the main difficulties seen above. Introduction of the alkyl group is fixed as it derived from aldehyde in the synthesis of the hydrazone. Reduction using the amine–borane complex $NMe_3.BH_3$, in acid medium, is completely selective as only the C=N group is involved.

Activation of the hydrazones toward the reduction by HCl allows a very easy workup, isolating the hydrazines as safe and stable hydrochloride salts; moreover, during crystallization the mixture of mono and dihydrochloride is converted to pure mono hydrochloride by release of HCl.[13, 22]



Scheme 1. Literature and present protocols for the reduction of azines to 1,2 dialkylhydrazines

In this paper, we wish to describe the reduction of azines to the corresponding 1,2-dialkylhydrazines as a new scope for the method previously reported (Scheme2).



Scheme 2. Reduction of hydrazones to the corresponding hydrazines.

2. Results and discussion

Although hydrazones and azines appear structurally similar, opposite conjugation effects are involved (Figure 1). Hydrazones can be termed "aza-enamines" exhibiting the highest electron density on the iminic carbon[23] and showing a nucleophilic behavior; on the contrary the azine unit is a conjugation stopper[24] where the two imine bounds can be considered polar acceptor groups oriented in opposite directions making azines ideal candidates for NLO materials.

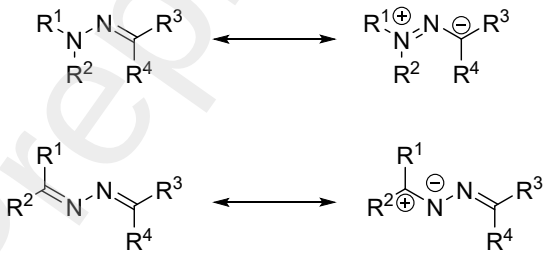


Figure 1 Resonance structures for hydrazones and azines.

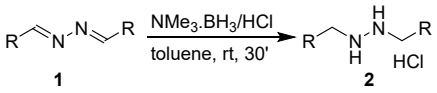
Reduction of azines, as well as hydrazones, is hampered by electron delocalization and improved by the presence of an acid as the protonation of the C=N group activates the attack of nucleophiles. The reducing agent $NMe_3.BH_3$ is well suited as source of hydride[25] under acidic condition as it is the most stable aliphatic amine borane in 1M HCl 50% aqueous ethylene glycol, it is very soluble in a wide range of protic and aprotic solvents and it is a crystalline solid which is stable indefinitely at room temperature and practically unaffected by air or moisture.[26] Although the reduction can be performed in different solvents, toluene was selected as it has a low percentage of water which is beneficial considering that azines are susceptible to hydrolysis in acidic condition. Moreover, the byproduct of reduction, $NMe_3.BClH_2$, is soluble in toluene but the products, hydrazines hydrochloride, are completely insoluble and easily isolable in pure form by filtration. In order to keep the procedure as easiest as possible, avoiding the danger of compressed gas, we prepared HCl gas[27] by slow addition of HCl 37% to H_2SO_4 98% and carrying the gas to the reaction by an empty claisen condenser (see Figure 1 in supplementary data); reaction was so fast that it was not necessary bubbling HCl in to the toluene solution but just streaming the gas on the surface of the solution.

The end of reaction was self-indicative as azines and the corresponding hydrochlorides are colored, instead products are white solids; moreover, an exothermic reaction was observed throughout the reduction. The reaction takes only few minutes but the slow flow of HCl was kept for 30 minutes for all the reactions to assure completeness. The work-up is operationally simple and with minimal waste of organic solvent. After centrifugation the crude product is resuspended with few mL of fresh toluene, recentrifuged and the solid dissolved in minimal amount of EtOH; it is reprecipitated with Et_2O, recentrifuged and the residual solvent removed by vacuum obtaining a high purity product without losses as all the purification process is inside a single centrifuge tube. The only byproduct in the crude is trace of trimethylammonium chloride derived from the reducing agent and, in case the product is necessary for a further reaction, the purification step could be skipped.

Reduction of aldazines (Table 1) was very effective with yield almost quantitative. The only exception of the 1,2-didecylhydrazine hydrochloride **2n** was ascribed to the not negligible solubility of the compound in toluene and Et_2O, as effect of its remarkable lipophilicity (however the reduction was complete). For the opposite reason, the synthesis of the hydrazine **2c** was conducted in DCM since the aldazine

1c was quite insoluble in toluene as well as the hydrochloride salt. The reaction was very selective as the nitro groups (Table 1, **2c**), the nitrile groups (Table 1, **2d**) and the conjugate double bonds (Table 1, **2m**) were not affected. In two cases (**2k** and **2p**) the stable dihydrochlorides were isolated. A 2/1 molar ratio of $BH_3.NMe_3$/azine ensured a fast and complete reaction.

Table 1 Reduction of aldazines **1** to 1,2-dialkylhydrazines **2**[a]



1 **2**

2a, 99%

2b, 98%

2c[b], 95%

2d, 98%

2e, 98%

2f, 94%

2g, 99%

2h, 98%

2i, 98%

2j, 97%

2k, 95%

2l, 96%

2m, 98%

2n, 56%

2o, 96%

2p, 98%

2q, 98%

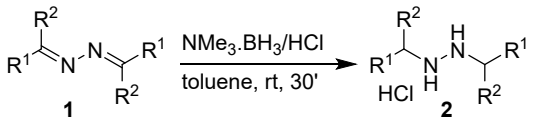
2r, 97%

[a]Reagents and conditions: aldazine **1** (1 mmol), $NMe_3.BH_3$ (2 mmol), 5 mL of toluene, room temperature, air, isolated yield. Gaseous HCl was generated by low addition of 10 mL of HCl 37% in 20 mL of H_2SO_4 98% (see supplementary data for the schematic description of the reaction apparatus).
[b]DCM as reaction solvent

