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Effective strategy for the systematic synthesis of hydrazine derivatives

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ABSTRACT

A new and efficient strategy for the systematic synthesis of hydrazine derivatives is reported. It allows the synthesis of up to tetrasubstituted hydrazine derivatives with minimal number of steps using only one protecting group or without any of them at all. Simple and readily available starting materials such as hydrazine hydrate or phenylhydrazine can be used. A variety of substrates were used to investigate scope and limitations of this strategy, additionally one full synthetic sequence was performed.

1. Introduction

Hydrazine derivatives are widely used compounds in the pharmaceutical, agrochemical, polymer and dye industries and also as precursors in organic synthesis.[1] Many hydrazine derivatives show significant biological activity and several compounds with hydrazine moiety were shown to be effective for treatment of tuberculosis, Parkinson's disease and hypertension.[2] In addition, some hydrazines display neuroprotective properties and are used as antidepressant drugs.[3] Hydrazine-based peptidomimetics (azapeptides) were found to be potent agents against hepatitis,[4] AIDS[5] and SARS.[6] Hydrazine derivatives are also being used for the derivatization of nanostructures.[7] Therefore, the synthesis of hydrazine derivatives is a matter of significant interest from both theoretical and practical perspectives.

The widespread use of hydrazine derivatives as precursors for heterocycles and peptidomimetics has led to the appearance of a numerous specific methods for synthesis of the target compound. Nevertheless, the development of a strategy that would provide a possibility for selective synthesis of any desired product using the same methodology has always been a tempting task for the chemists. However, despite all efforts in this area, only a few general methods have been described so far.

Most of the efforts have been concentrated on selective alkylation reactions, because direct alkylation of hydrazines generally proceeds unselectively and produces a mixture of starting compound, product and overalkylated side products. Thus, until recent time selective alkylation of hydrazines has been quite a complicated task.

Recently, some triprotected hydrazine precursors have been developed, which have provided a pathway for the selective alkylation and systematic synthesis of hydrazine derivatives.[8,9] These publications created an orthogonal protecting group strategy, which idea was in use of a precursor containing different protecting groups that can be selectively removed under non-overlapping conditions. After derivatization of the free position in such precursor the required protective group can be selectively removed and deprotected position can be derivatized again. This procedure can be repeated until the desired compound is formed. However, this strategy requires a lot of protection/deprotection steps for obtaining the desired product. Further investigations have led to the development of precursors containing only two protecting groups.[10] Only few general methods for synthesis of hydrazine derivatives, that do not utilize orthogonal protecting group strategy, have been published.[11]

The fast progress in field of structure–properties relationship, measurements of the acidity of organic compounds and wide distribution of strong bases such as organolithium compounds as synthetic reagents, led us to a development of the completely new strategy that is not based on the use of protecting groups.

Very recently we have described a new method for the alkylation of *tert*-butyl 2-phenylhydrazinecarboxylate via the corresponding dianion and studied the scope of this reaction using a variety of alkyl substituents.[12] Tetrasubstituted hydrazine derivatives can also be obtained using this procedure, but they necessarily contain Ph and Boc groups. Our current work expands the

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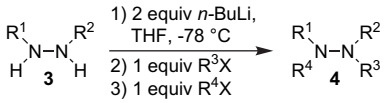
method from the alkylation of *tert*-butyl 2-phenylhydrazinecarboxylate to a fully functional strategy for obtaining up to tetrasubstituted hydrazines, including a variety of functional groups and starting only with hydrazine hydrate or simple commercially available monosubstituted hydrazines.

The main goal of our current work is to demonstrate the new general strategy for the systematic synthesis of hydrazine derivatives.

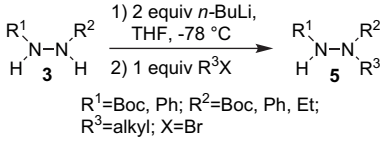
2. Results and discussion

The key step of our strategy is the formation of a dianion, which is subsequently used for obtaining the target compound. In our current work, we show that the dianion can be formed not only from PhNHNHBoc, as we have reported before, but also from a variety of hydrazine derivatives bearing alkyl, aryl and acyl groups, which can belong to a different classes of compounds (e.g., BocNHNHBoc, PhNHNHPh, EtNHNHBoc). This shows the scope and generality of the strategy. We also report one full synthetic sequence and numerous other examples in order to illustrate the benefits of this approach.

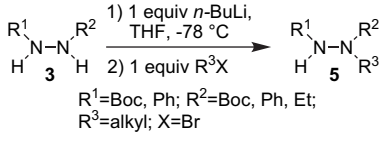
The first step of the synthesis is to obtain a monosubstituted hydrazine derivative **1**. This transformation can be done by variety of conventional methods.[13] The second step is the creation of a disubstituted derivative **3**. Commercially available mono and disubstituted reagents may also be used.



Scheme 1. Selective dialkylation of dianion.



Scheme 2. Synthesis of trisubstituted hydrazine derivatives (Method a).



Scheme 3. Synthesis of trisubstituted hydrazine derivatives (Method b).

The third step (Scheme 1) was carried out by addition of 2 equiv of *n*-BuLi to the compound **3** followed by the addition of 1 equiv of alkyl halide. After the first equivalent of alkyl halide has reacted, a second one was added. The first alkylation occurs on the most basic and nucleophilic nitrogen and the second happens on the other one. Generally reactions proceeded smoothly with high selectivity and yields. The dianions obtained from phenyl containing hydrazine derivatives are coloured substances. For example, the dianion obtained from BocNHNHPh (**3b**) is bright yellow and from PhNHNHPh (**3c**) is green, but dianions obtained from BocNHNHEt (**3a**) and BocNHNHBoc (**3d**) are colourless. Also the dianion obtained from BocNHNHBoc has a tendency to precipitate from the reaction mixture.

