Synthesis of Substituted 4-Amino-2-benzazepin-3-ones via *N*-Acyliminium Ion Cyclizations

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Abstract: Two versatile syntheses of 1- and 1,2-disubstituted 2-benzazepinones are presented, using *N*-acyliminium ions as reactive intermediates. The methodology for 1-substitution is based on the synthesis of benzotriazole adducts, which are cyclized upon addition of $AlCl_3$. The simultaneous introduction of 1- and 2-substitions is realized by an *N*-acylation of an imine.

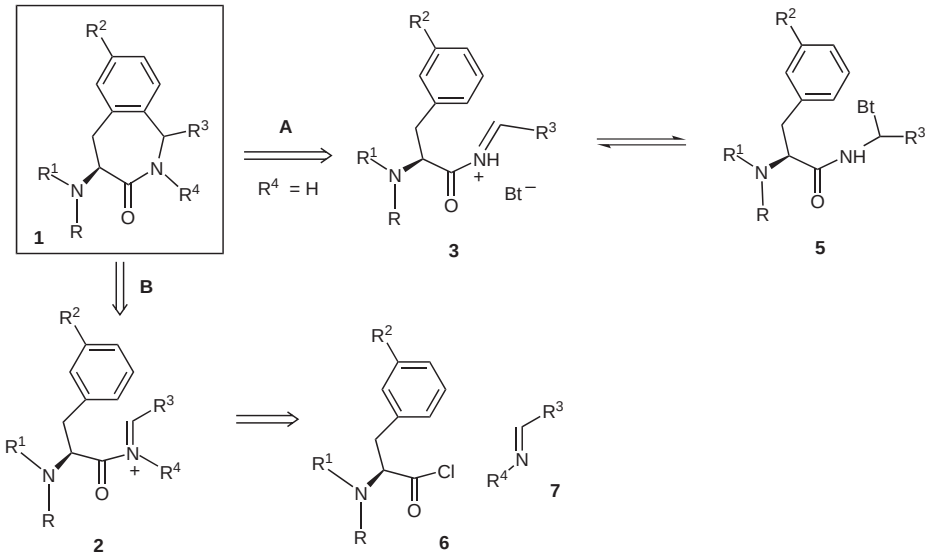
Key words: 4-amino-1,2,4,5-tetrahydro-2-benzazepin-3-one template, *N*-acyliminium ions, Friedel–Crafts alkylation, benzotriazole adducts

The tetrahydro-2-benzazepine skeleton is present in several bioactive compounds such as ACE, NEP, farnesyltransferase and factor Xa inhibitors, integrin and fibrinogen receptor antagonists, and analgesics.[1,2] Synthetic methods that allow the introduction of a variety of substituents at different positions are therefore highly valuable in medicinal chemistry. The methods available, however, do not allow an easy introduction of a substituent at the 1-position.[2] We now report our results on versatile synthetic methods for the preparation of 1- and 1,2-disubstituted 4-amino-1,2,4,5-tetrahydro-2-benzazepin-ones **1**, based on *N*-acyliminium ion cyclizations (Scheme 1).

The synthesis of the 1-substituted benzazepinones **1** was achieved through pathways A and B. Both synthetic pathways are based on the formation of *N*-acyliminium ion intermediates (**2** and **3**). Method A is based on the intramolecular cyclization developed by Katritzky et al. for the synthesis of substituted isoquinolines.[3,4] A benzotriazole adduct serves an a precursor for the *N*-acyliminium intermediate. Petrini and coworkers published a similar strategy using benzenesulfonyl derivatives.[5,6]

We prepared the benzotriazole adducts **5** (Scheme 2), starting from the corresponding *N*-phthaloyl-phenylalanine amide **9a** (R^2 = H) or **9b** (R^2 = OMe),[7] using benzotriazole (BtH) and an aldehyde in acid-catalyzed conditions by azeotropic removal of water.[8]

The equilibrium shift towards the *N*-acyliminium ion **3** is induced by the addition of a Lewis acid catalyst. The use of $SnCl_4$, $SbCl_5$, TFMSA and $Yb(OTf)_3$ resulted in the complete conversion of **5**[13] back into the starting material **9** (Table 1).



