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Solvent-free synthesis of hydrazones and their subsequent N-alkylation in a Ball-mill

Pierrick Nun, Charlotte Martin, Jean Martinez, Frédéric Lamaty*

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A B S T R A C T

A large variety of Boc-, Bz-, Ts-, and Fmoc- protected hydrazones were prepared via condensation of an equimolar amount of carbonyl-compound and the corresponding hydrazine using a ball-mill. Hydrazones were always obtained in a quantitative yield and no solvents were used at any step. In a second step, we realized the first solvent-free N-allylation and N-benylation of these hydrazones.

Keywords:

Ball-mill
Solvent-free synthesis
Green chemistry
Protected hydrazones
Condensation
Alkylation

1. Introduction

Ball-milling is a mechanochemical technique, that is, widely applied to the grinding of minerals into fine particles and to the preparation and modification of inorganic solids.¹ For synthetic applications, ball-mill chemistry is a practical method, which can be environmentally friendly since solvent-free conditions are generally used. In the last years, this technique has found interest in synthetic organic chemistry.² Among the reported examples, one can cite nitrene synthesis,³ functionalization of fullerenes,⁴ reductive benzylation of malonitrile,⁵ protection of amines,⁶ Knoevenagel reaction,⁷ aldol condensation,⁸ and its asymmetric version,⁹ Michael additions,⁷ preparation of phosphorus ylides,¹⁰ nucleoside chemistry,¹¹ oxidative coupling of 2-naphthol,¹² Heck-type cross-coupling reactions,¹³ peptide coupling,¹⁴ oxidations,¹⁵ Sonogashira reaction,¹⁶ click reactions.¹⁷

Hydrazones are an important class of chemical intermediates, which can act as electrophiles and as nucleophiles in Mannich-Type reactions,¹⁸ Mitsunobu reactions,¹⁹ asymmetric hydrocyanation,²⁰ allylation.²¹ They are also used in asymmetric synthesis in the SAMP-/RAMP-methodology.²² Biological activity of hydrazone derivatives was also investigated and some of them act as potent inhibitors of macrophage migration inhibitory factor (MIF) tautomerase.²³

Hydrazones are classically prepared by refluxing hydrazine with a slight excess of carbonyl compound in toluene or ethanol, and the pure product is finally isolated after crystallization, column chromatography or distillation. There are only few examples describing this synthesis in solvent-free conditions. Using microwaves, tosyl-hydrazones are prepared in a short time with a small amount of methanol using dichloromethane for the final extraction.²⁴ Acyl-hydrazones are prepared using an excess of liquid aldehyde and ethanol for washing,²⁵ while heterocyclic hydrazones are prepared using a large excess of hydrazine and ethanol for washing.²⁶ Hydrazones and semi-carbazones are also prepared in a mortar by grinding the aldehyde and hydrazine with sodium hydroxide and silica gel during a few minutes²⁷ with a final extraction step using dichloromethane or in a ball-mill in presence of Na₂CO₃.²⁸ To our knowledge, only two reports of totally solvent-free hydrazone synthesis, using a ball-mill and yielding pure hydrazones without any use of solvent.²⁹ This method was only used to prepare hydrazones with Bz- and Ph- as protecting groups. Surprisingly, this technique was not employed to prepare other hydrazones and microwave heating or refluxing methods seemed to be preferred.

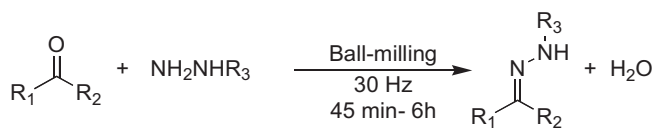
2. Results and discussion

In previous studies, we have already described the use of a ball-mill apparatus in peptide synthesis^{14a} and in the condensation of hydroxylamines on aldehydes for the synthesis of nitrones.³ We chose to extend this technique to the synthesis of a large variety

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of hydrazones, starting from commercially available Boc- (**1**), Bz- (**2**), and Ts-hydrazines (**3**) and from the synthesized Fmoc-hydrazine (**4**).³⁰

In order to respect the principles of green chemistry, it was necessary to work in stoichiometric conditions and when possible without any addition of solid support, such as silica gel and base (Scheme 1).²⁷



Scheme 1. Solvent-free synthesis of hydrazones.

The reactants were introduced into a stainless steel jar (5 mL). The reaction vessel was closed and fixed on the vibration arms of a ball-milling apparatus, along with two stainless steel balls of 5.0 mm diameter (Retsch MM200 mixer mill, Retsch GmbH, Haan, Germany), using a second parallel jar to equilibrate the system. Then, both vessels were vibrated vigorously at a rate of 30 Hz at room temperature. The reaction was monitored by HPLC, and stopped when all starting materials were consumed. Results obtained with various aldehydes, ketones, *tert*-butyl carbazate, benzoic, Fmoc, and tosyl hydrazide are presented in Table 1.

When the conversion of starting materials was complete, the apparatus was stopped, the jar opened and the pure expected hydrazone was recovered only by removing the powder from the jar and by drying under reduced pressure. In all cases there was no

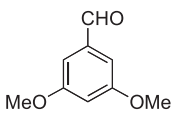
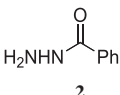
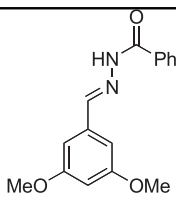

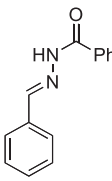
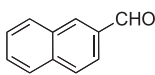
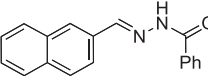

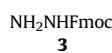
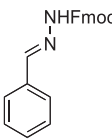

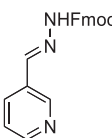

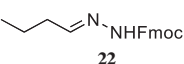
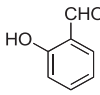
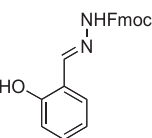
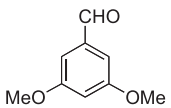
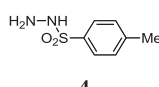
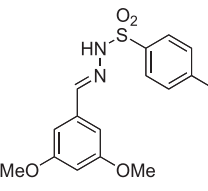
Table 1 (continued)

R ₁ CHO	R ₃ NHNH ₂	Reaction time	Product
	1	45 min	
	1	60 min	
	1	90 min	
	1 (2 equiv)	90 min	
	1	90 min	
	1	360 min	
	1	60 min	
	1	60 min	
	1	60 min	
	1	180 min	
	1	60 min	

