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Efficient asymmetric synthesis of α-(heteroaryl)alkylamines by 1,2-addition of lithiated hetarenes to aldehyde-SAMP-hydrazones

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Abstract—An efficient enantioselective synthesis of α-(heteroaryl)alkylamines by nucleophilic 1,2-addition of lithiated hetarenes to aldehyde-SAMP-hydrazones followed by SmI_2 or BH_3·THF N,N-single bond cleavage is described. The Cbz or benzoyl-protected amines are obtained in good overall yields (40–78%) and excellent enantiomeric excesses (ee = 88–99%).

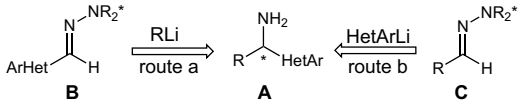
1. Introduction

Enantiomerically enriched amines bearing a stereogenic centre at the α-position are fundamental structures in organic chemistry.[1] In particular, α-(heteroaryl)alkylamines play a crucial role as these are characteristic motifs in bioactive natural products and pharmacologically important compounds. Furthermore, from a synthetic point of view they have proven to be efficient chiral ligands[2] in metal complex catalysis and useful building blocks in organic synthesis. Particularly interesting are the applications of α-(2-furyl)alkylamines: oxidative cleavage of the furan ring promoted by ozone or metal oxides have found widespread application in the synthesis of α-amino acids.[3] Moreover, the aza-Achmatowicz rearrangement[4] offers a straightforward entry into the piperidine skeleton and has thus been used in the synthesis of numerous alkaloids[5] and azasugars.[6] The broad utility of α-(heteroaryl)-alkylamine derivatives has stimulated a relentless pursuit of practical asymmetric routes to these valuable compounds.

To date, the majority of the approaches have focused on the use of chiral auxiliaries,[3c,7] although enzymatic[8] and chemical resolutions[9] of racemic amines or the enantioselective reduction of oximes[3a] have been used as well. Recently, a few cases have been reported where asymmetric catalytic methods were employed.[10] In view of the importance of α-(heteroaryl)alkylamines in organic synthesis and pharmaceutical research it is desirable to develop further general and efficient enantioselective entries to this class of compounds.

2. Results and discussion

Based on the broad applicability of the SAMP-/RAMP-hydrazone methodology[11] and the excellent asymmetric inductions in nucleophilic 1,2-additions to the CN double bond observed, two alternative pathways to the title compound **A** can be envisaged (Scheme 1): route a involves the 1,2-addition of alkyllithium reagents (RLi) to SAMP-hydrazones **B** derived from the corresponding hetarene carbaldehydes.



Scheme 1. Alternative general approaches to the title compounds **A**.

On the basis of our experience, we envisaged that the nucleophilic 1,2-addition of lithiated hetarenes (HetArLi) to simple aldehyde-SAMP-hydrazones **C** (route b) could furnish a general approach to **A** due to the great diversity and high reactivity of lithiated aromatic heterocycles. Furthermore, the 1,2-addition could be combined with the SAMP-hydrazone-α-alkylation to insert in straightforward manner a new stereogenic centre at the α-position of the CN double bond providing an entry into even more complex structures. Our general protocol for the asymmetric synthesis of

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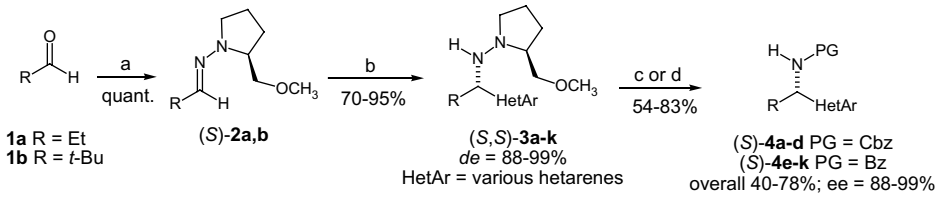
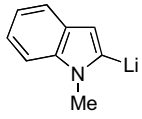
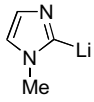
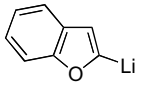


Scheme 2. Asymmetric synthesis of α-(heteroaryl)alkylamines: (a) SAMP, Et_2O, rt; (b) HetArLi, THF or Et_2O; (c) BH_3·THF, THF, reflux and then CbzCl, K_2CO_3, THF/H_2O; (d) DMAP, Et_3N, CH_2Cl_2, PhCOCl, rt, then SmI_2, THF, DMPU, rt.

