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The use of polyanions of hydrazines in the synthesis of heterocycles

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ABSTRACT

A novel method for the synthesis of cyclic hydrazine derivatives is reported. The new method for the generation of nitrogen-containing heterocycles is based on a polyanion strategy. The described method provides a convenient access to cyclic hydrazine derivatives, which are extensively used in drug industry and agriculture. The advantages and limitations of the new method are also demonstrated.

1. Introduction

Heterocyclic compounds are very abundant in nature. Their structural subunits are found in many natural products such as antibiotics, hormones, vitamins, etc. Heterocycles are also of significant importance in the production of all types of pharmaceuticals, dyes, and agrochemicals.[1]

The area of application of hydrazine derivatives is very wide. Many of them show remarkable biological activities and various similar compounds were discovered to be effective for treatment of hypertension, tuberculosis, and Parkinson's disease[2] as well to be active against hepatitis, AIDS, and SARS.[3]

It is obvious that *N*-aminopyrrolidines, pyrazolidines, and their homologs, which are heterocycles containing hydrazine moiety are of great interest in recent years. These heterocycles are extensively used as drugs, pesticides, and precursors in organic synthesis.[4] These applications have induced great interest in the synthesis of heterocyclic hydrazine derivatives.

A number of synthetic procedures for obtaining nitrogen-containing heterocycles have been developed. To construct *N*-aminoazacycloalkanes, most often nitrosation followed by $LiAlH_4$ reduction is used.[5] However, the area of application of this method is limited to aromatic substrates, in addition, products of nitrosation are highly carcinogenic.[6] Other methods have utilized reactions of hydrazines with difunctional substances, such as dihalides,[7] dimesylates[8] or dicarbonyl compounds.[9] These methods are sometimes limited by low yields and the availability of starting materials. A greater success has been achieved in the synthesis of pyrazolidines and their homologs using reaction of 1,2-disubstituted hydrazines with dihalides.[10] However, the scope of this strategy is cursorily studied and additional investigations should be carried out. These heterocycles are also prepared via Diels–Alder reaction of dienes with azo-compounds[11] often requiring the presence of commercially non-available starting materials, which should be additionally synthesized. Pyrazolidines can be also made by the cyclization of homoallylhydrazines,[12] however, this reaction does not proceed selectively tending to low yields.

As we have demonstrated in our previous works, a polyanion strategy has been successfully employed for alkylation of hydrazine derivatives.[13] In our current work we designed a new method of construction of *N*-aminoazacycloalkanes and pyrazolidine-type ring systems based on this strategy.

2. Results and discussion

The key step of our method is the formation of polyanions, which are further alkylated with dihalide to yield the corresponding heterocycle.

We have started with commercially available *tert*-butyl hydrazinecarboxylate, which was metalated in THF at −78 °C with 3 equiv of BuLi to form a trianion. This trianion was stable in the THF solution at low temperatures, but partial decomposition was detected at room temperature. We have also noticed that the trianion was unstable in the presence of air, so all reactions must be carried out in an inert atmosphere. The trianion can be alkylated

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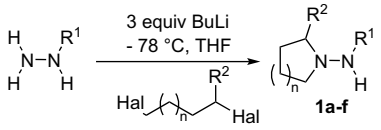
with dihalide to form corresponding pyrrolidine, piperidine or azepane ring systems (Scheme 1). We have also shown that 1,4-dibromopentane, which contains a secondary reaction center gave a good yield. Reactions were monitored by TLC, which showed that generally 4 h was required to obtain the desired product.



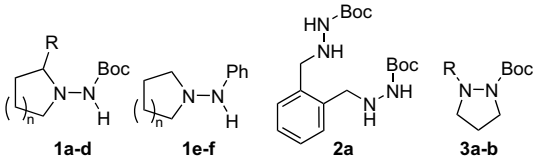
1a-c n = 1-3, R^1 = Boc, R^2 = H
1d n = 1, R^1 = Boc, R^2 = Me
1e-f n = 1-2, R^1 = Ph, R^2 = H
Hal = Cl, Br

Scheme 1. Alkylation of trianion.