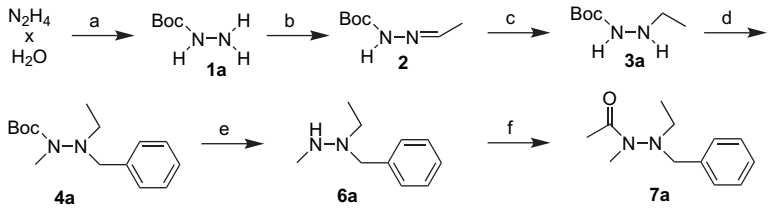
The metallation of PhNHNHPh (**3c**) must be conducted under a carefully controlled inert atmosphere. If there is significant amount of oxygen present, it will lead to a quick decomposition of the corresponding dianion. The water addition workup of the reaction mixture is also required before the purification step. Otherwise, the decomposition of the product may occur when it comes into contact with air. We suppose that decomposition is caused by a radical mechanism. For other substrates (**3a**, **3b** and **3d**) such a phenomenon has not been noticed.

In order to obtain trisubstituted derivative with one free NH group 1 equiv of alkylating agent has been used, yielding corresponding derivatives **5a**–**c** (Scheme 2). The alkylation also occurs on the most basic and nucleophilic nitrogen and the other one remains unreacted as lithium salt. After the addition of water the product is obtained.

Another possibility is to use only 1 equiv of *n*-BuLi in order to increase the atom efficiency (Scheme 3) of the reaction. Generally, the use of 1 equiv of *n*-BuLi should lead to the metallation and alkylation of the most acidic and less nucleophilic nitrogen.[12] However, it is not always so for the alkyl-substituted hydrazine derivatives. As we have reported before,[14] the catalytic cycle may lead to the formation of thermodynamically unfavoured product. Metallation of EtNHNHBoc (**3a**) with 1 equiv of *n*-BuLi followed by alkylation with allyl bromide should result in the formation of *tert*-butyl 1-allyl-2-ethylhydrazinecarboxylate, however, we have obtained *tert*-butyl 2-allyl-2-ethylhydrazinecarboxylate (**5a**) as the main product.

If obtained derivative **4** contains protecting groups as substituents (**4a**–**c**, **4f**), they can be removed by the appropriate method and optionally replaced with any desired group (Scheme 4).

We have performed one full sequence starting with hydrazine hydrate and ending with the fully substituted hydrazine derivative in order to illustrate our strategy (Scheme 4). In the first step $BocNHNH_2$ (**1a**) was made from hydrazine hydrate. Then hydrazone **2** was obtained by condensation of **1a** with ethanal. Then **2** has been reduced with lithium aluminium hydride yielding compound **3a**. A solution of **2** in dry THF was added to the suspension of LAH in THF on ice bath to prevent boiling. Compound **4a** was obtained via standard procedure (Scheme 1). Thereafter, the Boc group was removed with TFA solution in dichloromethane and the product was treated with aqueous 1 M KOH to obtain free hydrazine **6a**. Finally **6a** was acylated with Ac_2O in the presence of pyridine (Table 1).



Scheme 4. Example of systematic synthesis of tetrasubstituted hydrazine derivative. (a) Boc_2O, *i*-PrOH, 2 h, rt; (b) CH_3CHO, $CHCl_3$, 1 h, rt; (c) LAH, THF, 0 °C; (d) (1) 2 equiv *n*-BuLi, THF, −78 °C; (2) 1 equiv BnBr, 2 h, −60 °C to rt; (3) MeI, 3 h, rt; (e) (1) TFA/CH_2Cl_2 1:2, 1 h, rt; (2) KOH (aq); (f) Ac_2O, Py, CH_2Cl_2, 2 h, rt.

Table 1
Synthesized compounds

Compound	R^1	R^2	R^3	R^4	Yield, %
1a[19]	Boc	H	H	H	75
2[16]	Boc	$=CHCH_3$	—	H	100
3a[16]	Boc	Et	H	H	57
3b[17]	Boc	Ph	H	H	69
3d[3]	Boc	Boc	H	H	85
4a	Boc	Et	Bn	Me	60
4b	Boc	Ph	Allyl	Me	93
4c	Boc	Et	Allyl	Me	70
4d[15]	Ph	Ph	Me	Me	97
4e	Ph	Ph	Allyl	Me	71
4f[11]	Boc	Boc	Bn	Bn	97
5a	Boc	Et	Allyl	H	65
5b[18]	Ph	Ph	Allyl	H	96
5c[11]	Boc	Boc	Bn	H	71
5d[11]	Boc	Boc	Allyl	H	80
6a	H	Et	Bn	Me	93
6b[18]	H	Ph	Allyl	Me	97
7a	Ac	Et	Bn	Me	67
7b	Ac	Ph	Allyl	Me	98
7c	COOEt	Ph	Allyl	Me	97
7d	$COCF_3$	Ph	Allyl	Me	93

3. Conclusions

In summary, we have demonstrated a new strategy for the systematic synthesis of hydrazine derivatives using only one protective group or without any them at all. This strategy includes several methods, which are chosen according to the structure and complexity of the target compound. Tetrasubstituted products with any desired substituents are obtained in five steps starting from hydrazine hydrate. In contrast to that, all the methods reported before demand at least twice as much steps. Furthermore, desired product can be prepared in one step if starting from disubstituted hydrazine derivative. To the best of our knowledge, this is completely new and unprecedented result.