Scheme 1

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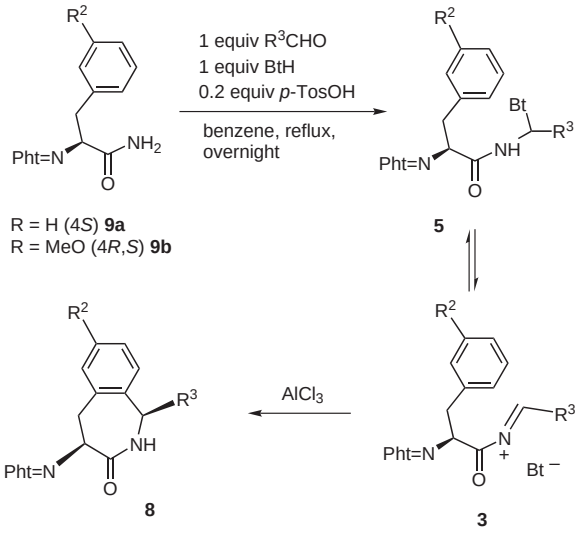


Scheme 2

Table 1 Synthesis of 1-Substituted Benzazepinones **8**[14,15,17]

Entry	Substrate	R^3	Yield of **8** (%)
1	**9a**	Ph	31
2	**9a**	4-ClPh	30
3	**9a**	4-BrPh	31
4	**9b**	Ph	71
5	**9b**	4-BrPh	68

We obtained compounds **8** (entry 1–3) using $AlCl_3$[3,8] under reflux conditions in dichloromethane in yields varying around 30%. By activation of the aromatic ring of the amino acid a much better yield was obtained (entries 4 and 5). The starting racemic amide for this entry was obtained through phase-transfer catalysis using ethyl *N*-(diphenylmethylene)glycinate and 3-methoxybenzylbromide with *n*-$Bu_4N^+HSO_4^-$ as the catalyst.[2c] In all cases the cyclization of the acyliminium ions **3** resulted in only one stereoisomer. The X-ray diffraction structure of **9a** indicated that the *cis* isomer was obtained (Figure 1).

A direct way to 1,2-disubstituted benzazepinones **1** consists of the *N*-acylation of an imine **7** (method B, Scheme 3). This reaction yields an *N*-acyliminium ion after addition of $SbCl_5$,[9] which cyclizes to **10** after an overnight reaction.

The use of $SnCl_4$ and $AgBF_4$ resulted in lower yields, whereas other metal halides ($TiCl_4$, $SbCl_5$) led to the hydrolysis of the *N*-acyliminium species **11**.

The reaction time for N-acylation was strongly dependent on the R^4 substituent: whereas the reaction with R^4 = benzyl or ethyl acetate required 45 minutes, the methyl propanoate substituent (entry 6, Table 2) needed 5 hours, probably due to increased steric hindrance. Literature proposes that the N-acylation step is an equilibrium step strongly dependent of the kind of imine used.[10] Steric hindrance might disfavor the N-acylated form.

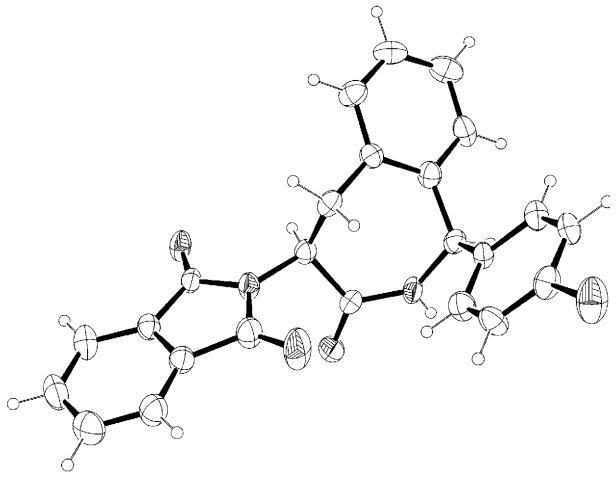


Figure 1

In contrast to method A, no diastereoselectivity is observed: the 1,2-disubstituted benzazepinones **10** are obtained in a 1:1 to 2:1 ratio (Table 2). One stereoisomer of **10** (entry 2, Table 2) was obtained by crystallization, and was shown by X-ray diffraction to be the *trans* isomer. We could observe that this isomer was formed selectively (1:10, *cis*/*trans*) when $SbCl_5$ was used in excess, but with yields <20% (Figure 2).