Table 1
Solvent-free synthesis of Boc-, Bz-, Fmoc-, and tosyl-hydrazones from aldehydes

R ₁ CHO	R ₃ NHNH ₂	Reaction time	Product
		60 min	
	1	360 min	
	1	60 min	
	1	180 min	

Table 1 (continued)

R ₁ CHO	R ₃ NHNH ₂	Reaction time	Product
		120 min	
	2	60 min	
	2	60 min	
		60 min	
	3	90 min	
	3	120 min	
	3	60 min	
		180 min	

by-product, conversion was always total as proved by direct analysis of the obtained product. So the reaction can be considered as quantitative. In each example of condensation, a solid powder was obtained and removed as such from the jar. Reaction times lasted between 45 min and 6 h but the hydrazones were mostly prepared in 90 min, a shorter time compared with methods that do not use microwave activation. For example, compound **7** was prepared in 60 min in a quantitative yield without any use of solvent, compared to 5 h in refluxing methanol.³¹

To confirm that the reaction was complete and no by-product was present in the isolated powder and that no further purification was needed, the cross polarization/magic angle spinning (CP/MAS) ¹³C NMR analysis of the reaction mixture without any treatment was performed. Results are presented below (Fig. 1).

The spectrum of the reaction mixture shows that no starting material could be detected in the crude final product. These results, coupled with ¹H, ¹³C NMR, and with LC/MS analysis showed that the powder obtained in the jar consisted in the clean hydrazone along with water. So the yield was always quantitative after drying the solid contrary to the described methods using microwaves or solid support. This method is also completely solvent-free because there is no need to filter or to wash the isolated solid with a toxic and volatile organic solvent. It is also important to notice that results were comparable starting from solid and liquid aldehydes, as, for example, with product **5** (starting from a solid aldehyde) and product **9** (starting from a liquid aldehyde). We also proved the applicability of this method to larger scale with the preparation of 1.7 g of hydrazone **7** in 120 min and using the same grinding jars.

The mechanochemical activation is also essential to obtain a quantitative conversion. With only a magnetical stirring in a 5 mL round-bottom flask, the highest conversion in hydrazone **7** after 24 h was only 41% (100% in 60 min with the ball-mill).

It is also important to note that this method is also applicable to some ketones. (Table 2) Usually condensations on aldehydes are quite easy but it is not always the case with ketones. Heating the reaction mixture to 70 °C or 125 °C is often required to achieve a quantitative yield. As described in a work published by Mokhtari et al. during the course of our study,^{29b} hydrazones from benzophenone could not be obtained just with milling. Nevertheless, this technique allowed us to prepare various hydrazones from cyclohexanone, 3-pentanone or acetophenone.

N-Alkylated hydrazones and hydrazines are important intermediates due to the increasing number of heterocyclic compounds bearing an N–N bond.³² N-allylhydrazones also proved interesting properties in the synthesis of dienes via copper (II) chloride or NBS and DBU promoted rearrangement.³³ We expanded our methodology to the allylation and benzylation of some hydrazones still in solvent-free conditions and without the use of metal as catalyst (Scheme 2).³⁴

Reaction conditions were optimized to 1 h of ball-milling at 30 Hz with 3 equiv of allylbromide and cesium carbonate. The use of a lower quantity of allylbromide or potassium carbonate as a base gave lower conversions. A simple aqueous wash and evaporation gave the pure allylhydrazone. These conditions were extended to other hydrazones and benzylbromide as alkylating agent (Table 3). Because the alkylation required the use of an excess of liquid alkylating agent, the reaction mixture was recovered as a paste from the jar. An interesting double allylation was also performed starting from hydrazone **16** derived from salicylaldehyde. Unfortunately, the use of other alkylating reagents like ethyl iodide or cyanopropargylbromide was unsuccessful. N-allylation of Fmoc-hydrazones in the same conditions gave no expected product, the starting materials were recovered.