We have observed that the yields of heterocycles strongly depended on the temperature of addition of dihalide (Table 1). The best yield for *tert*-butyl pyrrolidine-1-ylcarbamate was achieved when dihalide was added at −78 °C. Other heterocycles were obtained in moderate or good yields with the addition of dihalide at −40 °C. We propose that an increase in steric hindrance appears in the construction of bulkier heterocycles. Therefore, a higher temperature is required to overcome this problem. Further increasing the temperature of addition of the alkylating agent tended to lower yields of all heterocycles, probably due to partial decomposition of the trianion.

The trianion obtained from phenyl hydrazine is a much stronger base than the trianion obtained from *tert*-butyl carbazate. The alkylation also proceeds much faster even at low temperatures. We have noticed that the formation of heterocycles from phenyl hydrazine trianion was not very selective. For example, in case of 1-bromo-4-chlorobutane main products were *N*-phenylpyrrolidin-1-amine and phenylpiperidazine. We suppose that the difference in the acidities of PhNH and NH_2 groups is not sufficient for ensuring selectivity. In addition, the decrease of selectivity is obviously influenced by the difference of steric hindrances of phenyl and Boc group.

Table 1
Synthesis of heterocycles

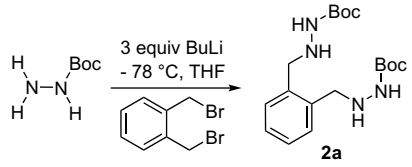


	R	*n*	Conditions	Yield, %
1a[13b]	H	1	$Br(CH_2)_4Cl$, 4 h, −78 °C to rt	71
1a	H	1	$Br(CH_2)_4Cl$, 4 h, −40 °C to rt	54
1a	H	1	$Br(CH_2)_4Cl$, 3 h, rt	52
1b[9]	H	2	$Br(CH_2)_5Br$, 4 h, −78 °C to rt	41
1b	H	2	$Br(CH_2)_5Br$, 4 h, −40 °C to rt	73
1b	H	2	$Br(CH_2)_5Br$, 4 h, −10 °C to rt	63
1b	H	2	$Br(CH_2)_5Br$, 3 h, rt	52
1c	H	3	$Br(CH_2)_6Br$, 4 h, −78 °C to rt	24
1c	H	3	$Br(CH_2)_6Br$, 4 h, −40 °C to rt	41
1c	H	3	$Br(CH_2)_6Br$, 4 h, −10 °C to rt	31
1d	Me	1	$Br(CH_2)_3CH(CH_3)Br$, 4 h, −78 °C to rt	48
1d	Me	1	$Br(CH_2)_3CH(CH_3)Br$, 4 h, −40 °C to rt	52
1e[15]		1	$Br(CH_2)_4Cl$, 2 h, rt	45
1f[9]		2	$Br(CH_2)_5Br$, 2 h, rt	34
2a			α,α′-Dibromo-*o*-xylene, 30 min, −40 °C to rt	45
3a[13c]	Ph		$I(CH_2)_3I$, 30 min, rt	87
3a	Ph		$Br(CH_2)_3Br$, 1 h, rt	64
3b	Et		$I(CH_2)_3I$, 3 h, −40 °C to rt	58
3b	Et		$Br(CH_2)_3Br$, 3 h, −40 °C to rt	38

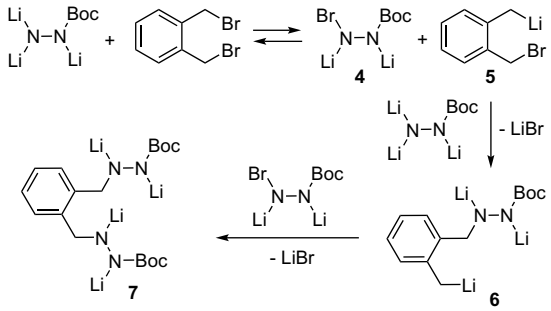
Moreover the elevated basicity of phenyl hydrazine trianion promotes transmetallation and elimination reactions.