4. Experimental

4.1. General

All reagents were obtained from commercial sources and were used without further purification. THF was freshly distilled from Na/benzophenone. NMR spectroscopy was performed on a Bruker Avance II 200 (200 MHz) spectrometer using TMS as internal standard. HRMS analyses were made on a Thermo Electron LTQ Orbitrap instrument using ESI ionization. Infrared spectra were measured on a Perkin–Elmer PC16 FTIR spectrometer, using KBr pellet technique for solid compounds and liquid film technique for oils. Melting points were determined on a Gallenkamp melting point apparatus.

4.1.1. *tert-Butyl hydrazinecarboxylate (**1a**)*[19]

Hydrazine monohydrate (80%, 32.5 g, 520 mmol) was mixed with isopropanol (100 mL) at 0 °C, then a solution of Boc_2O (50.0 g, 230 mmol) in isopropanol (50 mL) was added dropwise. The reaction mixture turned cloudy upon addition and stirring was continued at room temperature for 2 h. The solvent was removed, the residue dissolved in CH_2Cl_2 and dried over $MgSO_4$. Then CH_2Cl_2 was evaporated and the residue was recrystallized from hexane, resulting the *title compound* **1a** (22.8 g, 75%) as colourless crystals, mp 36–37 °C. R_f (EtOAc/hexane 1:1) 0.20. ^{1}H NMR (200 MHz, $CDCl_3$, TMS): δ=6.13 (s, 1H, *NH*), 3.68 (s, 2H, NH_2), 1.42 (s, 9H, $C(CH_3)_3$). ^{13}C NMR (50 MHz, $CDCl_3$, TMS): δ=158.3, 77.2, 28.5. FTIR ν (cm^{-1}): 3375, 3328, 2984, 2937, 1701, 1627, 1506, 1289, 1168, 592.

4.1.2. *tert-Butyl 2-ethylidenehydrazinecarboxylate (**2**)*[16]

Compound **1a** (5.000 g, 37.8 mmol) was dissolved in $CHCl_3$ (50 mL) and 1 equiv (2.12 mL, 37.8 mmol) of freshly distilled CH_3CHO was added. The reaction was monitored by TLC analysis (EtOAc/hexane 1:1). After 30 min the reaction was mainly complete. Then another portion of CH_3CHO (0.5 mL) and $MgSO_4$ were added. After 30 min the mixture was filtered and evaporated. The *title compound* **2** (5.985 g, 100%) was obtained as colourless solid, mp 82–84 °C. R_f (EtOAc/hexane 1:1) 0.28. ^{1}H NMR (200 MHz, $CDCl_3$, TMS): δ=8.59 (s, 1H, *NH*), 7.32 (q, J=5.3 Hz, 1H, $=CHCH_3$), 1.94 (d, J=5.4 Hz, 3H, $=CHCH_3$), 1.49 (s, 9H, $C(CH_3)_3$). ^{13}C NMR (50 MHz, $CDCl_3$, TMS): δ=153.1, 143.6, 80.7, 28.5, 18.1. FTIR ν (cm^{-1}): 3239, 3049, 2977, 2930, 1708, 1600, 1528, 1364, 1256, 1148, 747.

4.1.3. *tert-Butyl 2-ethylhydrazinecarboxylate (**3a**)*[16]

$LiAlH_4$ (1.44 g, 37.9 mmol) was suspended in dry THF (30 mL) under argon. Then a solution of **2** (5.930 g, 37.5 mmol) in THF (30 mL) was slowly added to the ice cooled reaction mixture. The reaction was monitored by TLC analysis (EtOAc/hexane 1:1). After 1 h the reaction was complete. The volatiles were removed, then Et_2O (100 mL) and 50 mL of 3 M NH_4Cl aqueous solution were added to the residue. The organic layer was separated and aqueous fraction was additionally extracted with Et_2O (2×100 mL). The organic layers were combined and evaporated. The residue was purified by column chromatography (EtOAc/hexane 1:1) resulting the *title compound* **3a** (3.44 g, 57%) as a colourless oil. R_f (EtOAc/hexane 1:1) 0.43. ^{1}H NMR (200 MHz, $CDCl_3$, TMS): δ=7.13 (s, 1H, Boc*NH*), 4.03 (s, 1H, Et*NH*), 2.87 (q, J=7.2 Hz, 2H, CH_2CH_3), 1.46 (s, 9H, $C(CH_3)_3$), 1.06 (t, J=7.2 Hz, 3H, CH_2CH_3). ^{13}C NMR (50 MHz, $CDCl_3$, TMS): δ=157.1, 80.1, 46.4, 28.5, 12.8. FTIR ν (cm^{-1}): 3295, 2977, 2874, 1703, 1451, 1287, 1251, 1158, 789.

4.1.4. *tert-Butyl 2-phenylhydrazinecarboxylate (**3b**)*[17]

Phenyl hydrazine (**1b**, 5.407 g, 50 mmol) was dissolved in acetonitrile (20 mL), then Boc_2O (11.5 mL, 50 mmol) was added. The reaction was stirred for 2 h. Then volatiles were removed and residue was recrystallized from hexane. The *title compound* **3b** (7.2 g, 69%) was obtained as colourless crystals, mp 91–92 °C. R_f (EtOAc/hexane 1:4) 0.28. ^{1}H NMR (200 MHz, $CDCl_3$, TMS): δ=7.13–7.21 (m, 2H, Ph), 6.71–6.87 (m, 4H, Ph, Boc*NH*), 5.92 (br s, 1H, Ph*NH*), 1.43 (s, 9H, $C(CH_3)_3$). ^{13}C NMR (50 MHz, $CDCl_3$, TMS): δ=156.5, 148.8, 129.1, 120.7, 113.3, 81.1, 28.4. FTIR ν (cm^{-1}): 3400, 3340, 2982, 2925, 1725, 1700, 1605, 1500, 1169, 748.