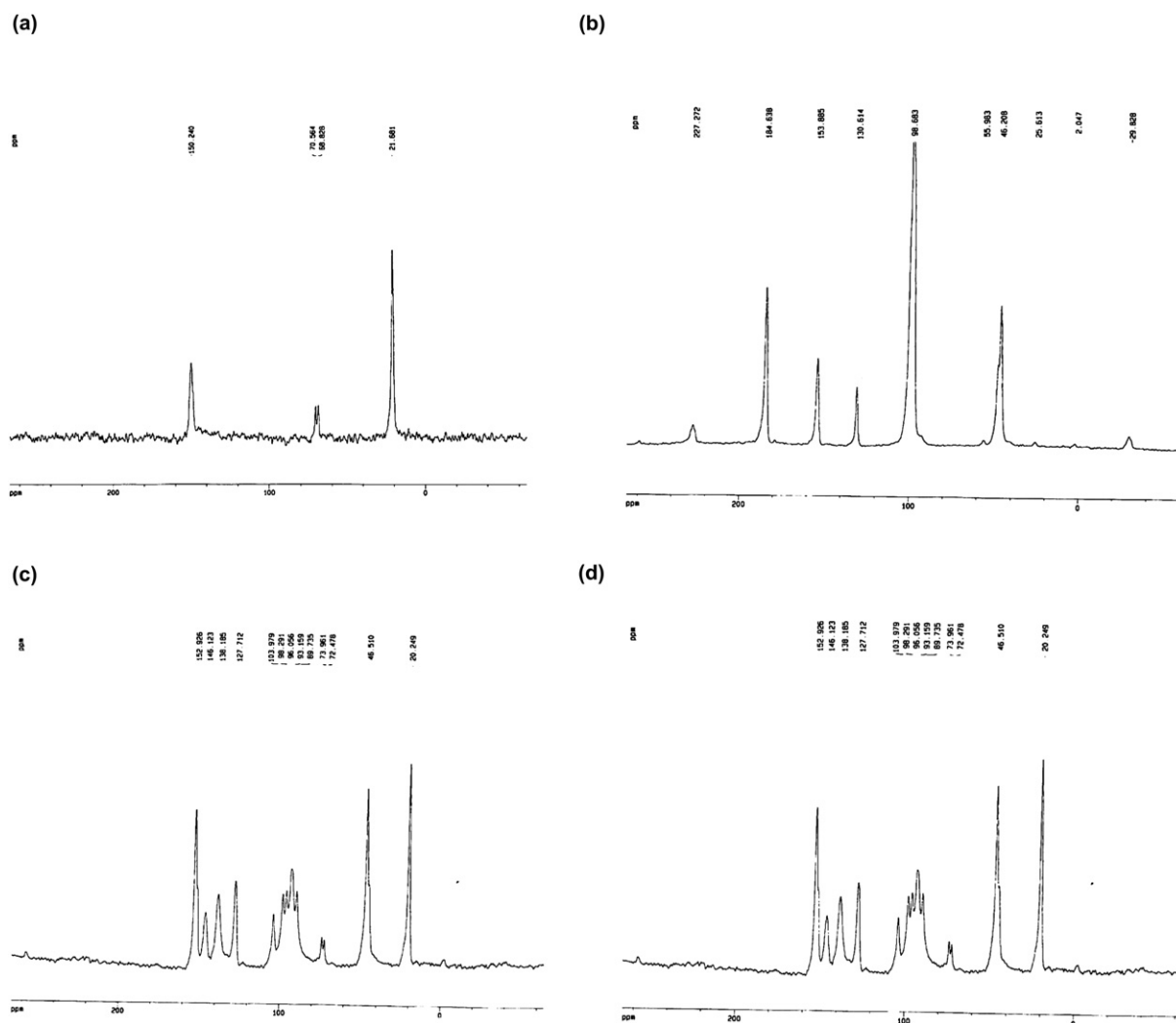


Fig. 1. ^{13}C CP/MAS spectra of (a) *tert*-butyl carbazate (b) 3,5-dimethoxybenzaldehyde (c) & (d) of *N'*-(3,5-dimethoxybenzylidene)-hydrazinecarboxylic acid *tert*-butyl ester.

3. Conclusion

In summary, we have shown that ball-milling can be a useful method for the preparation of diverse hydrazones starting from liquid and solid reactants. Their subsequent *N*-allyl and benzylation was also investigated with success still in solvent-free conditions using mechanical activation. This method proved its superiority in term of economy of solvent, yield, and reaction time. The methodology is highly profitable in terms of sustainable synthesis with efficiency in all respect, affording hydrazones in pure form without any purification. This shows also that two subsequent reactions could be performed using a ball-mill in the absence of solvent, opening the path to integrated organic synthesis in a ball-mill.

4. Experimental section

4.1. General

The Ball-milling experiments were performed in a Retsch MM200 mixer mill (Retsch GmbH, Haan, Germany) with two stainless balls of 5.0 mm diameter, into a stainless jar (5 mL) at a rate of 1800 rounds per minute (30 Hz) at room temperature.


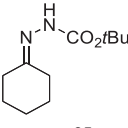

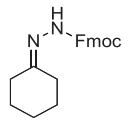
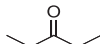
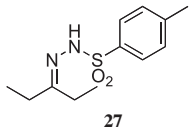

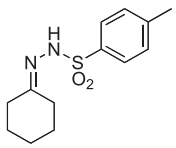
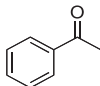
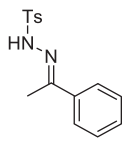
4.2. General experimental procedure for the synthesis of hydrazones (Table 1)

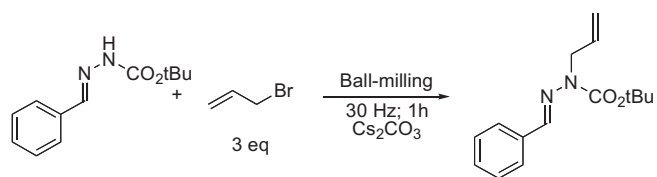
A mixture of aldehyde (0.5 mmol, 1 equiv) and hydrazine (0.5 mmol, 1.0 equiv) was ball-milled at 30 Hz for the specified time (see Table 1). When the reaction was complete, the product was recovered as a solid directly in the jar and then dried overnight under vacuo.

4.2.1. (*E*)-*tert*-Butyl-2-(3,5-dimethoxybenzylidene)hydrazinecarboxylate **5**³⁵ [106728-65-8]. White powder; mp 164 °C (lit. 161 °C). ^1H NMR (acetone- d_6) δ 1.36 (s, 9H), 3.68 (s, 6H), 6.36 (t, $J=2.1$ Hz, 1H), 6.71 (d, 2H, $J=2.1$ Hz), 7.9 (s, 1H), 9.71 (s, 1H); ^{13}C NMR (acetone- d_6) δ 28.5, 55.7, 80.5, 102.6, 105.32, 138.0, 144.0, 153.3, 162.0. MS (ESI) m/z : 303.0 $[\text{M}+\text{Na}]^+$, 281.2 $[\text{M}+\text{H}]^+$, 225.0, 181.0. HRMS calcd for $\text{C}_{14}\text{H}_{21}\text{N}_2\text{O}_4$: 281.1501. Found 281.1503.

4.2.2. (*E*)-*tert*-Butyl-2-(2-nitrobenzylidene)hydrazinecarboxylate **6**³⁵ [106728-63-6]. Yellow powder; mp 153 °C (lit. 151–152 °C). ^1H NMR (acetone- d_6) δ 1.50 (s, 9H), 7.63 (dd, 1H, $J=7.3, 7.0$ Hz), 7.77 (dd, 1H, $J=7.4, 7.3$ Hz), 8.01 (d, 1H, $J=8.0$ Hz), 8.15 (d, 1H, $J=7.7$ Hz), 8.53 (s, 1H), 10.2 (s, 1H); ^{13}C NMR (acetone- d_6) δ 28.5, 80.9, 125.4, 128.8, 130.3, 130.7, 134.1, 139.0, 149.3, 153.0. MS (ESI) m/z : 288.2 $[\text{M}+\text{Na}]^+$, 266.2 $[\text{M}+\text{H}]^+$, 210.0, 192.0.

Table 2
Hydrazones derived from ketones

R ₁ R ₂ CO	R ₃ NHNH ₂	Reaction time	Product
	1	60 min	 25
	3	60 min	 26
	4	150 min	 27
	4	60 min	 28
	4	90 min	 29




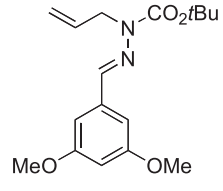
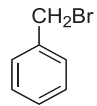
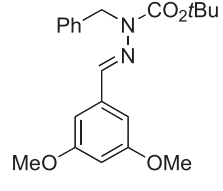

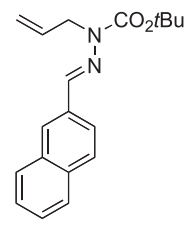

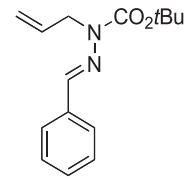

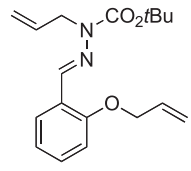

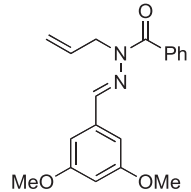
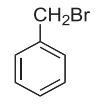
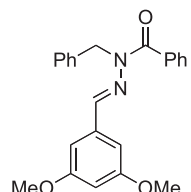
Scheme 2. Solvent-free N-allylation of hydrazones.