We have tried to prepare full range of heterocycles from phenyl hydrazine trianion, but only five and six-membered rings were obtained. In all other cases a complex mixture of products has formed. Attempts to optimize the reaction conditions varying equivalents of BuLi and the temperature of dihalide addition have given no results.

Reaction of *tert*-butyl carbazate trianion with α,α′-dibromo-*o*-xylene in ratio 1:1 has unexpectedly given di-*tert*-butyl 2,2′-[1,2-phenylenedi(methylene)]dihydrazinecarboxylate (Scheme 2). The structure of the product shows that one molecule of dibromide attaches to two trianions. At the next step we carried out the reaction reducing twice the amount of dibromide, but only traces of the desired product were found in this experiment. A probable mechanism for the reaction of trianion with α,α′-dibromo-*o*-xylene is based on transmetallation equilibrium (Scheme 3). We propose that α,α′-dibromo-*o*-xylene interacts with trianion generating dianion **4** and ionic intermediate **5**, which are stabilized by the aromatic nucleus and therefore no cyclization is possible. This intermediate attaches to one molecule of trianion to give intermediate **6**, which reacts with dianion **4** forming tetraanion **7**. According to this mechanism polyanion strategy is the key step in the formation of such type products and explains why compound **2a** have not been obtained even if the same substrates have been used in other reports.[14]



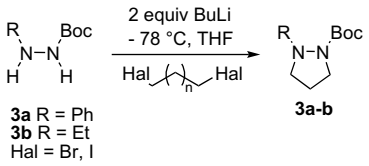
Scheme 2. Reaction of *tert*-butyl carbazate trianion with α,α′-dibromo-*o*-xylene.



Scheme 3. Proposed mechanism of the reaction of *tert*-butyl carbazate trianion with α,α′-dibromo-*o*-xylene.

To the best of our knowledge it is the first report exploring the synthesis of such kind compounds. Our method provides an easy and convenient access to other new hydrazine derivatives and heterocycles.

To obtain dianions from PhNHNHBoc and EtNHNHBoc, 2 equiv of BuLi has been used. These dianions have been alkylated with dihalides to yield corresponding pyrazolidines (Scheme 4). Reactions were normally complete within 3 h. Traces of by-products of elimination were observed if the dihalide was added to EtNHNHBoc at room temperature. This problem can be overcome by addition of the alkylating agent at −40 °C. Nevertheless, reaction of PhNHNHBoc with 1,3-dihalides proceeded selectively even if the addition was made at room temperature. We have also showed that diiodides exhibit the tendency to give better yields than dibromides. Reaction of dianions with 1,4-dihalides yielded products, in



Scheme 4. Alkylation of dianion.

which two dianion fragments were connected by the alkyl chain of dihalide, probably due to steric hindrances.

The dianion of BocNHNHCOOEt has been also obtained using 2 equiv of BuLi. However, it precipitates from the solution and does not show any reactivity even at 50 °C.

3. Conclusions

In summary, we have demonstrated a new strategy for the synthesis of nitrogen-containing heterocycles. The scope and limitations of this new method were also described. The formation of unexpected products was reported. Our method can be easily used for the construction of many different cyclic hydrazine derivatives.

4. Experimental

4.1. General

All reagents were obtained from commercial sources and used without further purification. THF was freshly distilled from Na/benzophenone. NMR spectroscopy was performed on a Bruker Avance II 200 MHz spectrometer using TMS as an internal standard. Infrared spectra were measured on a Perkin–Elmer Spectrum BXII FTIR spectrometer using attenuated total reflectance technique. HRMS were measured on Thermo Electron LTQ Orbitrap ESI mass-spectrometer. Melting points were determined on a Gallenkamp melting point apparatus. Compounds **1a**, **1b**, **1d**, **2a** are crystalline solids, others are oils.