4.1.5. *Di-tert-butyl hydrazine-1,2-dicarboxylate (**3d**)*[3]

Compound **1a** (5 g, 37.83 mmol) was added to liquid Boc_2O (9.08 g, 41.66 mmol). The reaction was monitored by TLC (EtOAc/hexane 1:1). Gas evolution was observed during the reaction and after the end of reaction the mixture became solid. Reaction was complete in 10 min. Recrystallization from hexane/chloroform 4:1 mixture gave the *title compound* **3d** (7.472 g, 85%) as colourless crystals, mp 122 °C. R_f (EtOAc/hexane 1:4) 0.23. ^{1}H NMR (200 MHz, $CDCl_3$, TMS): δ=6.60 (s, 2H, Boc*NH*), 1.47 (s, 9H, $C(CH_3)_3$). ^{13}C NMR (50 MHz, $CDCl_3$, TMS): δ=156.0, 81.4, 28.3. FTIR ν (cm^{-1}): 3316, 3013, 2982, 2925, 1698, 1482, 1241, 1148, 763.

4.2. General procedure for the syntheses of compounds 4a–f

4.2.1. *tert-Butyl 2-benzyl-2-ethyl-1-methylhydrazine-carboxylate (**4a**)*

An oven-dried flask was charged with **3a** (640 mg, 4 mmol), evacuated, backfilled with argon and then THF (20 mL) was added. The reaction mixture was cooled down to −78 °C, then 1.6 M *n*-BuLi (5 mL, 8 mmol) solution in hexane was added dropwise and the resulting mixture was allowed to warm up to −60 °C for 15 min. Then BnBr (0.48 mL, 4 mmol) was added and the reaction mixture

was allowed to warm up to room temperature in 1 h. Then reaction mixture was stirred for another 1 h at room temperature. After this MeI (0.25 mL, 4 mmol) was added and the reaction was stirred for additional 3 h. Then H_2O (0.1 mL) was added and volatiles were evaporated. To the resulting mixture $CHCl_3$ (40 mL) and $MgSO_4$ were added. Then mixture was filtered and volatiles were removed. The residue was purified by column chromatography on silica (EtOAc/hexane 1:4). The *title compound* **4a** (631 mg, 60%) was obtained as a colourless oil. R_f (EtOAc/hexane 1:4) 0.60. ^{1}H NMR (200 MHz, $CDCl_3$, TMS): δ=7.32–7.39 (m, 5H, Ph), 3.85–4.23 (m, 2H, CH_2Ph), 2.71–2.78 (m, 5H, CH_2CH_3, NCH_3), 1.46 (s, 9H, C$(CH_3)_3$), 1.04 (t, J=7.2 Hz, 3H, CH_2CH_3). ^{13}C NMR (50 MHz, $CDCl_3$, TMS): δ=156.0, 138.6, 129.3, 128.1, 127.1, 79.7, 59.0, 47.9, 28.7, 13.0. FTIR ν (cm^{-1}): 3064, 3033, 2972, 2925, 2864, 1693, 1359, 1148, 743, 691. HRMS (ESI): m/z calcd for $C_{15}H_{25}N_2O_2$ (MH^+): 265.1911; found: 265.1909.

4.2.2. *tert*-Butyl 2-allyl-1-methyl-2-phenylhydrazine-carboxylate (**4b**)

Compound **4b** was prepared as described for **4a** starting with **3b** and using allyl bromide as R^3X and MeI as R^4X. Crude product was purified by column chromatography on silica (EtOAc/hexane 1:4). After purification the *title compound* **4b** (2.431 g, 93%) was obtained as a colourless oil. R_f (EtOAc/hexane 1:4) 0.62. ^{1}H NMR (200 MHz, $CDCl_3$, TMS): δ=7.18–7.26 (m, 2H, Ph), 6.62–6.83 (m, 3H, Ph), 5.91–6.05 (m, 1H, CH=CH_2), 5.17–5.36 (m, 2H, CH=CH_2), 3.96–4.12 (m, 2H, NCH_2–CH=CH_2), 3.11 (s, 3H, NCH_3), 1.31/1.48 (s, 9H, C$(CH_3)_3$). ^{13}C NMR (50 MHz, $CDCl_3$, TMS): δ=155.9, 148.1, 134.3, 129.2, 119.0, 117.5, 112.6, 80.6, 55.0, 35.9, 28.4. FTIR ν (cm^{-1}): 3064, 3023, 2977, 2930, 1703, 1600, 1492, 1369, 1154, 747, 691. HRMS (ESI): m/z calcd for $C_{15}H_{23}N_2O_2$ (MH^+): 263.1754; found: 263.1752.