166.0, 149.0. HRMS calcd for C₁₂H₁₆N₃O₄: 266.1141. Found 266.1168.

4.2.3. (*E*)-*tert*-Butyl-2-(*naphthalen-1-ylmethylene*)hydrazinecarboxylate **7**³⁵ [106728-61-4]. White powder; mp 188 °C (lit. 167–168 °C). ¹H NMR (acetone-*d*₆) δ 1.50 (s, 9H), 7.53 (m, 2H), 7.82–8.05 (m, 5H), 8.27 (s, 1H), 9.89 (s, 1H); ¹³C NMR (acetone-*d*₆) δ 28.5, 80.5, 123.6, 127.4, 127.6, 128.7, 128.8, 129.1, 129.2, 133.9, 134.3, 134.9, 144.0, 153.3. MS (ESI) *m/z*: 293.3 [M+Na]⁺, 271.2 [M+H]⁺, 215.4. HRMS calcd for C₁₆H₁₉N₂O₂: 271.1447. Found 271.1471.


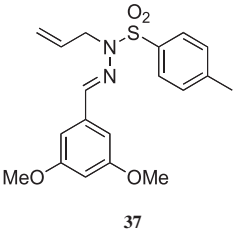

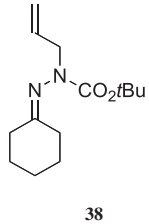

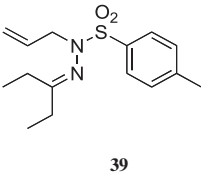
4.2.4. (*E*)-*tert*-Butyl-2-(4-methoxy-3-nitrobenzylidene)hydrazinecarboxylate **8** [355417-88-8]. Yellow powder; mp 149 °C. ¹H NMR (acetone-*d*₆) δ 1.49 (s, 9H), 4.02 (s, 3H), 7.45 (d, 1H, *J*=8.8 Hz), 7.92 (d, 1H, *J*=8.8 Hz), 8.01–8.19 (m, 2H), 9.91 (s, 1H); ¹³C NMR (acetone-*d*₆) δ 28.5, 57.3, 80.6, 115.1, 123.7, 128.9, 132.6, 141.0, 141.5, 153.2,

Table 3
Solvent-free alkylation of hydrazones

Hydrazone	R-X	Product	Isolated yield (%)
5			85
5			92
7			93
9			91
16			94
17			95
17			87

(continued on next page)

Table 3 (continued)

Hydrazone	R-X	Product	Isolated yield (%)
24			89
25			96
27			94%

153.9. MS (ESI) m/z : 334.1 [M+K]⁺, 318.2 [M+Na]⁺, 240.2. HRMS calcd for C₁₃H₁₈N₃O₅: 296.1256. Found 296.1246.

4.2.5. (*E*)-*tert*-Butyl-2-benzylidenehydrazinecarboxylate **9**³¹ [24469-50-9]. White powder; mp 190 °C (lit. 185 °C). ¹H NMR (acetone-*d*₆) δ 1.49 (s, 9H), 7.38 (m, 3H), 7.67 (m, 2H), 8.11 (s, 1H), 9.79 (s, 1H); ¹³C NMR (acetone-*d*₆) δ 28.5, 80.4, 127.5, 129.5, 130.2, 136.1, 143.9, 153.2. MS (ESI) m/z : 259.2 [M+K]⁺, 221.2 [M+H]⁺, 165.4. HRMS calcd for C₁₂H₁₇N₂O₂: 221.1290. Found 221.1298.

4.2.6. (*E*)-*tert*-Butyl-2-(furan-2-ylmethylene)hydrazinecarboxylate **10**³⁶ [113906-60-8]. White powder; mp 164 °C (lit. 158 °C). ¹H NMR (acetone-*d*₆) δ 1.48 (s, 9H), 6.54 (s, 1H), 6.72 (s, 1H), 7.62 (s, 1H), 8.04 (s, 1H), 9.78 (s, 1H); ¹³C NMR (acetone-*d*₆) δ 28.5, 80.5, 111.7, 112.6, 134.3, 144.8, 151.4, 153.2. MS (ESI) m/z : 233.2 [M+Na]⁺, 211.3 [M+H]⁺, 155.0, 137.2. HRMS calcd for C₁₀H₁₅N₂O₃: 211.1083. Found 211.1083.

4.2.7. (*E*)-*tert*-Butyl-2-(thiophen-2-ylmethylene)hydrazinecarboxylate **11** [180462-80-0]. White powder; mp 203 °C. ¹H NMR (acetone-*d*₆) δ 1.47 (s, 9H), 7.07 (m, 1H), 7.28 (m, 1H), 7.50 (m, 1H), 8.34 (s, 1H), 9.75 (s, 1H); ¹³C NMR (acetone-*d*₆) δ 28.5, 80.5, 111.7, 112.6, 134.3, 144.8, 151.4, 153.2. MS (ESI) m/z : 249.2 [M+Na]⁺, 227.2 [M+H]⁺, 171.0, 153.2, 110.1. HRMS calcd for C₁₀H₁₅N₂O₂S: 227.0854. Found 227.0857.

4.2.8. (*2E,2'E*)-*di-tert*-Butyl 2,2'-((1,4-phenylenebis(methan-1-yl-1-ylidene))bis(hydrazinecarboxylate) **12**. White powder; mp >260 °C. ¹H NMR (acetone-*d*₆+DMSO-*d*₆) δ 1.50 (s, 18H), 7.67 (s, 4H), 8.07 (s, 2H), 10.8 (s, 2H); ¹³C NMR (acetone-*d*₆+DMSO-*d*₆) δ 28.0, 79.5, 127.0, 136.1, 142.6, 152.7. MS (ESI) m/z : 363.1 [M+H]⁺, 307.2, 251.2, 207.3, 163.3. HRMS calcd for C₁₈H₂₇N₄O₄: 363.2032. Found 363.2047.