4.2. General procedure for the syntheses of compounds 1a–f

*4.2.1. tert-Butyl pyrrolidine-1-ylcarbamate (**1a**[13b])*

Method A. An oven-dried flask was charged with $BocNHNH_2$ (2 mmol, 264 mg), evacuated, and backfilled with argon. Thereafter THF (14 mL) was added to dissolve the solid. The reaction mixture was cooled down to −78 °C and 1.6 M BuLi solution in hexane (6 mmol, 3.75 mL) was added dropwise. The reaction mixture was stirred for 15 min and 1-bromo-4-chlorobutane (2 mmol, 0.23 mL) was added. After stirring for another 1 h at −78 °C, the reaction mixture was allowed to warm up to room temperature. After 4 h the reaction was mainly complete, but it was allowed to stir overnight. Then 0.1 mL of H_2O was added to the reaction mixture and the solvent was evaporated under reduced pressure. To the residue 15 mL of chloroform and $MgSO_4$ was added. The mixture was filtered and $MgSO_4$ was washed with chloroform (3×2 mL). The volatiles were removed under reduced pressure. The residue was purified by column chromatography on silica (Hexane/EtOAc 1:1), resulting *title compound* **1a** (263 mg, 71%) as colorless solid, mp 107–109 °C. R_f (EtOAc/hexane 1:1) 0.46. ^{1}H NMR (200 MHz, $CDCl_3$, TMS): δ=5.63 (br s, 1H, N*H*), 2.88 (m, 4H, NCH_2), 1.82 (m, 4H, NCH_2CH_2), 1.46 (s, 9H, $C(CH_3)_3$). ^{13}C NMR (50 MHz, $CDCl_3$, TMS): δ=155.1, 79.9, 55.0, 28.5, 22.6. FTIR ν (cm^{-1}): 3225, 2976, 2938, 2842, 1710, 1689, 1542, 1365, 1275, 1253, 1156, 1056, 1017, 862, 632, 624.

Method B. An oven-dried flask was charged with $BocNHNH_2$ (2 mmol, 264 mg), evacuated, and backfilled with argon. Thereafter THF (14 mL) was added to dissolve the solid. The reaction mixture was cooled down to −78 °C and 1.6 M BuLi solution in hexane (6 mmol, 3.75 mL) was added dropwise. The reaction mixture was allowed to warm up to −40 °C for another 15 min and 1-bromo-4-chlorobutane (2 mmol, 0.23 mL) was added. Then the reaction mixture was allowed to warm up to room temperature. After 4 h the reaction was mainly complete, but it was allowed to stir overnight. Then 0.1 mL of H_2O was added to the reaction mixture and the solvent was evaporated under reduced pressure. To the residue 15 mL of chloroform and $MgSO_4$ was added. The mixture was filtered and $MgSO_4$ was washed with chloroform (3×2 mL). The volatiles were removed under reduced pressure. The residue was purified by column chromatography on silica (Hexane/EtOAc 1:1), resulting *title compound* **1a** (199 mg, 54%) as colorless solid.

Method C. An oven-dried flask was charged with $BocNHNH_2$ (2 mmol, 264 mg), evacuated, and backfilled with argon. Thereafter THF (14 mL) was added to dissolve the solid. The reaction mixture was cooled down to −78 °C and 1.6 M BuLi solution in hexane (6 mmol, 3.75 mL) was added dropwise. The reaction mixture was allowed to warm up to room temperature for another 15 min and 1-bromo-4-chlorobutane (2 mmol, 0.23 mL) was added. After 3 h the reaction was mainly complete, but it was allowed to stir overnight. Then 0.1 mL of H_2O was added to the reaction mixture and the solvent was evaporated under reduced pressure. To the residue 15 mL of chloroform and $MgSO_4$ was added. The mixture was filtered and $MgSO_4$ was washed with chloroform (3×2 mL). The volatiles were removed under reduced pressure. The residue was purified by column chromatography on silica (Hexane/EtOAc 1:1), resulting *title compound* **1a** (195 mg, 52%) as colorless solid.