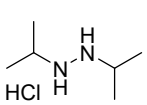
Reduction of ketazines (Table 2) was quite similar to the reduction of aldazines, with yields almost quantitative. In the synthesis of the 1,2-di(pentan-3-yl)hydrazine hydrochloride **2t** the reaction was complete, but the purification was affected by the partial solubility of the product in toluene and diethyl ether. Ketazine **1u**, bearing bulky alkyl groups, was inert in the reaction condition in accordance to the previously reported inertness to the reduction with $LiAlH_4$.[28]

As previously reported,[21, 29] the byproduct of reduction, $NMe_3.BH_2Cl$, offers the opportunity to generate, by reaction with a carboxylic acid *in situ*, a mixture of acyloxyboranes ($(RCO_2)_mBH_n.NMe_3$ with m=1-3 and n=0-2) that can effectively acylate the 1,2-alkylhydrazine hydrochloride (Table 3). A 2/3 molar ratio of $BH_3.NMe_3$/RCO_2H ensured a fast reaction with a good yield, whereas a 2/6 molar ratio did not further improve the reaction. Differently from the acylation of hydrazines with common acylating agents,[30] the reaction was completely selective without the formation of the related diacyl hydrazines side-products. The yields were susceptible to the bulkiness of the carboxylic acid obtaining good result for hydrazides **3**-**4** and a yield of 50% for the bulkier isopropyl group of hydrazide **5**; ketazines **1** were inert in the acylation step confirming this trend. Moreover, the tight steric requirement for the acylation by the acyloxyboranes could be a plausible explanation of the selectivity towards the mono acylation.

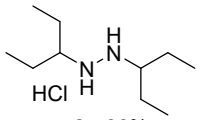
Table 2 Reduction of ketazines **1** to 1,2-dialkylhydrazines **2**[a]



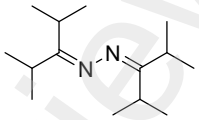
1 **2**



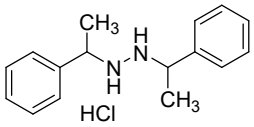
2s, 98%



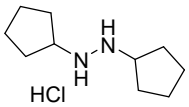
2t, 66%



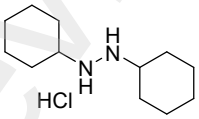
1u, n.r.



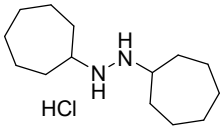
2v, 98%



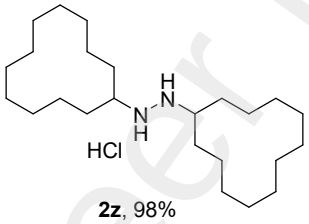
2w, 98%



2x, 95%



2y, 98%



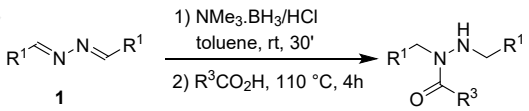
2z, 98%

[a]Reagents and conditions: ketazine **1** (1 mmol), $NMe_3.BH_3$ (2 mmol), 5 mL of toluene, room temperature, air, isolated yield. Gaseous HCl was generated by low addition of 10 mL of HCl 37% in 20 mL of H_2SO_4 98% (see supplementary data for the schematic description of the reaction apparatus).

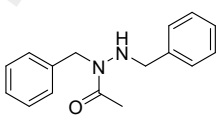
A plausible mechanism for the reduction and subsequent acylation, in accordance with the literature,[21, 29] is represented in Scheme 3. Initially, azina **1** is protonated to afford intermediate **6** that accounts for the initial change in color of the reaction mixture. Then, amine borane exchanges a hydrogen with the chlorine atom reducing the activated C=N group by hydride transfer. Hydrazone **7** repeats the sequence protonation and reduction affording hydrazine **9** and finally, the further protonation to the white precipitated of the hydrazine hydrochloride **2**.

In the acylation step, the byproduct of reduction $NMe_3.BH_2Cl$ initially reacts with the carboxylic acid to afford a mixture of acyloxyboranes and developing HCl and H_2. Finally, hydrazine hydrochloride **2** is acylated with further development of gaseous HCl and dissolution of the initial precipitate.

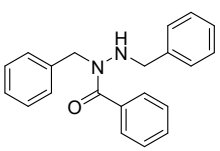
Table 3 Reduction and acylation *in situ* of aldazines **1** to N-acyl-1,2-dialkylhydrazines **3-5**[a,b]



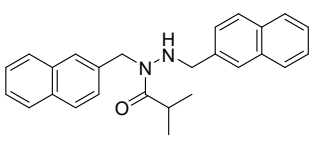
1 **3, 4, 5**



3, 81%



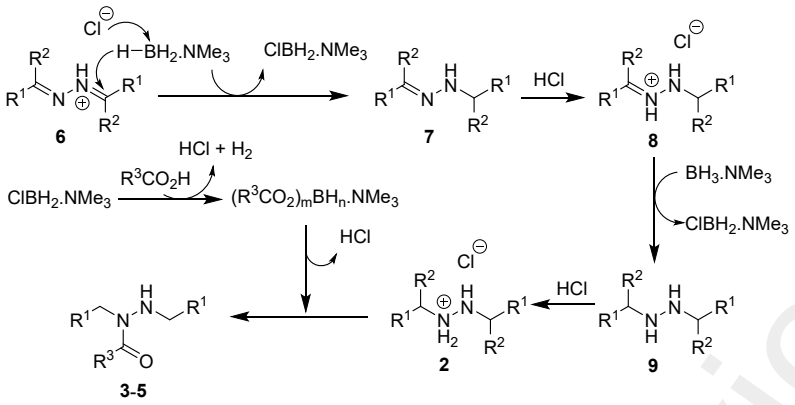
4, 83%



5[c], 50%

[a]Reagents and conditions for the reduction step: aldazine **1** (1 mmol), $NMe_3.BH_3$ (2 mmol), 5 mL of toluene, room temperature, air. Gaseous HCl was generated by low addition of 10 mL of HCl 37% in 20 mL of H_2SO_4 98% (see supplementary data for the schematic description of the reaction apparatus).
[b]Reagents and conditions for the acylation step; carboxylic acid (3 mmol), reflux for 4h, air, isolated yield.

