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The von Braun Reaction Applied to Azetidines

Karen Wright, Bruno Drouillat, Laurence Menguy, Jérôme Marrot and François Couty* [a]

Abstract: The von Braun reaction, that is the reaction of cyanogen bromide with tertiary amines, was applied to a series of functionalized *N*-alkyl azetidines. This reaction mainly leads to the cleavage of the strained four-membered ring, producing 3-bromo *N*-alkyl cyanamides in good yield and variable regioselectivity, which can be used as original building blocks for the synthesis of nitrogen heterocycles.

Introduction

Azetidines, due to their inherent ring-strain and growing availability by various synthetic methods,[1] have emerged as valuable substrates for the discovery of new reactions involving either ring-expansions[2] or ring-cleavages,[3] that have boosted their utility for the synthesis of nitrogen-containing compounds. Among numerous variations of such reactions, *N*-alkyl azetidines have been reported to react with chloroformates, leading to intermediate *N*-acyl azetidinium ions that are opened regioselectively by a chloride anion.[4] In the same vein, azetidines react with triphosgene, leading to dealkylation or ring cleavage, and the produced compounds can be converted into cyclic ureas upon reaction with amines.[5] (Scheme 1). The former reaction (tertiary amines reacting with chloroformates) now belongs to the toolbox of synthetic chemists facing the problem of a regioselective *N*-dealkylation reaction, and has supplanted the venerable von Braun reaction,[6] (tertiary amines reacting with cyanogen bromide) mainly used for this purpose at the dawn of the 20th century. Despite its precedence, the von Braun reaction has been applied only once to an azetidine in the course of a more comprehensive study looking at cyclic amines reacting with cyanogen bromide. Thus, Hageman *et al*[7] reported the cleavage of *N*-butyl azetidine **1**, leading to 3-bromo cyanamide **2**, and its subsequent reaction with diamine **3**, leading to bis-guanidine **4** (Scheme 1). As stated by the authors in this seminal article, "*although this reaction proceeds in good yield, the limiting factor in its usefulness is the lack of suitable methods for the synthesis of azetidines in good yield*". Since this situation is no longer valid, azetidines being available with different substitution patterns, even in homochiral form, we decided to revisit this reaction and its applications, with careful examination of the issues of its regio- and stereoselectivity, as well as the synthetic applications of the produced bromo cyanamides. This is the purpose of this article.

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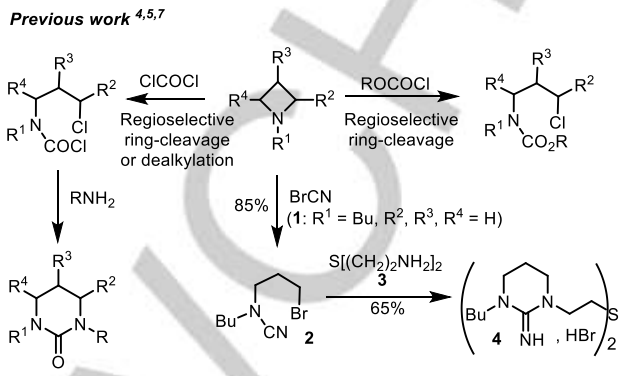


Scheme 1. Reaction of azetidines with chloroformates, triphosgene, and cyanogen bromide (von Braun reaction).

Results and Discussion

In order to examine in detail the scope of the von Braun reaction applied to azetidines, a set of different substrates was selected. It includes unsubstituted *N*-benzhydryl azetidine **5**, chosen to examine possible competition between ring and *N*-benzhydryl cleavages, and a series of differently substituted azetidines, (mono-, di- and trisubstituted, depicted in the different frames of Figure 1) in order to examine issues of regio- and stereoselectivity of the ring cleavage.