*4.2.2. tert-Butyl piperidine-1-ylcarbamate (**1b**[9])*

Method A. Compound **1b** was prepared as described for **1a** using 1,5-dibromopentane as dihalide. Product was purified by column chromatography on silica (Hexane/EtOAc 1:1), resulting *title compound* **1b** (164 mg, 41%) as colorless solid, mp 89–91. R_f (EtOAc/hexane 1:1) 0.71. ^{1}H NMR (200 MHz, $CDCl_3$, TMS): δ=5.50 (br s, 1H, N*H*), 2.72 (m, 4H, NCH_2), 1.67 (m, 4H, NCH_2CH_2), 1.47–1.37 (m, 11H, $C(CH_3)_3$, $N(CH_2)_2CH_2$). ^{13}C NMR (50 MHz, $CDCl_3$, TMS): δ=154.7, 79.9, 57.2, 28.6, 25.8, 23.5. FTIR ν (cm^{-1}): 3220, 2978, 2944, 2862, 1721, 1698, 1548, 1364, 1269, 1251, 1159, 1052, 1037, 856, 643.

Method B. Compound **1b** was prepared as described for **1a** using 1,5-dibromopentane as dihalide. Product was purified by column chromatography on silica (Hexane/EtOAc 1:1), resulting *title compound* **1b** (293 mg, 73%) as colorless solid.

Method C. Compound **1b** was prepared as described for **1a** using 1,5-dibromopentane as dihalide. Product was purified by column chromatography on silica (Hexane/EtOAc 1:1), resulting *title compound* **1b** (207 mg, 52%) as colorless solid.

Method D. An oven-dried flask was charged with $BocNHNH_2$ (2 mmol, 264 mg), evacuated, and backfilled with argon. Thereafter THF (14 mL) was added to dissolve the solid. The reaction mixture was cooled down to −78 °C and 1.6 M BuLi solution in hexane (6 mmol, 3.75 mL) was added dropwise. The reaction mixture was allowed to warm up to −10 °C for another 15 min and 1,5-dibromopentane (2 mmol, 0.27 mL) was added. After stirring for another 15 min at −10 °C the reaction mixture was allowed to warm up to room temperature. After 4 h the reaction was mainly complete, but it was allowed to stir overnight. Then 0.1 mL of H_2O was added to the reaction mixture and the solvent was evaporated under reduced pressure. To the residue 15 mL of chloroform and $MgSO_4$ was added. The mixture was filtered and $MgSO_4$ was washed with chloroform (3×2 mL). The volatiles were removed under reduced pressure. The residue was purified by column chromatography on silica (Hexane/EtOAc 1:1), resulting *title compound* **1b** (252 mg, 63%) as colorless solid.

*4.2.3. tert-Butyl azepane-1-ylcarbamate (**1c**)*

Method A. Compound **1c** was prepared as described for **1a** using 1,6-dibromohexane as dihalide. Product was purified by column chromatography on silica (Hexane/EtOAc 2:1), resulting *title compound* **1c** (103 mg, 24%) as a colorless oil. R_f (EtOAc/hexane 1:2) 0.57. ^{1}H NMR (200 MHz, $CDCl_3$, TMS): δ=5.88 (br s, 1H, N*H*), 3.00 (m, 4H, NCH_2), 1.62–1.45 (m, 17H, C(CH_3)$_3$, CH_2). ^{13}C NMR (50 MHz, $CDCl_3$, TMS): δ=155.2, 79.8, 58.6, 28.6, 27.1, 26.9. FTIR ν (cm^{-1}): 3247, 2977, 2913, 2862, 1714, 1499, 1365, 1269, 1252, 1169, 1133, 1095, 1018, 877, 755, 623. HRMS (ESI): *m*/*z* calcd for $C_{11}H_{22}N_2O_2$ [MH]$^+$: 215.1754; found: 215.1755.