[c]Reflux for 7h.



Scheme 3. A plausible mechanism for the reduction and acylation of azines

3. Conclusion

In summary, an efficient synthetic method was proposed for the preparation of symmetric 1,2-dialkylhydrazines starting from easily available corresponding azines. The highlights of this reaction include almost quantitative yields for most of the products, good functional group tolerance, fast reaction time, operationally simple procedure of isolation and purification of the final hydrazines. Moreover, products were isolated as hydrochloride salts, a safe and stable derivative of hydrazines. Finally, the byproduct of reduction was exploited for the selective synthesis *in situ* of the mono hydrazide extending the potentiality of the synthetic method described.

4. Experimental section

4.1. General information

All reagents and solvents employed in the present work were commercially available and used without further purification. Flash column chromatography (FCC) was performed on Merck silica gel 60 (240–400 mesh, Darmstadt, Germany) and analytical thin layer chromatography (TLC) was per-formed on Merck silica gel 60F254 (0.2 mm film, Darmstadt, Germany) precoated on aluminum foil. Spots on the TLC plates were visualized with UV light at 254 nm and staining the TLC plate with a solution of potassium permanganate. Melting points were recorded with a Büchi Melting Point B-540 apparatus and uncorrected. The IR spectra were recorded on a Perkin–Elmer FT-IR spectrum 100. The ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded on a Bruker AV 300 in the indicated solvents: for most of the products the solvent was $CDCl_3$ with the addition of few drops of CF_3CO_2H until dissolution. Chemical shifts (δ) are indicated in parts per million (ppm) downfield from tetramethylsilane (TMS) and coupling constants (J) are reported in hertz. Elemental analyses were performed by the CHN Analyzer PerkinElmer 2400. Electrospray ionization (ESI) mass spectra were recorded with a spectrometer FISONS-Vg Autospec-M246 using MeOH as solvent. Azines were prepared according to a synthetic method reported in letterature[31] (see supplementary data).

4.2 General procedure for the synthesis of 1,2-dialkylhydrazines hydrochloride **2a-z**.

A solution of azina **1** (1 mmol) and $NMe_3.BH_3$ (2 mmol) in toluene (5 mL), under vigorous magnetic stirring, was subjected to a stream of HCl gas generated by the controlled addition (in 30 minutes) of HCl 37% (10 mL) to H_2SO_4 98% (20 mL) in a flask connected to the reaction solution by an empty claisen condenser (see Figure 1 in supplementary data). The reaction mixture was transferred in a 10 mL centrifuge tube, diluted with 5 mL of toluene, centrifuged (6000 RPM for 4 minutes) and the supernatant removed. The solid was resuspended with 10 mL of fresh toluene, recentrifuged and the supernatant removed again. Finally, the solid was dissolved in minimal amount of EtOH (about 1 mL), reprecipitated by refilling the centrifuge tube with Et_2O, recentrifuged, the supernatant removed and the residual solvent removed by vacuum to afford the target product.

1,2-dibenzylhydrazine hydrochloride (2a). Yield: 247 mg (99 %); white solid; m.p.[32] 223-225 °C. ^{1}H NMR (300 MHz, $CDCl_3$+CF_3COOH): δ 7.50-7.25 (m, 10H), 4.32 (s, 4H). ^{13}C NMR (75 MHz, $CDCl_3$+CF_3COOH): δ 130.3, 130.2, 130.0, 129.6, 54.2. MS (ESI+, MeOH): *m/z* = 213 [M+H], 91 [$C_6H_5CH_2$]. Anal. Calcd for $C_{14}H_{17}ClN_2$: C, 67.60; H, 6.89; N, 11.26. Found: C, 67.57; H, 6.95; N, 11.33.

1,2-bis(4-methylbenzyl)hydrazine hydrochloride (2b). Yield: 271 mg (98 %); white solid; m.p. 238 °C. ^{1}H NMR (300 MHz, $CDCl_3$+CF_3COOH): δ= 7.35-7.15 (m, 8H), 4.31 (s, 4H), 2.37 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$+CF_3COOH): δ= 140.6, 130.2, 130.0, 127, 53.8, 21.1. MS (ESI+, MeOH): *m/z* = 519 [2M+K], 241 [M+H]. Anal. Calcd for $C_{16}H_{21}ClN_2$: C, 69.43; H, 7.65; N, 10.12. Found: C, 69.49; H, 7.43; N, 10.41.

1,2-bis(4-nitrobenzyl)hydrazine hydrochloride (2c). Yield: 322 mg (95 %); white solid; m.p. 224-225 °C (dec.). ^{1}H NMR (300 MHz, $CDCl_3$+CF_3COOH): δ = 8.27 (d, *J* = 9 Hz, 4H), 7.62 (d, *J* = 9 Hz, 4H), 4.49 (s, 4H). ^{13}C NMR (75 MHz, $CDCl_3$+CF_3COOH): δ= 148.9, 138.7, 131.3, 124.8, 53.6. IR (nujol): ν (cm^{-1}) 3204 (NH), 1351 (NO_2). MS (ESI+, MeOH): *m/z* = 605 [2M+H], 335 [M+H+MeOH], 303 [M+H], 136 [$NO_2C_6H_4CH_2$]. Anal. Calcd for $C_{14}H_{15}ClN_4O_4$: C, 49.64; H, 4.46; N, 16.54. Found: C, 49.21; H, 4.54; N, 16.81.