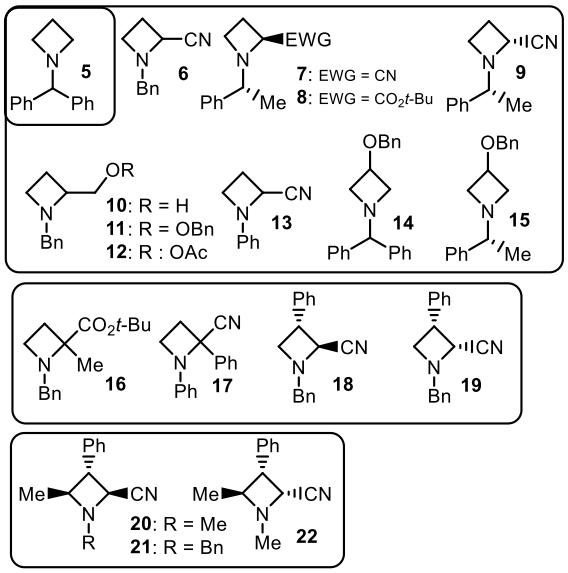
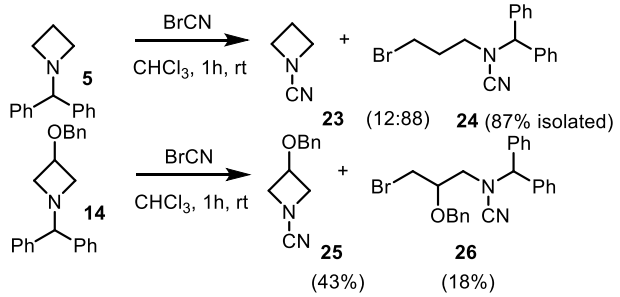


Figure 1. Structures of azetidines **5-22** used in this study

In this series, azetidines **7**-**9, 15** and **18-22** were used as homochiral substrates and other chiral compounds were used as racemic mixtures. All of them were either commercially available (**5**) or synthesized readily in a few steps.[1f,2c,8]

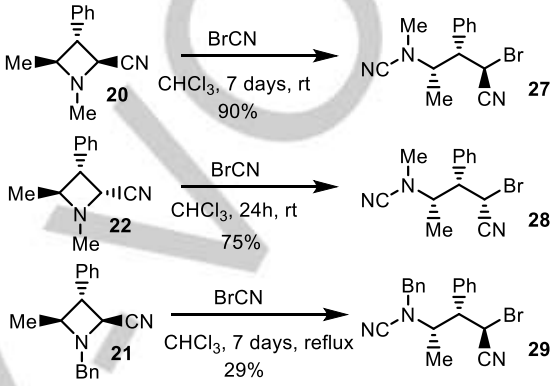
First the reaction of **5** with BrCN under standardized conditions (0.2 M solution of the azetidine in $CHCl_3$ at rt, 1.5 eq. of 3 M BrCN solution in dichloromethane) was examined. This led mostly to the cleavage of the azetidine ring after 1h at rt, leading to 3-bromo cyanamide **24** in excellent isolated yield**,** with a 12% ratio of *N*-cyano azetidine **23**. It is worthy to note that this preferential ring-cleavage contrasts with the reaction with triphosgene, which mostly leads to *N*-benzhydryl cleavage.[5] However, by encumbering the 3-position of the azetidine ring (**14**) with a benzyloxy substituent, cleavage of the *N*-benzhydryl group became the major event (Scheme 2).



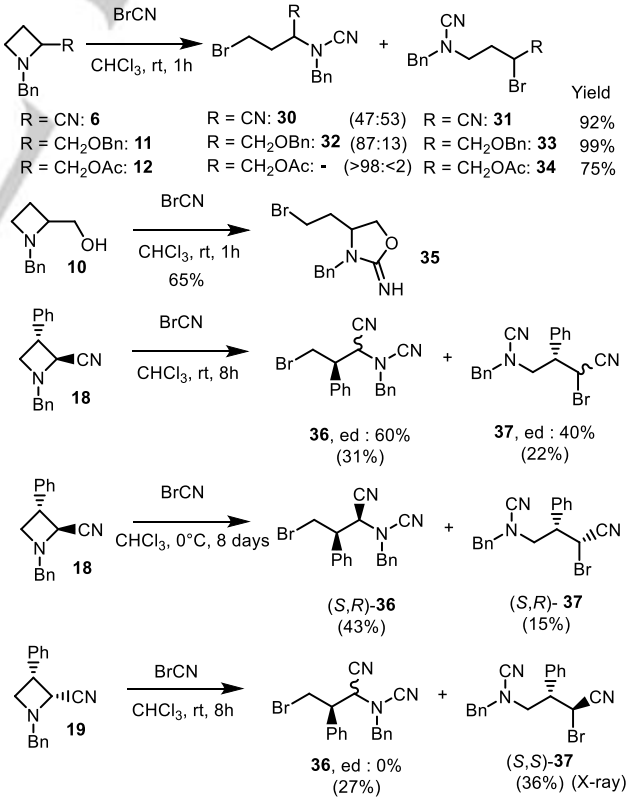
Scheme 2. Reaction of *N*-benzhydryl azetidine with cyanogen bromide.