4.2.9. (*E*)-*tert*-Butyl-2-butyridenehydrazinecarboxylate **13**³⁷ [149268-07-5]. White powder; mp 89 °C. ¹H NMR (acetone-*d*₆)

δ 0.93 (t, 3H, *J*=7.2 Hz), 1.44 (s, 9H), 1.35–1.62 (m, 2H), 2.19 (dt, 2H, *J*=6.6, 6.7 Hz), 7.38 (s, 1H), 9.29 (s, 1H). ¹³C NMR (acetone-*d*₆) δ 14.0, 20.7, 28.6, 34.9, 79.8, 147.4, 153.3. MS (ESI) m/z : 209.3 [M+Na]⁺, 187.3 [M+H]⁺, 130.8. HRMS calcd for C₉H₁₉N₂O₂: 187.1447. Found 187.1469.

4.2.10. (*E*)-*tert*-Butyl-2-((1*H*-indol-5-yl)methylene)hydrazinecarboxylate **14**. White powder; mp 195 °C. ¹H NMR (acetone-*d*₆) δ 1.49 (s, 9H), 6.51 (m, 1H), 7.35 (s, 1H), 7.43 (d, 1H, *J*=8.5 Hz), 7.59 (d, 1H, *J*=8.5 Hz), 7.78 (s, 1H), 8.17 (s, 1H), 9.59 (s, 1H), 10.43 (s, 1H); ¹³C NMR (acetone-*d*₆) δ 28.6, 80.0, 103.1, 112.6, 120.4, 121.4, 126.4, 126.6, 127.5, 129.0, 138.0, 145.9. MS (ESI) m/z : 260.3 [M+H]⁺, 204.0. HRMS calcd for C₁₄H₁₈N₃O₂: 260.1399. Found 260.1416.

4.2.11. (*E*)-*tert*-Butyl-2-(quinolin-3-ylmethylene)hydrazinecarboxylate **15**³⁸ [106869-44-7]. White powder; mp 200 °C. ¹H NMR (acetone-*d*₆) δ 1.52 (s, 9H), 7.62 (dd, 2H, *J*=7.5, 7.1 Hz), 7.77 (dd, 2H, *J*=7.5, 7.1 Hz), 8.03 (dd, 2H, *J*=8.4, 8.0 Hz), 8.33 (s, 1H), 8.41 (s, 1H), 9.30 (s, 1H), 10.09 (s, 1H); ¹³C NMR (acetone-*d*₆) δ 28.5, 80.7, 128.0, 128.6, 129.2, 129.3, 130.2, 130.7, 134.6, 141.5, 149.3, 153.1. MS (ESI) m/z : 271.96 [M+H]⁺, 216.2. HRMS calcd for C₁₅H₁₈N₃O₂: 272.1399. Found 272.1410.

4.2.12. (*E*)-*tert*-Butyl 2-(2-hydroxybenzylidene)hydrazinecarboxylate **16**³⁹ [187806-33-3]. White solid; mp 149 °C. ¹H NMR (acetone-*d*₆) δ 1.50 (s, 9H), 6.89 (dd, 2H, *J*=7.4, 8.4 Hz), 7.27 (dd, 2H, *J*=7.4, 8.3 Hz), 8.24 (s, 1H), 11.32 (s, 1H). ¹³C NMR (acetone-*d*₆) δ 28.4, 81.2, 117.4, 119.2, 119.9, 131.2, 131.5, 146.8, 152.9, 159.0. MS (ESI) m/z : 259.1 [M+K]⁺, 237.2 [M+H]⁺, 165.4.

4.2.13. (*E*)-*N'*-(3,5-Dimethoxybenzylidene)benzohydrazide **17** [6785 36-02-2]. White powder; mp 182 °C. ¹H NMR (acetone-*d*₆) δ 3.83 (s, 6H), 6.54 (m, 1H), 6.93 (m, 2H), 7.45–7.63 (m, 3H), 7.97 (d, 2H, *J*=7.0 Hz), 8.51 (s, 1H), 10.99 (s, 1H); ¹³C NMR (acetone-*d*₆+DMSO-*d*₆) δ 56.0, 103.1, 105.9, 128.8, 129.4, 132.6, 135.0, 138.0, 162.1, 164.5. MS (ESI) m/z : 307.0 [M+Na]⁺, 285.0 [M+H]⁺. HRMS calcd for C₁₆H₁₇N₂O₃: 285.1239. Found 285.1231.

4.2.14. (*E*)-*N'*-Benzylidenebenzohydrazide **18**⁴⁰ [956-07-0]. White powder; mp 206 °C (lit. 210 °C). ¹H NMR (acetone-*d*₆) δ 7.36–7.62 (m, 6H), 7.77 (m, 2H), 7.98 (d, 2H, *J*=7.1 Hz), 8.51 (s, 1H), 11.00 (s, 1H); ¹³C NMR (acetone-*d*₆+DMSO-*d*₆) δ 128.1, 128.8, 129.4, 129.7, 130.9, 132.6, 135.0, 136.0, 148.6, 164.2. MS (ESI) m/z : 247.2 [M+Na]⁺, 225.0 [M+H]⁺. HRMS calcd for C₁₄H₁₃N₂O: 225.1028. Found 225.1015.

4.2.15. (*E*)-*N'*-(Naphthalen-2-ylmethylene)benzohydrazide **19** [24091-07-4]. White powder; mp 212 °C. ¹H NMR (acetone+DMSO) δ 7.48–7.65 (m, 5H), 7.89–8.09 (m, 6H), 8.14 (s, 1H), 8.70 (s, 1H), 11.87 (s, 1H); ¹³C NMR (acetone+DMSO) δ 123.5, 127.2, 127.6, 128.4, 128.9, 129.0, 129.1, 129.2, 129.3, 132.2, 133.3, 133.8, 134.6, 134.7, 148.2, 163.8. MS (ESI) m/z : 275.3 [M+H]⁺. HRMS calcd for C₁₈H₁₅N₂O: 275.1184. Found 275.1188.