4,4'-(hydrazine-1,2-diylbis(methylene))dibenzonitrile hydrochloride (2d). Yield: 293 mg (98 %); white solid; m.p. 223-225 °C. ^{1}H NMR (300 MHz, $CDCl_3$+CF_3COOH): δ= 7.75 (d, *J* = 7.8 Hz, 4H), 7.55 (d, *J* = 7.8 Hz, 4H), 4.41 (s, 4H). ^{13}C NMR (75 MHz, $CDCl_3$+CF_3COOH): δ = 136.9,133.4, 130.9, 116.9, 112.6, 53.5. IR (nujol): ν (cm^{-1}) 3209 (NH), 2236 (CN). MS (ESI+, MeOH): *m/z* = 525 [2M+H], 263 [M+H], 116 [$CNC_6H_4CH_2$]. Anal. Calcd for $C_{16}H_{15}ClN_4$: C, 64.32; H, 5.06; N, 18.75. Found: C, 64.74; H, 4.98; N, 18.92.

1,2-bis(2-fluorobenzyl)hydrazine hydrochloride (2e). Yield: 279 mg (98 %); white solid; m.p. 187-189 °C. ^{1}H NMR (300 MHz, $CDCl_3$+CF_3COOH): δ = 7.49-7.30 (m, 4H), 7.23-7.04 (m, 4H) 4.44 (s, 4H). ^{13}C NMR (75 MHz, $CDCl_3$+CF_3COOH): δ= 161.7 (d, *J* = 247 Hz), 132.3 (d, *J* = 6.7 Hz), 132.1, 125.2, 118.0 (d, *J* = 14 Hz), 116.2 (d, *J* = 29 Hz), 47.7. MS (ESI+, MeOH): *m/z* = 271 [M+Na], 249 [M+H]. Anal. Calcd for $C_{14}H_{15}ClF_2N_2$: C, 59.06; H, 5.31; N, 9.84. Found: C, 58.99; H, 5.27; N, 9.72.

1,2-bis(2-chlorobenzyl)hydrazine hydrochloride (2f). Yield: 299 mg (94 %); white solid; m.p. 148-150 °C. ^{1}H NMR (300 MHz, $CDCl_3$+CF_3COOH): δ = 7.52-7.27 (m, 8H), 4.51 (s, 4H). ^{13}C NMR (75 MHz, $CDCl_3$+CF_3COOH): δ= 134.9, 132.6, 131.9, 130.5, 128.3, 128.1,

51.9. MS (ESI+, MeOH): *m/z* = 303 [M+Na], 281 [M+H]. Anal. Calcd for $C_{14}H_{15}Cl_3N_2$: C, 52.94; H, 4.76; N, 8.82. Found: C, 53.01; H, 4.68; N, 8.59.

1,2-bis(4-chlorobenzyl)hydrazine hydrochloride (2g). Yield: 314 mg (99 %); white solid; m.p.[20] 234 °C. ^{1}H NMR (300 MHz, $CDCl_3$+CF_3COOH): δ = 7.40-7.20 (m, 8H), 4.27 (s, 4H). ^{13}C NMR (75 MHz, $CDCl_3$+CF_3COOH): δ = 136.7, 131.3, 129.8, 128.8, 53.6. MS (ESI+, MeOH): *m/z* = 583 [2M+Na], 281 [M+H]. Anal. Calcd for $C_{14}H_{15}Cl_3N_2$: C, 52.94; H, 4.76; N, 8.82. Found: C, 53.11; H, 4.89; N, 8.95.

1,2-bis(4-bromobenzyl)hydrazine hydrochloride (2h). Yield: 398 mg (98 %); white solid; m.p. 243 °C. ^{1}H NMR (300 MHz, $CDCl_3$+CF_3COOH): δ = 7.53 (d, *J* = 9 Hz, 4H), 7.20 (d, *J* = 9 Hz, 4H), 4.25 (s, 4 H). ^{13}C NMR (75 MHz, $CDCl_3$+CF_3COOH): δ = 132.9, 131.6, 129.3, 124.9, 53.7. MS (ESI+, MeOH): *m/z* = 369 [M+H], 171 [Br $C_6H_4CH_2$]. Anal. Calcd for $C_{14}H_{15}Br_2ClN_2$: C, 41.36; H, 3.72; N, 6.89. Found: C, 41.18; H, 3.43; N, 7.01.

1,2-bis(2-methoxybenzyl)hydrazine hydrochloride (2i). Yield: 303 mg (98 %); white solid; m.p. 149-150 °C. ^{1}H NMR (300 MHz, DMSO *d6*): δ = 7.43-7.31 (m, 4H), 7.04 (d, *J* = 8.2 Hz, 2H), 6.96 (t, *J* = 7.4 Hz, 2H), 4.20 (s, 4H), 3.81 (s, 6H). ^{13}C NMR (75 MHz, DMSO *d6*): δ = 157.3, 130.6, 129.8, 121.5, 120.3, 110.9, 55.5, 46.2. MS (ESI+, MeOH): *m/z* = 567 [2M+Na], 295 [M+Na], 273 [M+H]. Anal. Calcd for $C_{16}H_{21}ClN_2O_2$: C, 62.23; H, 6.85; N, 9.07. Found: C, 62.11; H, 6.78; N, 9.12.

2,2'-(hydrazine-1,2-diylbis(methylene))diphenol hydrochloride (2j). Yield: 272 mg (97 %); white solid; m.p. 151-152 °C. ^{1}H NMR (300 MHz, $CDCl_3$+CF_3COOH): δ = 7.33 (t, *J* = 8.0 Hz, 2H), 7.21 (d, *J* = 7.4 Hz, 2H), 6.99 (t, *J* = 7.4 Hz, 2H), 6.88 (d, *J* = 8.0 Hz, 2H), 4.52 (s, 4H). ^{13}C NMR (75 MHz, DMSO *d6*): δ = 155.8, 130.8, 129.5, 119.7, 118.9, 115.3, 46.6. MS (ESI+, MeOH): *m/z* = 978 [4M+H], 511 [2M+Na], 267 [M+Na], 245 [M+H]. Anal. Calcd for $C_{14}H_{17}ClN_2O_2$: C, 59.89; H, 6.10; N, 9.98. Found: C, 59.92; H, 6.08; N, 9.91.