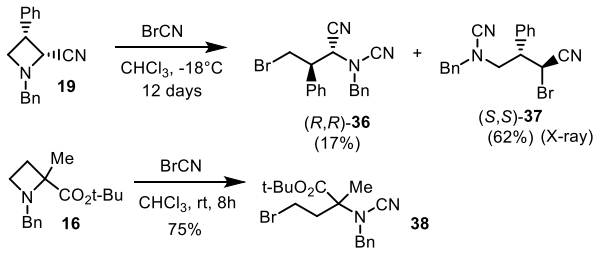
Among all the azetidines we tested in this reaction, **5** and **14** are the only substrates that showed competing *N*-alkyl cleavage, thus highlighting the positive effect of ring strain to promote ring-cleavage. Other tested compounds displayed contrasting reactivities, depending essentially on the nucleophilic character of the azetidine, which itself depends on the substitution pattern and on the nature of the *N*-substituent. Let us examine the different cases considering this last parameter. The smallest *N*-substituent is a methyl group present in ephedrine-derived azetidines **20** and **22**. These compounds reacted at rt with BrCN, but required protracted reaction time compared to **5**, yielding **27** and **28** with total regioselectivity as single diastereoisomers. The structure of **27** was determined by X-Ray crystallography, demonstrating the S_N2 process operating during ring cleavage.[9] Switching to a *N*-Bn group in **21** considerably lowered the reactivity and gave only a modest yield of similar ring opened product **29** after 7 days of heating at 80°C, demonstrating the critical parameter of steric crowding around the amine (Scheme 3).

The reactivity of other azetidines fitted with a *N*-Bn group varied upon the substitution pattern of the four-membered ring. Alpha-monosubstituted **6**,**11**,**12** and alpha-disubstituted **16** reacted rapidly at rt, leading to ring-opened products with varying levels of regioselectivity. In all cases, except for **6**, the regioisomer resulting from opening by the bromide anion at the unsubstituted position was privileged. With azetidine **10**, with a hydroxymethyl group, further reaction led to the unstable 2-iminooxazolidine **35**. With the α,β-disubstituted azetidines **18** and **19**, the outcome was more complicated, since mixtures of epimers and regioisomers **36** and **37** were obtained in both cases, together with small amounts of epimerized starting azetidine. By running the reactions at lower temperature (0°C for **18**, and -18°C for **19**), it was however possible to minimize epimerization, and we were able to produce each regioisomer with high diastereoisomeric excess. An X-ray structure of compound (*S*,*S*)-**37**,[9] resulting from ring opening at C-2 in **19**, allowed the determination of the structures of the produced products and gave insights into the mechanism of the reaction (vide supra). (Scheme 4).



Scheme 3. Switching from a *N*-methyl to a *N*-benzyl group lowers reactivity.

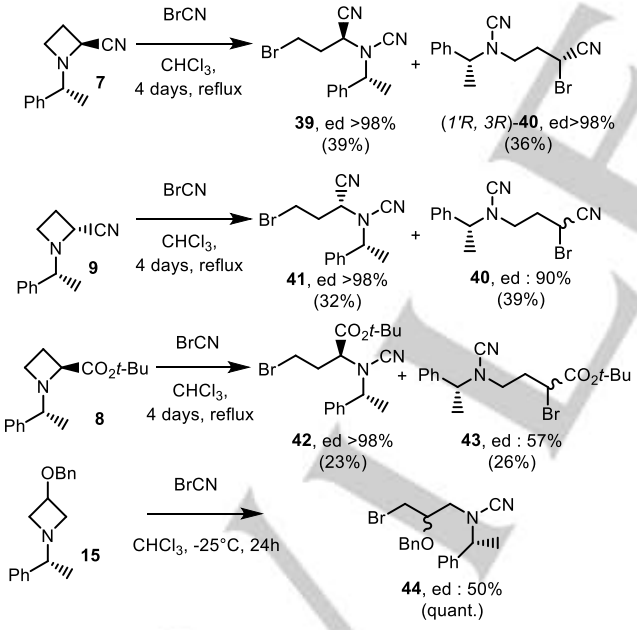




Scheme 4. Reaction of *N*-benzyl azetidines in the von Braun reaction.