4.3. Synthesis of Fmoc-hydrazine **3**³⁰

At 0 °C Fmoc chloride (2 mmol, 517.4 mg) dissolved in acetonitrile (30 mL) is added to hydrazine hydrate (20 mmol, 1 g, 10 equiv) dissolved in 10 mL of a 1/1 mixture water/acetonitrile. The reaction was stirred at 0 °C for 2 h (formation of a white precipitate), then allowed to warm up to room temperature and stirred for an additional hour. The mixture was concentrated under vacuo and the precipitate was washed with water, cyclohexane, and then dried under vacuo to afford the pure title compound as a white solid (481 mg, 95%). Mp 174 °C (lit. 172–173 °C).³⁰

¹H NMR (DMSO) δ 4.07 (s, 2H), 4.18–4.31 (m, 3H), 7.32 (t, 2H, $J=7.4$ Hz), 7.41 (t, 2H, $J=7.4$ Hz), 7.68 (d, 2H, $J=7.4$ Hz), 7.88 (d, 2H, $J=7.4$ Hz), 8.34 (s, 1H); ¹³C NMR (DMSO) δ 46.6, 65.6, 120.1, 125.2, 127.0, 127.6, 140.7, 143.8, 158.2. MS (ESI) m/z : 255.1 [M+H]⁺.

4.3.1. (*E*)-(9*H*-Fluoren-9-yl)methyl-2-benzylidene hydrazinecarboxylate **20** [1111765-75-3]. White powder; mp 193 °C. ¹H NMR (DMSO) δ 4.32 (dd, 1H, $J=5.9, 6.8$ Hz), 4.42–4.55 (m, 2H), 7.39–7.48 (m, 7H), 7.59–7.67 (m, 2H), 7.72–7.81 (m, 2H), 7.92 (d, 2H, $J=7.3$ Hz), 8.05 (s, 1H), 11.20 (s, 1H); ¹³C NMR (DMSO) δ 46.4, 65.7, 120.1, 125.1, 126.6, 127.1, 127.7, 128.7, 129.6, 134.4, 140.8, 143.7, 143.8, 153.2. MS (ESI) m/z : 365.1 [M+Na]⁺, 343.2 [M+H]⁺, 179.1, 165.2. HRMS calcd for C₂₂H₁₉N₂O₂: 343.1447. Found 343.1428.

4.3.2. (*E*)-(9*H*-Fluoren-9-yl)methyl-2-(pyridin-3-ylmethylene)hydrazinecarboxylate **21** [1158960-29-2]. White powder; mp 206 °C. ¹H NMR (DMSO) δ 4.32 (t, 1H, $J=6.9$ Hz), 4.43–4.59 (m, 2H), 7.35 (t, 2H, $J=7.3$ Hz), 7.39–7.52 (m, 3H), 7.71–7.81 (m, 2H), 7.91 (d, 2H, $J=7.6$ Hz), 8.05 (d, 1H, $J=7.8$ Hz), 8.09 (s, 1H), 8.59 (s, 1H), 8.79 (s, 1H), 11.38 (s, 1H); ¹³C NMR (DMSO) δ 46.5, 65.8, 120.1, 123.9, 125.1, 127.1, 127.7, 130.2, 133.0, 140.8, 143.6, 143.8, 148.2, 150.3, 153.2. MS (ESI) m/z : 343.9 [M+H]⁺, 179.1, 165.2. HRMS calcd for C₂₁H₁₈N₃O₂: 344.1399. Found 344.1379.

4.3.3. (*E*)-(9*H*-Fluoren-9-yl)methyl-2-butylidenehydrazinecarboxylate **22**. White powder; mp 162 °C. ¹H NMR (DMSO) δ 0.89 (t, 3H, $J=7.0$ Hz), 1.35–1.59 (m, 2H), 2.07–2.20 (m, 2H), 4.18–4.29 (m, 1H), 4.33–4.48 (m, 2H), 7.25–7.39 (m, 3H), 7.42 (t, 2H, $J=7.3$ Hz), 7.71 (d, 2H, $J=6.8$ Hz), 7.91 (d, 2H, $J=7.3$ Hz), 10.71 (s, 1H); ¹³C NMR (DMSO) δ 13.5, 19.4, 33.6, 43.6, 65.3, 120.1, 125.1, 127.0, 127.6, 140.7, 143.7, 148.2, 153.1. MS (ESI) m/z : 309.1 [M+H]⁺, 179.2, 172.1, 131.1. HRMS calcd for C₁₉H₂₁N₂O₂: 309.1603. Found 309.1600.

4.3.4. (*E*)-(9*H*-Fluoren-9-yl)methyl-2-(2-hydroxybenzylidene)hydrazinecarboxylate **23**. White powder; mp 188 °C. ¹H NMR (DMSO) δ 4.22–4.39 (m, 1H), 4.41–4.61 (m, 2H), 6.89 (d, 2H, $J=7.1$ Hz), 7.27 (t, 1H, $J=7.1$ Hz), 7.29–7.53 (m, 5H), 7.74 (d, 2H, $J=5.9$ Hz), 7.92 (d, 2H, $J=7.1$ Hz), 8.27 (s, 1H), 10.81 (s, 1H), 11.41 (s, 1H); ¹³C NMR (DMSO) δ 46.5, 65.9, 116.2, 119.0, 119.3, 120.1, 125.1, 127.1, 127.7, 128.6, 130.9, 140.8, 143.6, 144.9, 153.2, 156.8. MS (ESI) m/z : 359.1 [M+H]⁺, 181.0. HRMS calcd for C₂₂H₁₉N₂O₃: 359.1396. Found 359.1399.

4.3.5. (*E*)-*N'*-(3,5-Dimethoxybenzylidene)-4-methylbenzenesulfonylhydrazide **24** [67147-57-2]. White solid; mp 115 °C. ¹H NMR (acetone-*d*₆) δ 2.39 (s, 3H), 3.79 (s, 6H), 6.51 (t, 1H, $J=2.3$ Hz), 6.77 (d, 2H, $J=2.3$ Hz), 7.40 (d, 2H, $J=8.1$ Hz), 7.84 (d, 2H, $J=8.3$ Hz), 7.90 (s, 1H), 10.11 (s, 1H). ¹³C NMR (acetone-*d*₆) δ 21.5, 55.8, 103.0, 105.7, 128.6, 130.4, 137.0, 137.4, 144.7, 147.9, 162.0. MS (ESI) m/z : 335.2 [M+H]⁺.

4.3.6. *tert*-Butyl 2-cyclohexylidenehydrazinecarboxylate **25**⁴¹ [60295-11-6]. White powder; mp 131 °C (lit. 134–135 °C). ¹H NMR (acetone-*d*₆) δ 1.45 (s, 9H), 1.63 (m, 6H), 2.22–2.32 (m, 2H), 2.39–2.45 (m, 2H), 8.62 (s, 1H), ¹³C NMR (acetone-*d*₆) δ 26.4, 26.7, 27.2, 28.0, 28.6, 36.0, 79.5, 154.1, 156.4. MS (ESI) m/z : 213.3 [M+H]⁺, 157.0.