1,2-bis(2-(methylthio)benzyl)hydrazine dihydrochloride (2k). Yield: 358 mg (95 %); yellow solid; m.p. 142-143 °C (dec.). ^{1}H NMR (300 MHz, DMSO *d6*): δ = 7.60-7.48 (m, 2H), 7.44-7.32 (m, 4H), 7.28-7.18 (m, 2H), 4.32 (s, 4H), 2.50 (s, 6H). ^{13}C NMR (75 MHz, DMSO *d6*): δ = 137.8, 131.6, 129.6, 129.0, 126.7, 125.1, 48.8, 15.7. MS (ESI+, MeOH): *m/z* = 305 [M+H], 137 ($CH_3SC_6H_4CH_2$). Anal. Calcd for $C_{16}H_{22}Cl_2N_2S_2$: C, 50.92; H, 5.88; N, 7.42. Found: C, 51.01; H, 5.75; N, 7.54.

1,2-bis(4-methoxybenzyl)hydrazine hydrochloride (2l). Yield: 296 mg (96 %); white solid; m.p. 236-237 °C. ^{1}H NMR (300 MHz, DMSO *d6*): δ = 7.36 (broad s, 4H), 6.95 (d, *J* = 6 Hz, 4H), 4.10 (broad s, 4H), 3.76 (s, 6H). ^{13}C NMR (75 MHz, DMSO *d6*): δ = 159.3, 131.1, 113.8, 55.2, 51.0. MS (ESI+, MeOH): *m/z* = 273 [M+H], 121 [$CH_3OC_6H_4CH_2$]. Anal. Calcd for $C_{16}H_{21}ClN_2O_2$: C, 62.23; H, 6.85; N, 9.07. Found: C, 62.44; H, 6.795; N, 9.11.

1,2-dicinnamylhydrazine hydrochloride (2m). Yield: 295 mg (98 %); white solid; m.p. 206 °C. ^{1}H NMR (300 MHz, DMSO *d6*): δ = 10.36 (broad s), 7.50-7.18 (m, 10H), 6.73 (d, *J* = 15.8 Hz, 2H), 6.32 (dt, *J* = 15.8 Hz, *J* = 6.7 Hz, 2H), 3.80 (d, *J* = 6.7 Hz, 4H). ^{13}C NMR (75 MHz, DMSO *d6*): δ = 136.0, 128.7, 128.0, 126.4, 49.8. MS (ESI+, MeOH): *m/z* = 265 [M+H]. Anal. Calcd for $C_{18}H_{21}ClN_2$: C, 71.87; H, 7.04; N, 9.31. Found: C, 71.77; H, 7.00; N, 9.25.

1,2-didecylhydrazine hydrochloride (2n). Yield: 196 mg (56 %); white solid; m.p. 163 °C. ^{1}H NMR (300 MHz, $CDCl_3$+CF_3COOH): δ = 3.26 (t, *J* = 6 Hz, 4H), 1.68 (m, 4 H), 1.45-1.15 (m, 28 H), 0.88 (t, *J* = 6 Hz, 6 H). ^{13}C NMR (75 MHz, $CDCl_3$+CF_3COOH): δ = 50.7, 32.2, 29.7, 29.6, 29.3, 26.6, 25.6, 22.9, 13.8. MS (ESI+, MeOH): *m/z* = 313 [M+H], 156 [$CH_3(CH_2)_9NH$]. Anal. Calcd for $C_{20}H_{45}ClN_2$: C, 68.82; H, 13.00; N, 8.03. Found: C, 68.57; H, 12.94; N, 8.41.

1,2-diisopentylhydrazine hydrochloride (2o). Yield: 201 mg (96 %); white solid; m.p. 210-211 °C. ^{1}H NMR (300 MHz, $CDCl_3$+CF_3COOH): δ = 3.26 (t, *J* = 7.7 Hz, 4H), 1.74-1.60 (m, 2H), 1.60-1.48 (m, 4H), 0.93 (d, *J* = 6.4 Hz, 12H). ^{13}C NMR (75 MHz, $CDCl_3$+CF_3COOH): δ = 48.7, 34.3, 26.0, 21.8. MS (ESI+, MeOH): *m/z* = 345 [2M+1], 173 [M+1]. Anal. Calcd for $C_{10}H_{25}ClN_2$: C, 57.53; H, 12.07; N, 13.42. Found: C, 57.49; H, 12.31; N, 13.13.

1,2-bis(cyclohexylmethyl)hydrazine dihydrochloride (2p). Yield: 291 mg (98 %); white solid; m.p. 207 °C. ^{1}H NMR (300 MHz, $CDCl_3$+CF_3COOH): δ = 3.10 (d, *J* = 6.4 Hz, 4H), 1.9-0.9 (m, 22 H). ^{13}C NMR (75 MHz, $CDCl_3$+CF_3COOH): δ = 56.2, 34,9, 30.7, 25.8, 25.3. MS (ESI+, MeOH): *m/z* = 225 [M+H]. Anal. Calcd for $C_{14}H_{30}Cl_2N_2$: C, 56.56; H, 10.17; N, 9.42. Found: C, 56.81; H, 10.09; N, 9.34.