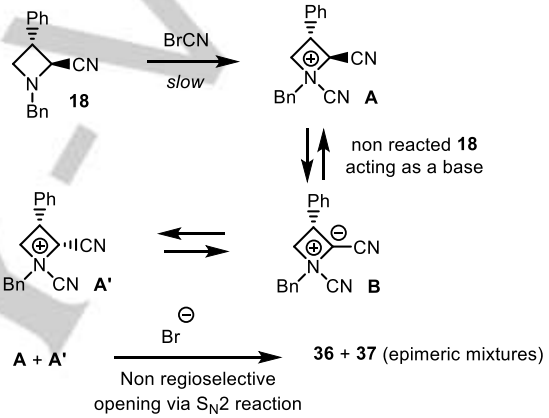
Altogether, this set of results demonstrate that *N*-Bn azetidines react with fair regioselectivity and reasonable rates when mono- or disubstituted at the 2 position, but the introduction of another substituent at C-3 is detrimental to attain good regioselectivity.

When a *N*-phenylethyl group is present, instead of a *N*-Bn group, then steric crowding is enhanced, and reactivity is dramatically lowered. Thus, azetidines **7**-**9** reacted sluggishly and required several days of reaction at 80°C to reach completion. Regioselectivity was poor, and epimerization was also detected in the produced compound **40**. An interesting substrate was the azetidine **15** devoid of substituents at C-2. This compound reacted readily at rt to give a diastereoisomeric mixture of opened products **44** in a 70:30 ratio. This could be improved to 75:25 by running the reaction at -25°C for 24h (Scheme 5). Finally, *N*-Ph azetidines **13** and **17** did not react with BrCN, even upon reflux, probably due to the decreased nucleophilic character of the *N*-aryl amine.



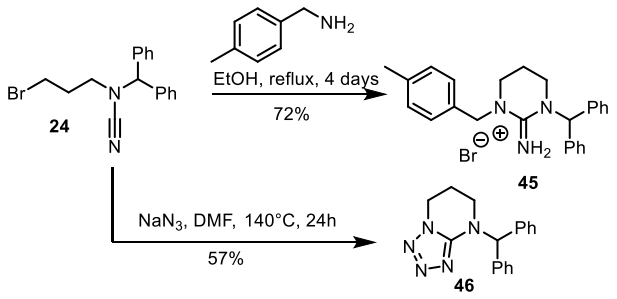
Scheme 5. Reaction of *N*-phenylethyl azetidines in the von Braun reaction.

All these results allow us to delineate general trends in this reaction. Regarding regioselectivity, it is clear that a good level of regioselectivity is attained if the azetidine ring is alpha mono- or disubstituted, with the bromide anion reacting on the unsubstituted carbon, in line with the general rules governing S_N2 reactions. This rule does not however apply to a nitrile substituent, for which the observed regioselectivity is poor, probably due to its small size. Reactivity is highly affected by the nature of the *N*-substituent and is dramatically lowered in the order Me > Bn > phenylethyl > aryl, which follows the nucleophilic character and/or the steric crowding of the tertiary amine. The epimerization observed in some cases can be explained by the reversible formation of an intermediate *N*-ylide **B**, produced by deprotonation of the intermediate ammonium salt **A**, **A'** by the unreacted azetidine acting as a base (Scheme 6). To the best of our knowledge, this possible side-reaction in the von Braun reaction is shown here for the first time and highlights the importance of the rates of the two elementary steps for the overall stereospecificity of the process, which depends on the substrate used .[10]



Scheme 6. Possible mechanism via a *N*-ylide, explaining the epimerization detected with some substrates (shown with **18**).

Having demonstrated the potential of the von Braun reaction applied to azetidines, we briefly focused on the use of the produced 3-bromo *N*-cyanamides as original building blocks for the synthesis of nitrogen heterocycles.[11] Indeed, the cyanamide moiety offers various opportunities to act as an electrophile or as a partner in cycloadditions and radical reactions.[12] The presence of an extra electrophilic carbon, in the bromoalkane group, renders these compounds particularly relevant. Thus, reaction of **24** with 4-methylbenzylamine in refluxing ethanol gave a good yield of cyclic guanidine **45**, isolated as its hydrobromide salt. Such cyclic guanidines have found increasing interest recently, particularly in the field of nucleophilic catalysis.[13] Alternatively, the substitution of the bromide by an azido group in **24**, followed by [3+2] intramolecular cycloaddition[14] gave a fair yield of tetrazole **46** over two steps (Scheme 7).