4.3.7. (9*H*-Fluoren-9-yl)methyl 2-cyclohexylidenehydrazinecarboxylate **26**⁴² [74105-60-5]. Colorless oil; ¹H NMR (acetone-*d*₆) δ 1.65 (m, 6H), 2.25–2.31 (m, 2H), 2.33–2.45 (m, 2H), 4.21–4.29 (m, 1H), 4.33–4.45 (m, 2H), 7.33 (t, 2H, $J=7.3$ Hz), 7.42 (t, 2H, $J=7.3$ Hz), 7.70–7.79 (m, 2H), 7.87 (d, 2H, $J=7.4$ Hz), 8.58 (s, 1H), 9.10 (s, 1H). ¹³C NMR (acetone-*d*₆+DMSO-*d*₆) δ 24.8, 25.2, 26.5, 34.6, 46.4, 65.5,

119.4, 124.9, 126.5, 127.1, 140.5, 143.5, 154.0, 161.6. MS (ESI) m/z : 335.2 [M+H]⁺, 179.2, 157.2.

4.3.8. 4-Methyl-*N'*-(pentan-3-ylidene)benzenesulfonylhydrazide **27** [28495-72-9]. Yellow solid; mp 101 °C. ¹H NMR (acetone-*d*₆) δ 0.93–1.02 (m, 6H), 2.15–2.29 (m, 4H), 3.40 (s, 3H), 7.36 (d, 2H, $J=7.8$ Hz), 7.77 (d, 2H, $J=8.3$ Hz), 8.81 (s, 1H). ¹³C NMR (acetone-*d*₆) δ 8.1, 21.5, 35.6, 128.9, 130.1, 137.7, 144.2, 211.2. MS (ESI) m/z : 255.1 [M+H]⁺.

4.3.9. *N'*-Cyclohexylidene-4-methylbenzenesulfonylhydrazide **28**⁴³ [4545-18-0]. White powder; mp 160 °C (lit. 162 °C). ¹H NMR (acetone-*d*₆) δ 1.58 (s, 6H), 2.13–2.19 (m, 2H), 2.24–2.34 (m, 2H), 2.42 (s, 3H), 7.36 (d, 2H, $J=8.1$ Hz), 7.77 (d, 2H, $J=8.2$ Hz), 8.96 (s, 1H). ¹³C NMR (acetone-*d*₆) δ 21.4, 25.6, 27.7, 35.6, 42.29, 130.1, 137.8, 144.2, 210.4. MS (ESI) m/z : 267.3 [M+H]⁺.

4.3.10. (*Z*)-4-Methyl-*N'*-(1-phenylethylidene)benzenesulfonylhydrazide **29**⁴⁴ [62460-99-5]. White powder; mp 142 °C (lit. 147 °C). ¹H NMR (acetone-*d*₆) δ 2.24 (s, 3H), 2.39 (s, 3H), 7.32–7.41 (m, 5H), 7.67–7.77 (m, 2H), 7.83 (d, 2H, $J=8.3$ Hz), 9.32 (s, 1H). ¹³C NMR (acetone-*d*₆) δ 16.4, 23.6, 129.1, 131.0, 131.2, 132.3, 139.6, 140.9, 146.6, 155.8. MS (ESI) m/z : 289.2 [M+H]⁺.

4.4. General experimental procedure for the N-alkylation of hydrazones (Table 2)

A mixture of hydrazone (0.3 mmol, 1 equiv), allyl or phenyl bromide (0.9 mmol, 3.0 equiv) and Cs₂CO₃ (0.9 mmol, 293 mg, 3.0 equiv) was ball-milled at 30 Hz during 1 h. AcOEt (5 mL) was added and the solution washed with water (3×5 mL). The organic layer was dried on MgSO₄ and concentrated under vacuo to recover the pure product.

4.4.1. (*E*)-*tert*-Butyl 1-allyl-2-(3,5-dimethoxybenzylidene)hydrazinecarboxylate **30**. White solid; mp 57 °C. ¹H NMR (acetone-*d*₆) δ 1.54 (s, 9H), 3.80 (s, 6H), 4.56 (d, 2H, $J=2.3$ Hz), 5.15 (dd, 2H, $J=15.8, 9.1$ Hz), 5.79–5.92 (m, 1H), 6.47 (t, 1H, $J=2.3$ Hz), 6.91 (m, 2H), 7.85 (s, 1H). ¹³C NMR (acetone-*d*₆) δ 28.4, 46.7, 55.6, 81.5, 102.2, 105.5, 116.6, 132.6, 138.7, 140.4, 153.8, 162.0. MS (ESI) m/z : 321.1 [M+H]⁺, 265.1. HRMS calcd for C₁₇H₂₅N₂O₄: 321.1814. Found 321.1809.

4.4.2. (*E*)-*tert*-Butyl 1-benzyl-2-(3,5-dimethoxybenzylidene)hydrazinecarboxylate **31**. White solid; mp 66 °C. ¹H NMR (acetone-*d*₆) δ 1.58 (s, 9H), 3.78 (s, 6H), 5.20 (m, 2H), 6.46 (t, 1H, $J=2.3$ Hz), 6.85 (d, 2H, $J=2.3$ Hz), 7.21–7.39 (m, 5H), 7.82 (s, 1H). ¹³C NMR (acetone-*d*₆) δ 28.4, 48.3, 55.6, 81.8, 102.2, 105.5, 127.5, 128.0, 129.5, 137.4, 138.5, 140.7, 154.5, 162.0. MS (ESI) m/z : 371.3 [M+H]⁺, 315.2. HRMS calcd for C₂₁H₂₇N₂O₄: 371.1971. Found 371.1972.

4.4.3. (*E*)-*tert*-Butyl 1-allyl-2-(naphthalen-2-ylmethylene)hydrazinecarboxylate **32**^{33a} [1005794-79-5]. White solid; mp 69 °C (lit. 67–70 °C). ¹H NMR (acetone-*d*₆) δ 1.58 (s, 9H), 4.65 (s, 2H), 5.19 (m, 2H), 5.86–5.97 (m, 1H), 7.52–7.57 (m, 2H), 7.90–7.97 (m, 3H), 8.04–8.09 (m, 3H). ¹³C NMR (acetone-*d*₆) δ 28.5, 46.9, 81.6, 116.7, 123.7, 127.4, 127.5, 128.7, 129.0, 129.1, 129.2, 132.8, 134.3, 134.4, 134.9, 140.8, 153.8. MS (ESI) m/z : 311.2 [M+H]⁺, 255.2.