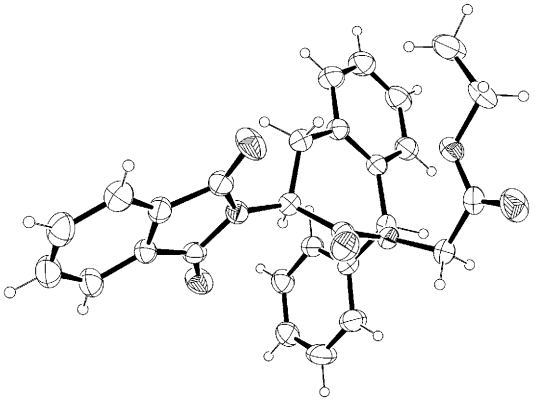
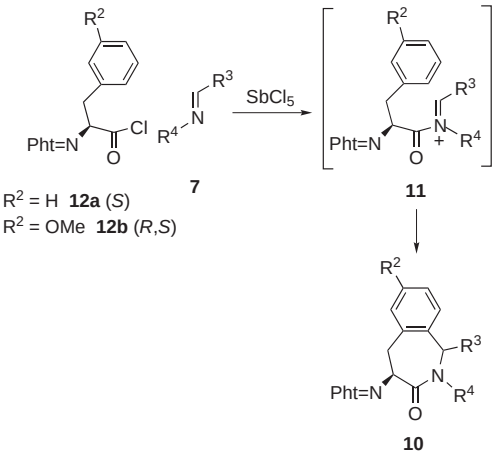


Figure 2



Scheme 3

It was impossible to obtain yields higher then 10% (HPLC quantification) for the 1-cyclohexyl analogue (entry 7). As apparent from Table 2, only non-enolizable aldehydes could be used to introduce a 1-substituent (R^3). The use of a cyclohexanecarboxaldehyde (entry 7) led to the formation of enamide **13** which could not be cyclized successfully (Scheme 4). Ring closure by protonation with TFMSA[11] did not result in the desired product.

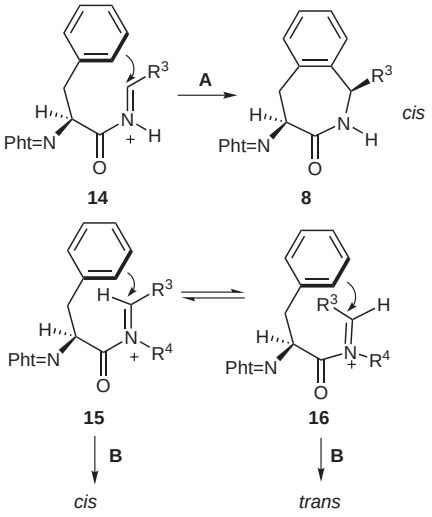
Table 2 Synthesis of 1,2-Disubstituted Benzazepinones **10**[14,16,17]

Entry	Substrate			Yield of **10** (%, *cis*/*trans*)
	R^2	R^3	R^4	
1	H	Ph	Bn	26 (1:1.2)
2	H	Ph	CH_2COOEt	50 (1:1)
3	H	4-ClPh	CH_2COOEt	52 (1:1.4)
4	H	4-BrPh	CH_2COOEt	54 (1:1.2)
5	H	4-PhPh	CH_2COOEt	45 (1:1.2)
6	H	Ph	(*S*)-$CH(CH_3)$ COOEt	36 (1:1)
7	H	Chex	CH_2COOEt	0
8	OMe	Ph	CH_2COOEt	75 (1:2)
9	OMe	4-ClPh	CH_2COOEt	70 (1:1.5)
10	OMe	4-BrPh	CH_2COOEt	69 (1:2)
11	OMe	4-PhPh	CH_2COOEt	71 (1:1.5)

Upon work up of the reaction a partial hydrolysis of the unreacted *N*-acyliminium ion intermediate **11** was observed. Ganesan et al. reported a similar iminium ion hydrolysis in Pictet–Spengler reactions using metal chloride Lewis acid catalysis.[11] Metal triflates ($M(OTf)_n$) were reported to avoid this side reaction and to result in high yields for the synthesis of tetrahydro-β-carboline ring systems. We investigated the use $Yb(OTf)_3$, $In(OTf)_3$ and $Sn(OTf)_2$ but unfortunately these catalysts were not effective, leading to no conversion to the ring-closed products **10** whatsoever.