4.2.3. *tert*-Butyl 2-allyl-2-ethyl-1-methylhydrazinecarboxylate (**4c**)

Compound **4c** was prepared as described for **4a** starting with **3a** and using allyl bromide as R^3X and MeI as R^4X. Crude product was purified by column chromatography on silica (EtOAc/hexane 1:1). After purification the *title compound* **4c** (150 mg, 70%) was obtained as a colourless oil. R_f (EtOAc/hexane 1:4) 0.54. ^{1}H NMR (200 MHz, $CDCl_3$, TMS): δ=5.78–5.99 (m, 1H, CH=CH_2), 5.06–5.22 (m, 2H, CH=CH_2), 3.24–3.64 (m, 2H, NCH_2–CH=CH_2), 2.88 (s, 3H, NCH_3), 2.63–2.72 (m, 2H, CH_2CH_3), 1.47 (s, 9H, C$(CH_3)_3$), 1.03 (t, J=7.2 Hz, 3H, CH_2CH_3). ^{13}C NMR (50 MHz, $CDCl_3$, TMS): δ=155.9, 135.6, 117.1, 79.7, 57.9, 48.1, 28.7, 12.9. FTIR ν (cm^{-1}): 2977, 2920, 2869, 1698, 1364, 1148. HRMS (ESI): m/z calcd for $C_{11}H_{23}N_2O_2$ (MH^+): 215.1754; found: 215.1752.

4.2.4. 1,2-Dimethyl-1,2-diphenylhydrazine (**4d**)[15]

Compound **4d** was prepared as described for **4a** starting with **3c**. Crude product was purified by column chromatography on silica (EtOAc/hexane 1:8). After purification the *title compound* **4d** (206 mg, 97%) was obtained as a colourless crystals, mp 32–33 °C. R_f (EtOAc/hexane 1:8) 0.72. ^{1}H NMR (200 MHz, $CDCl_3$, TMS): δ=7.17–7.25 (m, 4H, Ph), 6.74–6.83 (m, 6H, Ph), 2.92 (s, 6H, NCH_3). ^{13}C NMR (50 MHz, $CDCl_3$, TMS): δ=149.1, 129.3, 118.6, 112.6, 33.7. FTIR ν (cm^{-1}): 3095, 3064, 3023, 2982, 2951, 2869, 2802, 1600, 1492, 1318, 1102, 753, 686, 501.

4.2.5. 1-Allyl-2-methyl-1,2-diphenylhydrazine (**4e**)

Compound **4e** was prepared as described for **4a** starting with **3c** and using allyl bromide as R^3X and MeI as R^4X. Crude product was purified by column chromatography on silica (EtOAc/hexane 1:8). After purification the *title compound* **4e** (170 mg, 71%) was obtained as yellowish oil. R_f (EtOAc/hexane 1:8) 0.74. ^{1}H NMR (200 MHz, $CDCl_3$, TMS): δ=7.15–7.22 (m, 4H, Ph), 6.73–6.78 (m, 6H, Ph), 5.84–6.03 (m, 1H, CH=CH_2), 5.07–5.27 (m, 2H, CH=CH_2), 3.97–4.00 (m, 2H, NCH_2–CH=CH_2), 2.99 (s, 3H, NCH_3). ^{13}C NMR (50 MHz, $CDCl_3$, TMS): δ=149.2, 148.1, 134.8, 129.3, 122.9, 118.8, 118.3, 117.2, 113.1, 112.2, 52.7, 35.7. FTIR ν (cm^{-1}): 3059, 3028, 2977, 2930, 2890, 2807, 1595, 1498, 1333, 1241, 994, 917, 743, 691, 501. HRMS (ESI): m/z calcd for $C_{16}H_{19}N_2$ (MH^+): 239.1543; found: 239.1541.

4.2.6. Di-*tert*-butyl 1,2-dibenzylhydrazine-1,2-dicarboxylate (**4f**)[11]

Compound **4f** was prepared as described for **4a** starting with **3d**. Crude product was purified by column chromatography on silica (EtOAc/hexane 1:4). After purification the *title compound* **4f** (402 mg, 97%) was obtained as a colourless oil. R_f (EtOAc/hexane 1:4) 0.58. ^{1}H NMR (200 MHz, $CDCl_3$, TMS): δ=7.24 (s, 10H, Ph), 4.23–4.53 (m, 4H, CH_2Ph), 1.29/1.44 (s, 18H, C$(CH_3)_3$). ^{13}C NMR (50 MHz, $CDCl_3$, TMS): δ=155.1, 138.0, 137.4, 129.5, 129.0, 128.8, 128.2, 127.4, 81.0, 53.6, 28.2. FTIR ν (cm^{-1}): 3090, 3064, 3028, 2977, 2930, 2874, 1708, 1390, 1225, 1169, 742, 691.

4.3. General procedure for compounds 5a–c

4.3.1. *tert*-Butyl 2-allyl-2-ethylhydrazinecarboxylate (**5a**)

Method a. An oven-dried flask was charged with **3a** (160 mg, 1 mmol), evacuated, backfilled with argon and then THF (5 mL) was added. The reaction mixture was cooled down to −78 °C, then 1.6 M *n*-BuLi (1.25 mL, 2 mmol) solution in hexane was added dropwise and the resulting mixture was allowed to warm up to −60 °C for 15 min. Then allyl bromide (0.09 mL, 1 mmol) was added and the reaction mixture was allowed to warm up to room temperature. The reaction was complete in 1 h. Then H_2O (0.1 mL) was added and volatiles were evaporated. To the resulting mixture $CHCl_3$ (10 mL) and $MgSO_4$ were added. The mixture was filtered and volatiles were removed. The residue was purified by column chromatography on silica (EtOAc/hexane 1:1). The *title compound* **5a** (130 mg, 65%) was obtained as a colourless oil. R_f (EtOAc/hexane 1:1) 0.60. ^{1}H NMR (200 MHz, $CDCl_3$, TMS): δ=5.81–6.02 (m, 1H, BocNH), 5.53 (s, 1H, CH=CH_2), 5.13–5.25 (m, 2H, CH=CH_2), 3.37–3.40 (m, 2H, NCH_2–CH=CH_2), 2.76 (q, J=7.2 Hz, 2H, CH_2CH_3), 1.44 (s, 9H, C$(CH_3)_3$),1.1 (t, J=7.2 Hz, 3H, CH_2CH_3). ^{13}C NMR (50 MHz, $CDCl_3$, TMS): δ=155.6, 134.3, 118.1, 79.7, 60.7, 51.2, 28.5, 12.2. FTIR ν (cm^{-1}): 3269, 2972, 2925, 2864, 1713, 1528, 1446, 1246, 1169, 917. HRMS (ESI): m/z calcd for $C_{10}H_{21}N_2O_2$ (MH^+): 201.1598; found: 201.1597.