4.4.4. (*E*)-*tert*-Butyl 1-allyl-2-benzylidenehydrazinecarboxylate **33**. Colorless oil; ¹H NMR (acetone-*d*₆) δ 1.54 (s, 9H), 4.57–4.59 (m, 2H), 5.15 (m, 2H), 5.79–5.88 (m, 1H), 7.33–7.42 (m, 3H), 7.72 (d, 2H, $J=7.7$ Hz), 7.87 (s, 1H). ¹³C NMR (acetone-*d*₆) δ 28.4, 46.8, 81.4, 116.6, 127.7, 129.4, 129.9, 132.7, 136.6, 140.8, 153.8. MS (ESI) m/z :

261.2 [M+H]⁺, 205.0. HRMS calcd for C₁₅H₂₁N₂O₂: 261.1603. Found 261.1599.

4.4.5. (*E*)-*tert*-Butyl 1-allyl-2-(2-(allyloxy)benzylidene)hydrazine-carboxylate **34**. Colorless oil; ¹H NMR (acetone-*d*₆) δ 1.54 (s, 9H), 4.57–4.59 (m, 2H), 5.15 (m, 2H), 5.79–5.88 (m, 1H), 7.33–7.42 (m, 3H), 7.72 (d, 2H, *J*=7.7 Hz), 7.87 (s, 1H). ¹³C NMR (acetone-*d*₆) δ 28.4, 46.8, 81.4, 116.6, 127.7, 129.4, 129.9, 132.7, 136.6, 140.8, 153.8. MS (ESI) *m/z*: 261.2 [M+H]⁺, 205.0. HRMS calcd for C₁₅H₂₁N₂O₂: 261.1603. Found 261.1599.

4.4.6. (*E*)-*N*-Allyl-*N'*-(3,5-dimethoxybenzylidene)benzohydrazide **35**. White solid; mp 99 °C. ¹H NMR (acetone-*d*₆) δ 3.71 (s, 6H), 4.86 (m, 2H), 5.21–5.26 (m, 2H), 5.89–6.02 (m, 1H), 6.44 (s, 1H), 6.71 (s, 2H), 7.47–7.50 (m, 3H), 7.72–7.76 (m, 2H), 7.86 (s, 1H). ¹³C NMR (acetone-*d*₆) δ 44.0, 55.6, 102.7, 105.6, 117.1, 128.1, 130.6, 130.8, 131.9, 136.9, 138.2, 140.4, 162.0, 171.0. MS (ESI) *m/z*: 325.3 [M+H]⁺ HRMS calcd for C₁₉H₂₁N₂O₃: 325.1552. Found 325.1550.

4.4.7. (*E*)-*N*-Benzyl-*N'*-(3,5-dimethoxybenzylidene)benzohydrazide **36**. White solid; mp 120 °C. ¹H NMR (acetone-*d*₆) δ 3.68 (s, 6H), 5.50 (s, 2H), 6.41 (t, 1H, *J*=2.3 Hz), 6.62 (s, 1H), 7.34–7.41 (m, 6H), 7.52–7.66 (m, 2H), 7.76–7.83 (m, 2H), 7.86 (s, 1H). ¹³C NMR (acetone-*d*₆) δ 45.8, 56.0, 103.1, 106.0, 128.1, 128.6, 130.2, 131.0, 131.4, 136.9, 137.3, 138.4, 140.9, 162.4, 172.1. MS (ESI) *m/z*: 375.2 [M+H]⁺ HRMS calcd for C₂₃H₂₃N₂O₃: 375.1709. Found 375.1703.

4.4.8. (*E*)-*N*-Allyl-*N'*-(3,5-dimethoxybenzylidene)-4-methylbenzenesulfonohydrazide **37**. White solid; mp 113 °C. ¹H NMR (acetone-*d*₆) δ 2.41 (s, 3H), 3.81 (s, 6H), 4.47–4.51 (m, 2H), 5.20–5.29 (m, 2H), 5.80–5.88 (m, 1H), 6.51 (t, 1H, *J*=2.3 Hz), 6.83 (s, 2H), 7.40 (d, 2H, *J*=8.1 Hz), 7.74 (s, 1H), 7.90 (d, 2H, *J*=8.3 Hz). ¹³C NMR (acetone-*d*₆) δ 19.4, 47.9, 53.7, 100.8, 103.6, 116.0, 127.0, 128.4, 130.5, 134.3, 135.4, 142.4, 143.1, 160.0. MS (ESI) *m/z*: 375.2 [M+H]⁺. HRMS calcd for C₁₉H₂₃N₂O₄S: 375.1379. Found 375.1374.

4.4.9. *tert*-Butyl 1-allyl-2-cyclohexylidenehydrazinecarboxylate **38**. Colorless oil; ¹H NMR (acetone-*d*₆) δ 1.42 (s, 9H), 1.61–1.69 (m, 6H), 2.24–2.34 (m, 4H), 4.04 (m, 2H), 5.03–5.13 (m, 2H), 5.71–5.89 (m, 1H). ¹³C NMR (acetone-*d*₆) δ 27.0, 27.6, 28.7, 29.2, 31.4, 36.6, 42.9, 53.7, 80.8, 117.5, 136.0, 153.7, 178.9. MS (ESI) *m/z*: 253.3 [M+H]⁺, 197.0. HRMS calcd for C₁₄H₂₅N₂O₂: 253.1916. Found 253.1941.

4.4.10. *N*-Allyl-4-methyl-*N'*-(pentan-3-ylidene)benzenesulfonohydrazide **39**. Yellow oil; ¹H NMR (acetone-*d*₆) δ 1.07 (t, 3H, *J*=7.5 Hz), 1.10 (t, 3H, *J*=7.7 Hz), 2.37 (q, 2H, *J*=7.4 Hz), 2.45 (s, 3H), 2.63 (q, 2H, *J*=7.7 Hz), 3.56 (d, 2H, *J*=6.7 Hz), 5.07 (m, 2H), 5.67 (m, 1H), 7.43 (d, 2H, *J*=8.0 Hz), 7.69 (d, 2H, *J*=8.3 Hz). ¹³C NMR (acetone-*d*₆) δ 10.8, 11.0, 21.6, 26.2, 29.1, 56.0, 119.6, 130.0, 130.2, 133.7, 144.8, 187.9. MS (ESI) *m/z*: 295.4 [M+H]⁺, 273.2. HRMS calcd for C₁₅H₂₃N₂O₂S: 295.1480. Found 295.1457.

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