As in method A, the reaction yields are much improved by having an activating methoxy substituent (entries 8–11). No side-product due to the hydrolysis of the acyliminium intermediate was observed on HPLC analysis, and after purification by flash chromatography satisfying yields (69–75%) were obtained. When on the other hand Pht-*p*Br-Phe, Pht-*p*I-Phe or Pht-*p*Cl-Phe were used, only the hydrolyzed products were observed, due to a decreased reactivity of the aromatic ring.

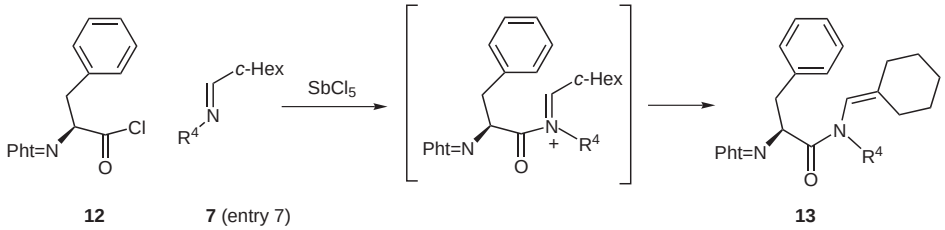
The selectivity for the formation of the *cis* isomer during the iminium ion cyclization of **3** is consistent with a previously reported example ($R^3 = COOCH_3$) for which the preferred transition state **14** was proposed (Scheme 3).[2a] A major aspect in **14** is that it results in an equatorial disposition of the imino substituent when the aromatic ring approaches from the top side.



Scheme 5

When an R^4 substituent is present, the *N*-acyliminium intermediate **11** does not exist in a single *E* configuration, but as the *E*/*Z* mixture **15** and **16** (Scheme 5). Cyclization then results in a diastereomeric mixture.

In conclusion we have developed two versatile strategies for the 1-substitution (pathway A) and 1,2-disubstitution (pathway B) of 4-amino-1,2,4,5-tetrahydro-2-benzazepin-3-ones **1**. Good yields are obtained, provided that the aromatic ring has an activating substituent, which is in agreement with other studies.[12] The *cis* product is solely formed using the benzotriazole pathway, whereas the strategy through a N-acylation of an imine gave a diastereomeric mixture.



12 **7** (entry 7) **13**

Scheme 4

Acknowledgment

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(13) **General Procedure for the Preparation of Compounds 5 (Entries 1–3).**
N-Phthaloyl-(*S*)-phenylalanine amide **9a** (0.5 g, 1.7 mmol), benzotriazole (1 equiv, 0.202 g, 1.7 mmol) and *p*-TsOH (0.1 equiv, 32 mg, 0.17 mmol) were added to an oven-dried 100-mL flask, and dissolved in dry benzene (15 mL). After addition of the aldehyde (1 equiv, 1.7 mmol) the flask was heated by means of an oil bath (105 °C) and the solution was refluxed over night. After evaporation of the solvent, trituration with Et_2O gave compound **5** (entries 1–3) in quantitative yields.

(14) **General Procedure for the Preparation of Compounds 8 (Entries 1–5).**
Benzotriazole adducts **5** (100 mg) were dissolved in dry CH_2Cl_2 (10 mL). Then, 10 equiv of $AlCl_3$ were added and these mixtures were refluxed over a period varying between 3 h and 5 h. The reaction mixtures were cooled down to r.t. after which H_2O (10 mL) was added. The organic phase was isolated and washed with brine (10 mL). After drying over $MgSO_4$ the solvent was removed in vacuo. Flash chromatography (15% EtOAc in hexanes) or crystallization (from EtOH) yielded compounds **8** (entries 1–5).

(15) **General Procedure for the Preparation of Compounds 10 (Entries 1–7).**
In an oven-dried 25-mL flask, Pht-Phe (150 mg, 0.5 mmol) was dissolved in α,α-dichloromethyl methyl ether (5 mL) and the reaction mixture was stirred at 60 °C (oil bath temperature) over night. After evaporation the residue was re-dissolved in dry benzene (10 mL) and evaporated (2 times). The resulting white solid was dissolved in dry CH_2Cl_2 (5 mL) and cooled down to 0 °C by means of an ice bath. The flask was filled with argon, the imine **7** (1.5 equiv) was added, the reaction mixture was stirred during 45 min at 0 °C after which 1.2 equiv (0.6 mL, 0.60 mmol) of a 1 M solution of $SbCl_5$ in CH_2Cl_2 was added. Overnight reaction at r.t. was followed by quenching with H_2O (5 mL). Isolation of the organic phase, evaporation and flash chromatography yielded the benzazepinones **10** (entries 1–7).