Method b (1 equiv *n*-BuLi). An oven-dried flask was charged with *tert*-butyl 2-ethylhydrazinecarboxylate (**3a**, 160 mg, 1 mmol), evacuated, backfilled with argon and then THF (5 mL) was added. The reaction mixture was cooled down to −78 °C, then 1.6 M *n*-BuLi (0.65 mL, 1 mmol) solution in hexane was added dropwise and the resulting mixture was stirred for 15 min. Then allyl bromide (0.09 mL, 1 mmol) was added and the reaction mixture was maintained at −40 °C for 4 h, then allowed to warm up to room temperature. Then H_2O (0.1 mL) was added and volatiles were evaporated. To the resulting mixture $CHCl_3$ (10 mL) and $MgSO_4$ were added. Then mixture was filtered and volatiles were removed. The residue was purified by column chromatography on silica (EtOAc/hexane 1:1). Colourless oil of 76 mg was obtained, which gave exactly the same results of analysis as **5a**. Yield was 40%.

4.3.2. 1-Allyl-1,2-diphenylhydrazine (**5b**)[18]

Method a. Compound **5b** was prepared as described for **5a** starting with **3c**. Crude product was purified by column chromatography on silica (EtOAc/hexane 1:8). After purification the *title compound* **5b** (214 mg, 96%) was obtained as yellowish oil. R_f (EtOAc/hexane 1:8) 0.61. ^{1}H NMR (200 MHz, $CDCl_3$, TMS): δ=7.16–7.22 (m, 4H, Ph), 6.92–6.96 (m, 2H, Ph), 6.75–6.84 (m, 4H, Ph), 5.76–5.96 (m, 1H, CH=CH_2), 5.61 (s, 1H, PhNH), 5.14–5.24 (m, 2H, CH=CH_2), 4.06–4.08 (m, 2H, NCH_2–CH=CH_2). ^{13}C NMR (50 MHz, $CDCl_3$, TMS): δ=150.0, 147.6, 132.4, 129.4, 129.2, 120.0, 119.1, 118.6, 113.4, 113.0, 54.0. FTIR ν (cm^{-1}): 3326, 3054, 3018, 2977, 2905, 2859, 1595, 1492, 1302, 1256, 1225, 989, 922, 748, 686.

Method b (1 equiv *n*-BuLi). An oven-dried flask was charged with **3c** (184 mg, 1 mmol), evacuated, backfilled with argon and then THF (5 mL) was added. Reaction mixture was cooled down to −78 °C, then 1.6 M *n*-BuLi (0.65 mL, 1 mmol) solution in hexane was added dropwise and the resulting mixture was stirred for 15 min. The mixture was allowed to warm up to −60 °C for 15 min and allyl bromide (0.09 mL, 1 mmol) was added. Reaction mixture was allowed to warm up to room temperature. Reaction was complete in 2 h as judged from TLC. Then H_2O (0.1 mL) was added and volatiles were evaporated. To the resulting mixture $CHCl_3$ (10 mL) and $MgSO_4$ were added. Then mixture was filtered and volatiles were removed. Residue was purified by column chromatography on silica (EtOAc/hexane 1:8). Colourless oil of 204 mg was obtained, which gave exactly the same results of analysis as **5b**. Yield was 91%.

4.3.3. Di-tert-butyl 1-benzylhydrazine-1,2-dicarboxylate (**5c**)[11]

Method a. Compound **5c** was prepared as described for **5a** starting with **3d**. Crude product was purified by column chromatography on silica (EtOAc/hexane 1:4). The *title compound* **5c** (230 mg, 71%) was obtained as colourless crystals, mp 103–105 °C. R_f (EtOAc/hexane 1:4) 0.38. ^{1}H NMR (200 MHz, $CDCl_3$, TMS): δ=7.29 (s, 5H, Ph), 6.33 (s, 1H, Boc*NH*), 4.63 (s, 2H, *CH*$_2$Ph), 1.48 (s, 9H, C(*CH*$_3$)$_3$), 1.43 (s, 9H, C(*CH*$_3$)$_3$). ^{13}C NMR (50 MHz, $CDCl_3$, TMS): δ=155.4, 155.1, 137.4, 128.6, 127.6, 81.5, 81.2, 53.9, 28.4, 28.3. FTIR ν (cm^{-1}): 3326, 3090, 3069, 3038, 2977, 2936, 2879, 1708, 1364, 1395, 1251, 1159, 747, 696.