1,2-bis(naphthalen-2-ylmethyl)hydrazine hydrochloride (2q). Yield: 342 mg (98 %); white solid; m.p. 260-262 °C. ^{1}H NMR (300 MHz, $CDCl_3$+CF_3COOH): δ = 7.87-7.79 (m, 4H), 7.78-7.68 (m, 4H), 7.60-7.48 (m, 4H), 7.35 (d, *J* = 8.3 Hz, 2H), 4.49 (s, 4H). ^{13}C NMR (75 MHz, $CDCl_3$+CF_3COOH): δ = 134.0, 133.4, 130.2, 129.8, 128.1, 127.7, 127.4, 126.3, 54.6. MS (ESI+, MeOH): *m/z* = 625 [2M+H], 313 [M+H], 141 [$C_{10}H_7CH_2$]. Anal. Calcd for $C_{22}H_{21}ClN_2$: C, 75.74; H, 6.07; N, 8.03. Found: C, 75.63; H, 6.21; N, 8.19.

1,2-bis(thiophen-2-ylmethyl)hydrazine hydrochloride (2r). Yield: 253 mg (97 %); white solid; m.p. 182-183 °C (dec.). ^{1}H NMR (300 MHz, DMSO *d6*): δ = 10.73 (broad s), 7.56 (d, *J* = 3 Hz, 2H), 7.21 (broad s, 2H), 7.05 (dd, *J* = 3 Hz, *J* = 6 Hz, 2H), 4.40 (s, 4H). ^{13}C NMR (75 MHz, DMSO *d6*): δ = 134.1, 126.9, 45.9. MS (ESI+, MeOH): *m/z* = 257 [M+MeOH+H], 225 [M+H], 97 ($C_4H_3SCH_2$). Anal. Calcd for $C_{10}H_{13}ClN_2S_2$: C, 46.05; H, 5.02; N, 10.74. Found: C, 46.21; H, 5.18; N, 10.51.

1,2-diisopropylhydrazine hydrochloride (2s). Yield: 150 mg (98 %); white solid; m.p.[22] 203-204 °C. ^{1}H NMR (300 MHz, $CDCl_3$+CF_3COOH): δ = 3.53 (set, *J* = 6.3 Hz, 2H), 1.31 (d, *J* = 6.3 Hz, 12H). ^{13}C NMR (75 MHz, DMSO *d6*): δ = 51.2, 19.6. MS (ESI+, MeOH): *m/z* = 117 [M+H]. Anal. Calcd for $C_6H_{17}ClN_2$: C, 47.21; H, 11.22; N, 18.35. Found: C, 47.18; H, 11.25; N, 18.46.

1,2-di(pentan-3-yl)hydrazine hydrochloride (2t). Yield: 137 mg (66 %); white solid; m.p. 178-180 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.11 (q, *J* = 5.9 Hz, 2H), 1.87-1.57 (m, 8H), 0.98 (t, *J* = 7.5 Hz, 12 H). ^{13}C NMR (75 MHz, $CDCl_3$+CF_3COOH): δ = 63.8, 22.9, 8.9. MS (ESI+, MeOH): *m/z* = 383 [2M+K], 345 [2M+Na], 173 [M+H], 86 [Et_2CHNH]. Anal. Calcd for $C_{10}H_{25}ClN_2$: C, 57.53; H, 12.07; N, 13.42. Found: C, 57.41; H, 12.11; N, 13.25.

1,2-bis(1-phenylethyl)hydrazine hydrochloride (2v). Yield: 271 mg (98 %); white solid; m.p.[13a] 187-188 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 12.2 (broad s), 7.47-7.27 (m, 10H), 4.48-4.30 (m, 2H), 1.60, 1.57 (d, *J* = 7.0 Hz, 6H for two diast.). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 138.2, 128.9, 128.8, 128.0, 59.4, 20.0, 19.6. MS (ESI+, MeOH): *m/z* = 241 [M+H]. Anal. Calcd for $C_{16}H_{21}ClN_2$: C, 69.43; H, 7.65; N, 10.12. Found: C, 69.61; H, 7.42; N, 10.33.

1,2-dicyclopentylhydrazine hydrochloride (2w). Yield: 201 mg (98 %); white solid; m.p. 195 °C. ^{1}H NMR (300 MHz, $CDCl_3$+CF_3COOH): δ = 3.85-3.71 (m, 2H), 2.12-1.94 (m, 4H), 1.90-1.58 (m, 12H). ^{13}C NMR (75 MHz, $CDCl_3$+CF_3COOH): δ = 62.5, 30.1, 24.2. MS (ESI+, MeOH): *m/z* = 375 [2M+K], 169 [M+H]. Anal. Calcd for $C_{10}H_{21}ClN_2$: C, 58.66; H, 10.34; N, 13.68. Found: C, 58.51; H, 10.49; N, 13.44.

1,2-dicyclohexylhydrazine hydrochloride (2x). Yield: 222 mg (95 %); white solid; m.p. 191 °C. ^{1}H NMR (300 MHz, $CDCl_3$+CF_3COOH): δ = 3.25-3.05 (m, 2H), 2.10-1.94 (m, 4H), 1.94-1.78 (m, 4H), 1.78-1.66 (m, 2H), 1.42-1.14 (m, 10H). ^{13}C NMR (75 MHz, $CDCl_3$+CF_3COOH): δ = 60.7, 29.6, 25.1, 24.3. MS (ESI+, MeOH): *m/z* = 197 [M+1], 98 [$C_6H_{11}NH$], 83 [C_6H_{11}]. Anal. Calcd for $C_{12}H_{25}ClN_2$: C, 61.91; H, 10.82; N, 12.03. Found: C, 61.53; H, 10.97; N, 12.34.

1,2-dicycloheptylhydrazine hydrochloride (2y). Yield: 255 mg (98 %); white solid; m.p. 223-225 °C. ^{1}H NMR (300 MHz, $CDCl_3$+CF_3COOH): δ = 3.44-3.30 (m, 2H), 2.10-1.96 (m, 4H), 1.82-1.68 (m, 4H), 1.68-1.37 (m, 16H). ^{13}C NMR (75 MHz, $CDCl_3$+CF_3COOH): δ = 62.9, 30.9, 27.8, 23.7. MS (ESI+, MeOH): *m/z* = 225 [M+H]. Anal.