α-(heteroaryl)alkylamines is depicted in Scheme 2. We selected as a study compound the simple propanal-SAMP-hydrazone **2a** and treated it with nine different lithiated aromatic heterocycles[12] prepared by modified literature procedures.[13] We found that the addition of either 2- or 3-thienyllithium was ideally carried out by

Table 1. Asymmetric synthesis of α-(heteroaryl)alkylhydrazines **3**

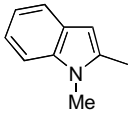
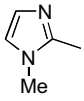
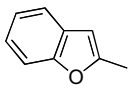
Entry	Product	HetAr	R	Equivalents	Solvent	*T* (°C)	Time[a] (h)	Yield[a] (%)	De[b] (%)
1	**3a**		Et	3.2	Et_2O	−78 to rt	2	91	⩾95
2	**3b**		*t*-Bu	3.2	Et_2O	−78 to rt	2	82	93
3	**3c**		Et	3.2	THF	−78 to rt	14	70[c]	88
4	**3d**		Et	3.2	Et_2O	−78 to rt	5	86	94
5	**3e**		Et	5.0	Et_2O	−78	14	79	⩾95
6	**3f**		Et	8.0	Et_2O	−100	5	82	⩾95
7	**3g**		Et	3.2	THF	−78 to rt	14	75[c]	94
8	**3h**		Et	3.2	THF	−78 to rt	14	95	⩾95
9	**3i**		Et	3.2	THF	−78 to rt	2	91	⩾95
10	**3j**		Et	3.2	Et_2O	−78 to rt	2	85	⩾95
11	**3k**		*t*-Bu	3.2	THF	−78 to rt	18	80	⩾95

[a] Yield of crude product (⩾95% purity as determined by ^1H and ^{13}C NMR spectroscopy).
[b] Determined by ^1H and ^{13}C NMR spectroscopy.
[c] Conversion (determined by ^1H and ^{13}C NMR spectroscopy).

using diethyl ether as reaction solvent (Table 1, entries 1 and 4). Highest conversions and diastereomeric excesses were obtained by treating **2a** with 3 equiv of the organolithium compound at −78 °C for 30 min after which the cooling bath was removed and the reaction mixture was allowed to warm to room temperature. The NMR spectrum of the crude products showed only the desired hydrazine **3a** in high diastereomeric purity without starting material or side products. Both 3-pyridyllithium (entry 5) and 2-pyridyllithium (entry 6) reacted well with **2a** in Et_2O at low temperature but 5 and 8 equiv of organolithium species had to be used, respectively. THF was preferred as solvent in the case of 1-methyl-2-lithiopyrrole (entry 3), 1-methyl-2-lithio-indole (entry 7) and 1-methyl-2-lithio-imidazole (entry 8) providing highest diastereoselectivities when the reactions were allowed to reach room temperature overnight. 2-Furyllithium (entry 9) and 2-benzofuryllitihum (entry 10) showed different results concerning the solvent: THF was the solvent of choice in the former case, Et_2O in the latter.

In order to demonstrate the generality of our approach we performed the 1,2-addition using 2-lithiothiophene

Table 2. Asymmetric synthesis of N-Protected α-(heteroaryl) alkylamines **4**

4	HetAr	R	Cleavage	Yield[a] (%)	Ee[b] (%)
a		Et	BH_3·THF	83	99
b		*t*-Bu	BH_3·THF	70	93
c		Et	BH_3·THF	64	88
d		Et	BH_3·THF	80	94
e		Et	SmI_2	73	99
f		Et	SmI_2	71	96
g		Et	SmI_2	54	94
h		Et	SmI_2	82	99[c]
i		Et	SmI_2	82	99
j		Et	SmI_2	81	97
k		*t*-Bu	SmI_2	68	98

[a] Yields of isolated products over two steps.
[b] Determined by HPLC over chiral stationary phase (Daicel AD 2 or Daicel OD 3).
[c] Determined by GC over chiral stationary phase (Chirasil L-VAL).

and 2-lithiofuran on the sterically more hindered hydrazone **2b** (entry 2 and 11, respectively). We were pleased to find that the yields and selectivities were not significantly altered by the presence of the sterically demanding *tert*-butyl group on the hydrazone. Due to the sensitivity of the obtained hydrazines we decided to use the crude products **3a–k** directly in the next steps without any purification. Cleavage of the chiral auxiliary proceeded smoothly without detectable racemization by refluxing the hydrazines **3a–d** with a large excess of $BH_3 \cdot THF$[14] complex for 6–48 h. The corresponding polar amines were not isolated but directly protected with CbzCl to afford the carbamates **4a–d**,[15] which could be easily purified by flash chromatography on silica gel.