Method B. Compound **1c** was prepared as described for **1a** using 1,6-dibromohexane as dihalide. Product was purified by column chromatography on silica (Hexane/EtOAc 2:1), resulting *title compound* **1c** (174 mg, 41%) as a colorless oil.

Method D. Compound **1c** was prepared as described for **1a** using 1,6-dibromohexane as dihalide. Product was purified by column chromatography on silica (Hexane/EtOAc 2:1), resulting *title compound* **1c** (137 mg, 32%) as a colorless oil.

*4.2.4. tert-Butyl 2-methylpyrrolidine-1-ylcarbamate (**1d**)*

Method A. Compound **1d** was prepared as described for **1a** using 1,4-dibromopentane as dihalide. Product was purified by column chromatography on silica (Hexane/EtOAc 1:1), resulting *title compound* **1d** (193 mg, 48%) as colorless solid, mp 81–83. R_f (EtOAc/hexane 1:1) 0.63. ^{1}H NMR (200 MHz, $CDCl_3$, TMS): δ=5.39 (br s, 1H, N*H*), 3.29 (m, 1H, NC*H*), 2.65 (m, 2H, NCH_2), 1.98–1.68 (m, 4H, CH_2), 1.46 (m, 9H, C(CH_3)$_3$), 1.12 (d, *J*=6.0 Hz, 3H, CH_3). ^{13}C NMR (50 MHz, $CDCl_3$, TMS): δ=155.5, 79.8, 61.0, 55.1, 30.9, 28.6, 20.6, 18.4. FTIR ν (cm^{-1}): 3223, 2970, 2932, 2874, 1693, 1538, 1365, 1273, 1252, 1160, 1051, 1026, 1007, 819, 763, 640. HRMS (ESI): *m*/*z* calcd for $C_{10}H_{20}N_2O_2$ [MH]$^+$: 201.1598; found: 201.1598.

Method B. Compound **1d** was prepared as described for **1a** using 1,4-dibromopentane as dihalide. Product was purified by column chromatography on silica (Hexane/EtOAc 1:1), resulting *title compound* **1d** (207 mg, 52%) as colorless solid.

*4.2.5. N-Phenylpyrrolidin-1-amine (**1e**[15])*

An oven-dried flask was charged with $PhNHNH_2$ (2 mmol, 216 mg), evacuated, and backfilled with argon. Thereafter THF (14 mL) was added. The reaction mixture was cooled down to −78 °C and 1.6 M BuLi solution in hexane (6 mmol, 3.75 mL) was added dropwise. The reaction mixture was allowed to warm up to room temperature for another 15 min and 1-bromo-4-chlorobutane (2 mmol, 0.23 mL) was added. After 2 h the reaction was mainly complete. To the residue 15 mL of chloroform and $MgSO_4$ was added. The mixture was filtered and $MgSO_4$ was washed with chloroform (3×2 mL). The volatiles were removed under reduced pressure. The residue was purified by column chromatography on silica (Hexane/EtOAc 4:1), resulting *title compound* **1e** (145 mg, 45%) as colorless oil. R_f (EtOAc/hexane 1:4) 0.59. ^{1}H NMR (200 MHz, $CDCl_3$, TMS): δ=7.20 (m, 2H, Ph), 6.89 (m, 2H, Ph), 6.76 (m, 1H, Ph), 4.25 (br s, 1H, N*H*), 2.77 (m, 4H, NCH_2), 1.83 (m, 4H, NCH$_2$CH_2). ^{13}C NMR (50 MHz, $CDCl_3$, TMS): δ=149.0, 129.1, 119.1, 113.4, 55.9, 22.1. FTIR ν (cm^{-1}): 3239, 3050, 3022, 2963, 2875, 2807, 1602, 1495, 1256, 887, 749, 693.