(16) Analytical data of *N*-phthaloyl-(4*S*)-amino-1-phenyl-1,2,4,5-tetrahydrobenzo[*c*]azepin-3-one (**8**, entry 1): white solid, R_f = 0.70 (EtOAc), mp 222–224 °C. MS (ESP^+): *m/z* calcd for $C_{24}H_{19}N_2O_3$: 383.13. Found: 383 $[M + H]^+$. HPLC: t_R = 21.2 (min). ^1H NMR (250 MHz, $CDCl_3$): δ = 2.65 (dd, *J* = 13.5 Hz, *J* = 3.0 Hz, 1 H), 3.19 (br s, 1 H), 3.71 (dd, *J* = 13.0 Hz, *J* = 12.6 Hz, 1 H), 4.90 (dd, *J* = 12.5 Hz, *J* = 3.0 Hz, 1 H), 4.19 (m, 3 H), 4.86 (dd, *J* = 3.0 Hz, *J* = 14.0 Hz, 1 H), 5.65 (d, *J* = 6.5 Hz, 1 H), 7.21–7.40 (m, 9 H), 7.74 (m, 2 H), 7.85 (m, 2 H). ^{13}C NMR (63 MHz, $CDCl_3$): δ = 34.6, 52.7, 123.9, 126.9, 128.0, 128.0, 129.0, 129.7, 130.0, 131.0, 132.9, 134.5, 136.8, 139.3, 141.1, 167.8, 172.0.

(17) Analytical data of *N*-phthaloyl[1-phenyl-(4*S*)-amino-3-oxo-1,2,4,5-tetrahydrobenzo[*c*]azepin-2-yl]acetic acid ethyl ester) (**10**, entry 2): white solid, R_f = 0.68 (EtOAc), mp 108–110 °C. MS (ESP^+): *m/z* calcd for $C_{28}H_{25}N_2O_5$: 468.17. Found: 469 $[M + H]^+$. HPLC: t_R = 24.1 and 24.3 (min). ^1H NMR (250 MHz, $CDCl_3$): δ = 1.08 and 1.22 (t, *J* = 7.1 Hz, 3 H), 2.55 and 3.18 (dd, *J* = 17.0 Hz, *J* = 4.0 Hz, 1 H), 4.11 (q, *J* = 7.1 Hz, 2 H), 3.62 and 4.25 (d, *J* = 17.0 Hz, 1 H), 4.32 (m, 1 H), 4.91 and 5.12 (d, *J* = 17.0 Hz, 1 H), 4.85 and 5.32 (dd, *J* = 12.0 Hz, *J* = 4.0 Hz, 1 H), 5.65 and 5.70 (s, 1 H), 7.15–7.50 (m, 9 H), 7.68–7.82 (m, 4 H). ^{13}C NMR (63 MHz, $CDCl_3$): δ = 14.2 and 14.6, 33.7 and 34.6, 53.1, 52.3 and 54.0, 61.7 and 61.8, 69.3 and 70.4, 123.8, 126.9, 128.0, 129.0, 129.5, 130.3, 131.9, 134.5, 136.0, 137.5, 139.6, 139.3, 141.5, 169.2, 169.5, 170.1.

(18) X-ray structure analysis of compounds **8** (entry 1) and **10** (entry 2). Suitable crystals were mounted on glass fibers. Data collections were performed at 295 nm on a Nonius BV MACH diffractometer with graphite monochromated CuKα (λ = 1.54178 Å). Both structures were solved with direct methods using the SHELXS97[19] and refined with SHELXL97[20] software. Refinements were performed anisotropically for all non-hydrogen atoms using the full-matrix least-squares method. In general, hydrogen atoms were assigned to idealized positions and were allowed to ride with thermal parameters fixed at 1.2 U_{eq} of the parent atom. The residual electron densities were of no chemical significance. Accordingly, CCDC-279757 [**8** (entry 1)], and CCDC-279758 [**10** (entry2)] contain the supplementary crystallographic data for this paper. These data can be obtained free of charge at http://www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; e-mail: deposit@ccdc.cam.sc.uk).

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