4.3.4. Di-tert-butyl 1-allylhydrazine-1,2-dicarboxylate (**5d**)[11]

Method b. Compound **5d** was prepared as described for **5b** starting with **3d**. Crude product was purified by column chromatography on silica (EtOAc/hexane 1:4). The *title compound* **5d** (218 mg, 80%) was obtained as colourless crystals, mp 74–75 °C. R_f (EtOAc/hexane 1:4) 0.44. ^{1}H NMR (200 MHz, $CDCl_3$, TMS): δ=6.51/6.26 (s, 1H, Boc*NH*), 5.75–5.95 (m, 1H, *CH*=CH$_2$), 5.13–5.21 (m, 2H, CH=*CH*$_2$), 4.04–4.07 (m, 2H, N*CH*$_2$–CH=CH$_2$), 1.47 (s, 18H, C(*CH*$_3$)$_3$). ^{13}C NMR (50 MHz, $CDCl_3$, TMS): δ=155.2, 133.3, 117.5, 81.3, 81.1, 53.0, 28.3. FTIR ν (cm^{-1}): 3311, 3079, 2972, 2930, 1698, 1390, 1354, 1251, 1148, 927, 850, 753.

4.3.5. 1-Benzyl-1-ethyl-2-methylhydrazine (**6a**)

Compound **4a** (0.604 g, 2.28 mmol) was dissolved in TFA/CH_2Cl_2 1:2 mixture (10 mL). After 1 h, when reaction was complete, volatiles were removed. Then residue was dissolved in CH_2Cl_2 (20 mL) and 1 M KOH (10 mL) was added to the obtained solution. The fractions were separated and aqueous fraction was additionally extracted with CH_2Cl_2 (3×10 mL). The organic fractions were combined together and dried with $MgSO_4$. Then volatiles were removed yielding the *title compound* **6a** (350 mg, 93%) as a colourless oil. R_f (EtOAc/hexane 1:4) 0.50. ^{1}H NMR (200 MHz, $CDCl_3$, TMS): δ=7.26–7.33 (m, 5H, Ph), 3.75 (s, 2H, *CH*$_2$Ph), 2.73 (s, 1H, *NH*), 2.59 (q, *J*=7.2 Hz, 2H, *CH*$_2$CH$_3$), 2.52 (s, 3H, N*CH*$_3$), 1.10 (t, *J*=7.2 Hz, 3H, CH$_2$*CH*$_3$). ^{13}C NMR (50 MHz, $CDCl_3$, TMS): δ=138.5, 129.2, 128.2, 127.0, 60.1, 49.3, 35.6, 12.1. FTIR ν (cm^{-1}): 3208, 3069, 3023, 2966, 2936, 2869, 2828, 1682, 1446, 1354, 1138, 732, 686. HRMS (ESI): *m*/*z* calcd for $C_{10}H_{17}N_2$ (MH$^+$): 165.1386; found: 165.1383.

4.3.6. 1-Allyl-2-methyl-1-phenylhydrazine (**6b**)[18]

Compound **4b** (1.71 g, 6.5 mmol) was dissolved in TFA/CH_2Cl_2 1:2 mixture (30 mL). After 1 h, when reaction was complete, volatiles were removed. Then CH_2Cl_2 (30 mL) and 1 M KOH (30 mL) were added to the residue. Fractions were separated and aqueous fraction was additionally extracted with CH_2Cl_2 (3×15 mL). The organic fractions were combined together and dried with $MgSO_4$. Then volatiles were removed yielding the *title compound* **6b** (1.023 g, 97%) as a colourless oil. R_f (EtOAc/hexane 1:4) 0.50. ^{1}H NMR (200 MHz, $CDCl_3$, TMS): δ=7.16–7.24 (m, 2H, Ph), 6.91–6.96 (m, 2H, Ph), 6.69–6.76 (m, 1H, Ph), 5.72–5.91 (m, 1H, *CH*=CH$_2$), 5.16–5.25 (m, 2H, CH=*CH*$_2$), 3.96–3.99 (m, 2H, N*CH*$_2$–CH=CH$_2$), 3.40 (s, 1H, *NH*), 2.54 (s, 3H, N*CH*$_3$). ^{13}C NMR (50 MHz, $CDCl_3$, TMS): δ=150.1, 133.6, 129.0, 118.3, 117.6, 113.8, 53.2, 34.9. FTIR ν (cm^{-1}): 3337, 3064, 3028, 2982, 2941, 2874, 1595, 1498, 1333, 1230, 917, 737, 691.

4.3.7. N′-Benzyl-N′-ethyl-N-methylacetohydrazide (**7a**)

Compound **6a** (281 mg, 1.71 mmol) was dissolved in CH_2Cl_2 (5 mL), then pyridine (0.14 mL, 1.71 mmol) and Ac_2O (0.16 mL, 1.71 mmol) were added. After 2 h the reaction was complete. Then CH_2Cl_2 (20 mL) and 1 M KOH (10 mL) were added. The fractions were separated and the aqueous fraction was additionally extracted with CH_2Cl_2 (2×10 mL). The organic fractions were combined together and dried with $MgSO_4$. Then the volatiles were removed. The residue was purified by column chromatography (EtOAc/hexane 1:1) yielding the *title compound* **7a** (236 mg, 67%) as a colourless oil. R_f (EtOAc/hexane 1:1) 0.33. ^{1}H NMR (200 MHz, $CDCl_3$, TMS): δ=7.23 (s, 5H, Ph), 3.76 (s, 2H, *CH*$_2$Ph), 2.89 (s, 3H, N*CH*$_3$), 2.66–2.78 (m, 2H, *CH*$_2$CH$_3$), 1.97 (s, 3H, CO*CH*$_3$), 0.98 (t, *J*=7.2 Hz, 3H, CH$_2$*CH*$_3$). ^{13}C NMR (50 MHz, $CDCl_3$, TMS): δ=174.2, 136.7, 129.3, 128.5, 127.7, 59.2, 47.2, 22.9, 20.8, 12.2. FTIR ν (cm^{-1}): 3079, 3074, 3023, 2977, 2936, 2838, 1651, 1441, 1384, 753, 701. HRMS (ESI): *m*/*z* calcd for $C_{12}H_{19}N_2O$ (MH$^+$): 207.1492; found: 207.1492.