*4.2.6. N-Phenylpiperidin-1-amine (**1f**[9])*

Compound **1f** was prepared as described for **1e** using 1,5-dibromopentane as dihalide. Product was purified by column chromatography on silica (Hexane/EtOAc 8:1), resulting *title compound* **1f** (121 mg, 34%) as colorless oil. R_f (EtOAc/hexane 1:4) 0.73. ^{1}H NMR (200 MHz, $CDCl_3$, TMS): δ=7.18 (m, 2H, Ph), 6.88 (m, 2H, Ph), 6.75 (m, 1H, Ph), 4.32 (br s, 1H, N*H*), 2.64 (m, 4H, NCH_2), 1.67 (m, 4H, NCH$_2$CH_2), 1.42 (m, 2H, N(CH$_2$)$_2$CH_2). ^{13}C NMR (50 MHz, $CDCl_3$, TMS): δ=148.0, 129.1, 119.2, 113.7, 57.8, 26.1, 23.8. FTIR ν (cm^{-1}): 3245, 3050, 3021, 2935, 2854, 2784, 1601, 1495, 1253, 1036, 879, 864, 801, 749. 693.

4.3. General procedure for the synthesis of compound 2a

4.3.1. Di-tert-butyl 2,2′-(1,2-phenylenedi(methylene))-dihydrazinecarboxylate

An oven-dried flask was charged with $BocNHNH_2$ (11.36 mmol, 1.50 g), evacuated, and backfilled with argon. Thereafter THF (80 mL) was added to dissolve the solid. The reaction mixture was cooled down to −78 °C and 1.6 M BuLi solution in hexane (34.08 mmol, 21.3 mL) was added dropwise. The reaction mixture was allowed to warm up to −40 °C for another 15 min and α,α′-dibromo-*o*-xylene (11.17 mmol, 2.95 g) was added. Then the reaction mixture was allowed to warm up to room temperature. After 30 min the reaction was mainly complete. Then 1 mL of H_2O was added to the reaction mixture and the solvent was evaporated under reduced pressure. To the residue 75 mL of chloroform and $MgSO_4$ was added. The mixture was filtered and $MgSO_4$ was washed with chloroform (3×2 mL). The volatiles were removed under reduced pressure. The residue was purified by column chromatography on silica (Hexane/EtOAc 1:1) resulting *title compound* **2a** (932 mg, 45%) as yellowish solid, mp 120–122. R_f (EtOAc/hexane 1:1) 0.48. ^{1}H NMR (200 MHz, $CDCl_3$, TMS): δ=7.27 (m, 4H, C$_6H_4$), 6.81 (br s, 2H, BocN*H*), 4.53/4.06 (br s/s, 6H, N*H*CH$_2$/CH_2), 1.46 (s, 18H, C(CH_3)$_3$). ^{13}C NMR (50 MHz, $CDCl_3$, TMS): δ=156.9, 137.2, 131.3, 128.0, 80.3, 54.3, 28.6. FTIR ν (cm^{-1}): 3336, 3307, 3226, 2977, 2934, 2867, 1698, 1552, 1482, 1454, 1367, 1271, 1251, 1152, 1007, 854, 844, 739, 615. HRMS (ESI): *m*/*z* calcd for $C_{18}H_{30}N_4O_4$ [MH]$^+$: 367.2340; found: 367.2340.