Calcd for $C_{14}H_{29}ClN_2$: C, 64.46; H, 11.21; N, 10.74. Found: C, 64.21; H, 11.36; N, 10.51.

1,2-dicyclododecylhydrazine hydrochloride (2z). Yield: 393 mg (98 %); white solid; m.p. 210-211 °C (dec.). ^{1}H NMR (300 MHz, $CDCl_3$+CF_3COOH): δ = 3.35-3.20 (m, 2H), 1.85-1.50 (m, 8H), 1.50-1.20 (m, 36H). ^{13}C NMR (75 MHz, $CDCl_3$+CF_3COOH): δ = 58.5, 26.8, 24.2, 23.8, 23.3, 21.0. MS (ESI+, MeOH): *m/z* = 729 [2M+H], 365 [M+H]. Anal. Calcd for $C_{24}H_{49}ClN_2$: C, 71.86; H, 12.31; N, 6.98. Found: C, 71.61; H, 12.51; N, 7.10.

4.3 General procedure for the "one pot" synthesis of N-acyl-1,2-dialkylhydrazines **3-5**.

After the previously reported step of reduction, the carboxylic acid (3 mmol) was added to the reaction mixture and heated to reflux for 4h (7h for **5**), observing a complete dissolution of the solid. The organic solution was washed with a saturated solution of sodium bicarbonate and the aqueous solution was extracted with ethyl acetate (2x20 mL). The organic layers were collected, dried over Na_2SO_4, and the solvent removed in vacuum. The crude product was purified by column chromatography on silica gel, eluting with DCM for the byproducts and AcOEt for the target product.

N,N'-dibenzylacetohydrazide (3). Yield: 206 mg (81 %); colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ (two rotamers, *Z* and *E*) = 7.45-7.20 (m, 10 H), 4.92, 4.75 (s, 2H), 4.02, 3.96 (s, 2H), 3.5-2.7 (broad s, 1H, exchange with D_2O), 2.18 (s, 3H). ^{13}C NMR ($CDCl_3$): δ (two rotamers, *Z* and *E*) = 173.6, 169.7, 137.2, 136.9, 136.3, 135.6, 128.9, 128.8, 128.3, 128.2, 127.6, 127.3, 126.7, 54.1, 52.3, 45.6, 20.9. IR (neat): ν (cm^{-1}) 3281 (NH), 1654 (CO). HRMS (ESI+, MeOH): *m/z* [M+H] Calcd for $C_{16}H_{19}N_2O$: 255.1497; Found: 255.1491.

N,N'-dibenzylbenzohydrazide (4). Yield: 263 mg (83 %); colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ (two rotamers, *Z* and *E*) = 7.6-7.0 (m, 15 H), 4.62 (broad s, 2H), 4.03 (s, 2H). ^{13}C NMR ($CDCl_3$): δ (two rotamers, *Z* and *E*) = 171.8, 136.8, 135.7, 129.9, 129.1, 128.3, 127.6, 55.2, 53.9, 46.0. IR (neat): ν (cm^{-1}) 3284 (NH), 1634 (CO). HRMS (ESI+, MeOH): *m/z* [M+H] Calcd for $C_{21}H_{21}N_2O$: 317.1648; Found: 317.1652.

N,N'-bis(naphthalen-2-ylmethyl)isobutyrohydrazide (5). Yield: 191 mg (50 %); white solid; mp 129 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ (two rotamers, *Z* and *E*) = 7.95-7.30 (m, 14 H), 5.14, 4.75 (s, 2H), 4.16 (s, 2H), 4.03-3.66 (broad s, 1H, exchange with D_2O), 3.54, 2.80 (set, *J* = 6.7 Hz, 1H), 1.16, 1.12 (d, *J* = 6.7 Hz, 6 H). ^{13}C NMR ($CDCl_3$): δ (two rotamers, *Z* and *E*) 180.4, 177.1, 135.1-132.6, 129.6-124.6, 54.6, 53.8, 53.1, 46.0, 30.8, 29.7, 19.5. IR (nujol): ν (cm^{-1}) 3266 (NH), 1650 (CO). HRMS (ESI+, MeOH): *m/z* [M+Na] Calcd for $C_{26}H_{26}N_2NaO$: 405.1943; Found: 405.1946.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

The author was financially supported by the Università degli Studi di Milano (PSR2021_DIP_005_PI_FVASI).