4.3.8. N′-Allyl-N-methyl-N′-phenylacetohydrazide (**7b**)

Compound **6b** (162 mg, 1 mmol) was dissolved in CH_2Cl_2 (5 mL), then pyridine (0.9 mL, 1.1 mmol) and Ac_2O (0.10 mL, 1 mmol) were added. After 2 h the volatiles were evaporated. The residue was purified by column chromatography (EtOAc/hexane 1:1) yielding the *title compound* **7b** (200 mg, 98%) as a colourless oil. R_f (EtOAc/hexane 1:1) 0.51. ^{1}H NMR (200 MHz, $CDCl_3$, TMS): δ=7.25–7.33 (m, 2H, Ph), 6.71–6.95 (m, 3H, Ph), 5.87–6.06 (m, 1H, *CH*=CH$_2$), 5.25–5.40 (m, 2H, CH=*CH*$_2$), 3.86–4.22 (m, 2H, N*CH*$_2$–CH=CH$_2$), 2.96 (s, 3H, N*CH*$_3$), 2.14 (s, 3H, CO*CH*$_3$). ^{13}C NMR (50 MHz, $CDCl_3$, TMS): δ=174.8, 146.5, 132.7, 129.7, 120.6, 119.1, 113.6, 54.2, 29.9, 20.4. FTIR ν (cm^{-1}): 3069, 3013, 2977, 2930, 2838, 1662, 1600, 1492, 1374, 1235, 747. HRMS (ESI): *m*/*z* calcd for $C_{12}H_{17}N_2O$ (MH$^+$): 205.1335; found: 205.1334.

4.3.9. Ethyl 2-allyl-1-methyl-2-phenylhydrazinecarboxylate (**7c**)

Compound **6b** (162 mg, 1 mmol) was dissolved in CH_2Cl_2 (5 mL), then pyridine (0.9 mL, 1.1 mmol) and ClCOOEt (0.10 mL, 1 mmol) were added. After 2 h the volatiles were evaporated. The residue was purified by column chromatography (EtOAc/hexane 1:4) yielding the *title compound* **7c** (228 mg, 97%) as a colourless oil. R_f (EtOAc/hexane 1:4) 0.46. ^{1}H NMR (200 MHz, $CDCl_3$, TMS): δ=7.18–7.26 (m, 2H, Ph), 6.63–6.84 (m, 3H, Ph), 5.87–6.03 (m, 1H, *CH*=CH$_2$), 5.17–5.36 (m, 2H, CH=*CH*$_2$), 4.00–4.15 (m, 4H, O*CH*$_2$CH$_3$, N*CH*$_2$–CH=CH$_2$), 3.10 (s, 3H, N*CH*$_3$), 1.12/1.26 (t, *J*=6.9/7.1 Hz, 3H, OCH$_2$*CH*$_3$). ^{13}C NMR (50 MHz, $CDCl_3$, TMS): δ=156.9, 147.6, 134.1, 129.3, 119.3, 117.7, 112.7, 61.9, 54.6, 35.4. FTIR ν (cm^{-1}): 3064, 2982, 2936, 2900, 1708, 1600, 1503, 1338, 1174, 747. HRMS (ESI): *m*/*z* calcd for $C_{13}H_{19}N_2O_2$ (MH$^+$): 235.1441; found: 235.1440.

4.3.10. N′-Allyl-2,2,2-trifluoro-N-methyl-N′-phenylacetohydrazide (**7d**)

Compound **6b** (162 mg, 1 mmol) was dissolved in CH_2Cl_2 (5 mL), then pyridine (0.9 mL, 1.1 mmol) and TFAA (0.15 mL, 1 mmol) were added. After 2 h the volatiles were evaporated. The residue was purified by column chromatography (EtOAc/hexane 1:4) yielding the *title compound* **7d** (240 mg, 93%) as a colourless oil. R_f (EtOAc/hexane 1:4) 0.46. ^{1}H NMR (200 MHz, $CDCl_3$, TMS): δ=7.25–7.33 (m, 2H, Ph), 6.94–7.01 (m, 1H, Ph), 6.79–6.83 (m, 2H, Ph), 5.91–6.11 (m, 1H, *CH*=CH$_2$), 5.25–5.40 (m, 2H, CH=*CH*$_2$), 3.92–4.24 (m, 2H, N*CH*$_2$–CH=CH$_2$), 3.01 (s, 3H, N*CH*$_3$). ^{13}C NMR (50 MHz, $CDCl_3$, TMS):

δ=159.8 (q, J=35 Hz), 146.3, 132.5, 129.5, 122.0, 119.5, 116.7 (q, J=285 Hz), 115.5, 56.0, 31.1. FTIR ν (cm^{-1}): 3074, 3038, 2982, 2936, 2843, 1703, 1600, 1492, 1158, 753, 686. HRMS (ESI): m/z calcd for $C_{12}H_{13}F_3N_2O$ (MH^+): 259.1053; found: 259.1050.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2008.04.096.

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