4.4. General procedure for the syntheses of compounds 3a, 3b

*4.4.1. tert-Butyl 2-phenylpyrazolidine-1-carboxylate (**3a**[13c])*

Method E. An oven-dried flask was charged with PhNHNHBoc (1 mmol, 208 mg), evacuated, and backfilled with argon. Thereafter THF (5 mL) was added to dissolve the solid. The reaction mixture was cooled down to −78 °C and 1.6 M BuLi solution in hexane (2.1 mmol, 1.30 mL) was added dropwise. The reaction mixture was allowed to warm up to room temperature for another 15 min and 1,3-diiodopropane (1 mmol, 0.115 mL) was added. After 30 min the reaction was mainly complete. Volatiles were removed under reduced pressure. To the residue 7 mL of chloroform and 3 mL of 1 M KOH was added. KOH solution was separated and extracted with chloroform (2×3 mL). The organic fractions were combined and dried over anhydrous $MgSO_4$. The mixture was filtered and the volatiles were removed under reduced pressure. The residue was purified by column chromatography on silica (Hexane/Et_2O 1:1), resulting *title compound* **3a** (216 mg, 87%) as colorless oil. R_f (Et_2O/hexane 1:1) 0.36. ^{1}H NMR (200 MHz, $CDCl_3$, TMS): δ=7.24 (m, 2H, Ph), 6.93 (m, 3H, Ph), 3.57 (m, 4H, NCH_2), 1.98 (quin, *J*=7.0 Hz, 2H, NCH$_2$CH_2), 1.47 (s, 9H, C(CH_3)$_3$). ^{13}C NMR (50 MHz, $CDCl_3$, TMS): δ=156.1, 151.5, 128.9, 121.2, 115.6, 80.7, 53.9, 45.0, 28.5, 25.6. FTIR ν (cm^{-1}): 2972, 2933, 2894, 1688, 1598, 1489, 1452, 1390, 1364, 1249, 1161, 1128, 858, 760, 700.

Method F. Compound **3a** was prepared as described in method E using 1,3-dibromopropane as dihalide. Product was purified by column chromatography on silica (Hexane/Et_2O 1:1), resulting *title compound* **3a** (165 mg, 64%) as colorless oil.

*4.4.2. tert-Butyl 2-ethylpyrazolidine-1-carboxylate (**3b**)*

Method G. An oven-dried flask was charged with EtNHNHBoc (2 mmol, 320 mg), evacuated, and backfilled with argon. Thereafter THF (8 mL) was added. The reaction mixture was cooled down to −78 °C and 1.6 M BuLi solution in hexane (4.2 mmol, 2.63 mL) was added dropwise. The reaction mixture was allowed to warm up to −40 °C for another 15 min and 1,3-diiodopropane (2 mmol, 0.23 mL) was added. Then the reaction mixture was allowed to warm up to room temperature. After 3 h the reaction was mainly complete. The volatiles were removed under reduced pressure. To

the residue 14 mL of chloroform and 6 mL of 1 M KOH was added. KOH solution was separated and extracted with chloroform (2×3 mL). The organic fractions were combined and dried over anhydrous $MgSO_4$. The mixture was filtered and volatiles were removed under reduced pressure. The residue was purified by column chromatography on silica (Hexane/EtOAc 1:1) resulting *title compound* **3b** (234 mg, 58%) as colorless oil. R_f (EtOAc/hexane 1:1) 0.39. ^{1}H NMR (200 MHz, $CDCl_3$, TMS): δ=3.51 (m, 2H, BocNCH_2), 3.01 (t, J=6.8 Hz, 2H, EtNCH_2), 2.67 (q, J=7.2 Hz, 2H, NCH_2CH$_3$), 2.08 (m, 2H, NCH$_2$CH_2), 1.49 (s, 9H, C(CH_3)$_3$), 1.11 (t, J=7.0 Hz, 3H, NCH$_2$CH_3). ^{13}C NMR (50 MHz, $CDCl_3$, TMS): δ=156.5, 79.8, 53.0, 51.5, 44.6, 28.6, 24.4, 13.1. FTIR ν (cm^{-1}): 2976, 2936, 2892, 1714, 1687, 1455, 1390, 1364, 1247, 1170, 1143, 766, 730. HRMS (ESI): m/z calcd for $C_{10}H_{20}N_2O_2$ [MH]$^+$: 201.1598; found: 201.1598.

Method H. Compound **3b** was prepared as described in method G using 1,3-dibromopropane as dihalide. Product was purified by column chromatography on silica (Hexane/EtOAc 1:1), resulting *title compound* **3b** (154 mg, 38%) as colorless oil.

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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.2009.04.040

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