The chemical yields over two steps as well as enantiomeric excesses are given in Table 2. Unfortunately, the hydrazines **3e–k** did not exhibit comparable reactivity and thus treatment with $BH_3 \cdot THF$ gave relatively poor results. In order to find suitable conditions capable of removing the chiral auxiliary we examined the SmI_2 promoted N,N-single bond cleavage.[16] For this purpose the tertiary hydrazines **3e–k** had to be activated by conversion to benzoyl derivatives. To this end, **3e–k** were reacted with benzoyl chloride using an equimolar amount of triethylamine as base and a catalytic amount of DMAP. The obtained *N*-benzoyl hydrazines were very stable and could be isolated after purification as a mixture of amide *E*/*Z* isomers. We were pleased to find that when the N-protected hydrazines were treated with 2–3 equiv of SmI_2 in the presence of an equimolar amount of DMPU, cleavage of the chiral auxiliary took place smoothly affording after purification the corresponding benzoyl amines **4e–k** in good overall yields (Table 2).[17] More importantly, the analysis by HPLC employing a chiral stationary phase showed that the reaction proceeded without detectable epimerization or racemization.

The (*S*)-configuration of the enantioenriched title compounds **4** (ee = 88–99%) is in agreement with the relative topicity observed for all the 1,2-additions of nucleophiles to the CN double bond of aldehyde-SAMP-hydrazones.[18,19]

3. Conclusion

In summary, we have developed a general and efficient approach for the asymmetric synthesis of α-(heteroaryl) alkylamines based on the 1,2-addition of various lithiated hetarenes to aldehyde-SAMP-hydrazones followed by N–N-single bond cleavage. The extension of this methodology to the synthesis of biologically important compounds is currently in progress in our laboratories.

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12. Representative procedure for the nucleophilic 1,2-addition of hetarenes to aldehyde-SAMP-hydrazones. Benzofuran (380 mg, 3.2 mmol) was dissolved in 10 mL of dry ether under argon and cooled to 0 °C. *n*-Butyllithium (1.6 M, 2 mL, 3.2 mmol) was added to the solution over 5 min. The cooling bath was removed and the solution was allowed to warm up to room temperature. The mixture was stirred for 60 min and then cooled to −78 °C. Hydrazone **2a** (170 mg, 1.0 mmol) in 4 mL of Et_2O was slowly added to the solution and after 30 min the cooling bath was removed. The reaction was stirred for 2 h at room temperature and then quenched with 5 mL of a saturated solution of NH_4Cl. After separation of the layers, the aqueous phase was extracted three times with Et_2O. The combined organic solutions were dried over $MgSO_4$ and the solvent was removed under reduced pressure. The resulting crude hydrazine **3j** (245 mg, 85% yield) was directly used in the next steps without any purification.
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15. Typical procedure for the N,N-single bond cleavage with BH_3·THF and Cbz-protection of the amino group. Hydrazine **3a** (230 mg, 0.91 mmol) was dissolved in dry THF (10 mL) and refluxed with 15 equiv of BH_3·THF (1.0 M in THF) for 18 h. The reaction was cooled to room temperature, acidified with aqueous hydrochloric acid and stirred for 1 h. The THF was evaporated under reduced pressure and the aqueous solution was basified with a saturated solution of $NaHCO_3$ and extracted three times with CH_2Cl_2. The combined organic layers were concentrated in vacuo and the residue was dissolved in a mixture of H_2O/THF (1:1). K_2CO_3 (2.0 equiv) was added to the mixture, followed by 1.8 equiv of CbzCl and the heterogeneous solution was stirred at room temperature for 16 h. Et_2O was added to the reaction, the layers were separated and the aqueous phase was washed with two further portion of Et_2O. The combined organic extracts were dried and evaporated. The crude product was purified via column chromatography over silica gel (Et_2O/pentane 1:2) to afford **4a** (208 mg, 83% yield) as colourless solid.
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17. Representative procedure for the protection of hydrazines with benzoyl chloride and for the N,N-single bond cleavage with SmI_2. The crude hydrazine **3j** (245 mg, 0.85 mmol) was dissolved in 10 mL of dry CH_2Cl_2 in presence of a catalytic amount of DMAP and 4 equiv of dry Et_3N. Benzoyl chloride (4 equiv) was added dropwise to the stirred mixture at room temperature. After 18 h the solvent was evaporated in vacuo and the crude product purified via column chromatography over silica gel (Et_2O/pentane 1:2). The resulting *N*-benzoyl-protected hydrazine was dissolved in 10 mL of dry THF in presence of 3 equiv of DMPU. Three equivalents of SmI_2 (0.1 M solution in THF) were slowly added to the mixture and the reaction was stirred for 2 h. Quenching was performed by adding a mixture of $NaHCO_3$ solution and CH_2Cl_2 (5:2), the layers were separated and the aqueous phase extracted three times with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. The crude product was purified via column chromatography over silica gel (Et_2O/pentane 1:3) to afford **4j** (192 mg, 81% yield) as colourless solid.
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