Appendix A. Supplementary data

Supplementary data to this article can be found online at

References

1. (a) *Hydrazine and its Derivatives*, Kirk-Othmer Encyclopedia Chemical Technology; Wiley: New York, 4th ed., 13 (2004).
2. Toth, B. *Hydrazines and Cancer*, Harwood Academic Publishers, Amsterdam, (2000).
3. https://list.essentialmeds.org
4. (a) Le Goff, G.; Ouazzani, J.; *Bioorg. Med. Chem.* 22 (2014) 6529-6544. (b) Lachlan M. Blair, M. L.; Sperry, J. *J. Nat. Prod.* 76 (2013) 794-812.
5. Ragnarsson, U. *Chem. Soc. Rev.* 30 (2001) 205-213.
6. (a) Tarchoun, K.; Yousef, M.; Bánóczi, Z. *Future Pharm.* 2 (2022) 293–305. (b) Chingle, R.; Proulx, C.; Lubell, D. W. *Acc. Chem. Res.* 50 (2017) 1541-1556.
7. (a) Meyer, K. G.; *Synlett* (2004) 2355-2356. (b) Brosse, N.; Pinto, M.-F.; Jamart-Grégoire, B. *Eur. J. Org. Chem.* (2003) 4757-4764. (c) Grehn, L.; Lönn, H.; Ragnarsson, U. *Chem. Commun.* (1997) 1381-1382.
8. Chong, C. C.; Hirao, H.; Kinjo, R. *Angew. Chem. Int. Ed.* 53 (2014) 3342-3346.
9. (a) Jnaneshwara, G. K.; Sudalai, A.; Deshpande, V. H. *J. Chem. Research (S)* (1998) 160–161. (b) Biel, J. H.; Drukker, A. E.; Mitchell, T. F.; Sprengeler, E. P.; Nuhfer, P. A.; Conway, A. C.; Horita, A. *J. Am. Chem. Soc.* 81 (1959) 2805–2813.
10. Feuer, H.; Brow, F. *J. Org. Chem.* 35 (1970) 1468-1471.
11. Zhang, Y.; Tang, Q.; Luo, M. *Org. Biomol. Chem.* 9 (2011) 4977-4982.
12. (a) Kawase, Y.; Yamagishi, T.; Kato, J.; Kutsuma, T.; Kataoka, T.; Iwakuma, T.; Yokomatsu, T. *Synthesis* 46 (2014) 455-464. (b) Casarini, M. E.; Ghelfi, F.; Libertini, E.; Pagnonia, U. M.; Parsons A. F. *Tetrahedron* 58 (2002) 7925-7932.
13. (a) Schulze, W. A.; Lochte, H. L. *J. Am. Chem. Soc.* 48 (1926) 1030-1035. (b) Lochte, H. L.; Noyes, W. A.; Bailey, J. R. *J. Am. Chem. Soc.* 44 (1922) 2556-2567.
14. (a) Yun, J.; Jeong, D.; Xie, Z.; Lee, S.; Kim, J.; Surmeier, D. J.; Silverman, R. B.; Kang, S. *ACS Omega* 7 (2022) 14252-14263. (b) Ly, H.V.; Forster, T. D.; Corrente, A. M.; Eisler, D. J.; Konu, J.; Parvez, M.; Roesler, R. *Organometallics* 26 (2007) 1750-1756. (c) Daub, G. H.; Cannizzo, L. F. *J.Org. Chem.* **1982**, 47, 5034. (d) Schwan, T. J. *J. Heterocycl. Chem.* 20 (1983) 547-549. (e) Gibian, M. J.; Corley, R. C. *J. Am. Chem. Soc.* 94 (1972) 4178-4183. (f) Fox, H. H.; Gibas, J. T. *J. Org. Chem.* 20 (1955) 60-69. (g) Renaud, R.; Leitch, L. C. *Can. J. Chem.* 32 (1954) 545-549.
15. Blair, J. A.; Gardner, R. J. *J. Chem. Soc. (C)* (1970) 1714-1717.
16. (a) Charistoudi, E.; Kallitsakis, M. G.; Charisteidis, I.; Triantafyllidis, K. S.; Lykakis I. N. *Adv. Synth. Catal.* 359 (2017) 2949-2960. (b) Gerwalt Zinner, G.; Blab, H.; Kilwing, W.; Geister, B. *Archiv der Pharmazie* 317 (1984) 1024-1028. (c) Kornet, M. J.; Daniels, R. *J. Heterocycl. Chem.* 16 (1979) 1485-1486.

17. Khurana, J. M.; Kandpal, B. M.; Sharma, P.; Gupta, M. *Monatsh. Chem.* 146 (2015) 187-190.
18. Kostyanovsky, R. G.; Rademacher, P.; El'natanov, Y. L.; Kadorkina, G. K.; Nikiforov, G. A.; Chervin, I. I.; Usachev, S. V.; Kostyanovsky V. R. *Russ. Chem. Bull.* 46 (1997) 1291-1299.
19. Jana, S.; Dalapati, S.; Alam,M. A.; Guchhait, N. Spectrochimica Acta Part A 92 (2012) 131–136.
20. Langley, B. W.; Lythgoe, B.; Rayner, L. S. *J. Chem. Soc.* (1952) 4191-4198.
21. Perdicchia, D.; Licandro, E.; Maiorana, S.; Baldoli, C.; Giannini, C. *Tetrahedron* 59 (2003) 7733-7742.
22. Tapale, K. A. *Ber. Dtsch. Chem. Ges.* 56B **(**1923) 954-962.
23. Brehme, R.; Enders, D.; Fernandez, R.; Lassaletta, J. M. *Eur. J. Org. Chem.* (2007) 5629–5660.
24. (a) Glaser, R.; Chen, G. S. *J. Comput. Chem.* 19 (1998) 1130-1140. (b) Safari, J.; Gandomi-Ravandi, S. *RSC Adv.* 4 (2014) 46224-46249.
25. Funke, M.-A.; Mayr, H. *Chem. Eur. J.* 3 (1997) 1214-1222.
26. Hutchins, R. O.; Learn, K.; Nazer, B.; Pytlewski, D.; Pelter, A. *Org. Prep. Proced. Int.* 16 (1984) 335-372.
27. Borders, C. L. Jr.; Blech, D. M.; McElvany, K. D. *J. Chem. Educ.* 61 (1984) 814-815.
28. Bruch M., Jun Y. M., Luedtke A. E., Schneider M., Timberlake J. W. *J. Org. Chem.* 51 (1986) 2969-2973.
29. Licandro, E.; Perdicchia, D. *Eur. J. Org. Chem.* (2004) 665-675.
30. Hulme, A. N.; McNab, H.; Wight, P. *Synlett* (2005) 1571–1574.
31. Nanjundaswamy, H. M.; Pasha, M. A. *Synth. Commun.* 36 (2006) 3161–3165.
32. Bickel, A. F.; Waters, W. A. *Rec. Trav. Chim. Pays-Bas.* 69 (1950) 312-20.