Scheme 7. Two example of the use of 3-bromo *N*-cyanamides for the synthesis of nitrogen heterocycles.

Conclusions

In conclusion, we have studied in detail the von Braun reaction applied to azetidines, and have shown that excellent levels of regio- and stereoselectivity can be reached in the ring-opening process, which is the favored pathway in most cases, even with a *N*-benzydryl group. Considering the recent progress made in the preparation of azetidines, allowing the easy preparation of a vast array of diversely substituted compounds even in non-racemic forms,[1] coupled with the synthetic relevance of the 3-bromo *N*-cyanamide as original building blocks to create nitrogen containing heterocycles, we feel that this revival of the von Braun reaction when applied to azetidines should be of interest for the synthetic community.

Experimental Section

General information: ^{1}H and ^{13}C NMR spectra were recorded at 200 or 300 and 75 MHz, respectively; chemical shifts (δ) are reported in ppm and coupling constants (*J*) reported in Hertz and rounded up to 0.1 Hz. Splitting patterns are abbreviated as follows: singlet (s), doublet (d), triplet (t), quartet (q), septuplet (sep), multiplet (m), broad (br), or a combination of these. Solvents were used as internal standard when assigning NMR spectra (δ H : $CDCl_3$ 7.26 ppm ; δ C: $CDCl_3$ 77.0 ppm). Assignments for signals from ^{1}H and ^{13}C in the NMR spectra were validated by two-dimensional correlated spectroscopy (2D COSY) and Heteronuclear Multiple Bond Correlation (HMBC). IR data were collected with an ATR-FT-IR spectrometer. All reactions were carried out under argon. Column chromatography was performed on silica gel (230–400 mesh) with use of various mixtures of CH_2Cl_2, EtOAc, petroleum ether (35-60°C fraction) (PE) and methanol. TLC was performed on Merck Kieselgel 60 F254 plates. Melting points are uncorrected. Isomeric ratios were determined by NMR analysis of crude reaction mixtures before purification.

General procedure for the Von Braun reaction with azetidines

To a solution of the required azetidine in chloroform (concentration: 0.2 M) was added dropwise a 3 M solution of BrCN in CH_2Cl_2 (1.5 equiv.). The reaction was monitored by TLC. When no reaction was detected immediately after the addition, it was heated at 80°C. In the case of protracted reaction time, an additional 1 equiv. of BrCN was added each 24h. After completion, solvent was evaporated under reduced pressure, and the residue was purified by flash chromatography or by thin layer chromatography over silica gel.

***N*-benzhydryl-(3-bromo-propyl)-cyanamide 24**

From *N*-benzhydryl azetidine **5**, 12% of azetidine carbonitrile **23** and 1,1-diphenylbromomethane were detected in the crude reaction mixture. Compound **24** was purified as a colourless oil (87%); Rf= 0.55 (PE/EtOAc : 80/20); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.48-7.30 (m, 10H, Ar), 5.32 (s, 1H, NC*H*Ph_2), 3.56 (t, 2H, *J*=6.0 Hz, C*H*$_2$Br), 3.30 (t, 2H, *J*=6.0 Hz, C*H*$_2$N), 2.29 (appt. quint., 2H, *J*=6.0 Hz, CH_2) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 137.2 (C_q), 129.0, 128.7, 128.3 (CH_{Ar}), 116.1 (CN), 69.2 (NCH), 49.3, 30.4, 29.8 (CH_2) ppm. IR: vmax = 3325(b), 2969, 2835, 1610, 1511, 1244, 1171, 1031, 817, 792, 510 cm^{-1}. HRMS (TOF MSES positive mode) *m/z* calcd for $C_{17}H_{17}BrN_2Na$ $[M+Na]^+$: 351.0473; found : 351.0460.

3-benzyloxy-azetidine-1-carbonitrile 25 and ***N*-benzhydryl-(2-benzyloxy-3-bromo-propyl)-cyanamide 26**

From azetidine **14**, compounds **25** (43%) and **26** (18%) were isolated.
25 Colourless oil (43%); Rf= 0.34 (PE/EtOAc : 75/25); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.41-7.30 (m, 5H, Ar), 4.45 (bs, 2H, OC*H*$_2$Ph), 4.42-4.34 (m, 1H, C*H*OBn), 4.24-4.19 (m, 2H, C*H*HNC*H*H), 4.10-4.05 (m, 2H, C*H*HNC*H*H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 136.5 (C_q), 128.5, 128.2, 127.9 (CH_{Ar}), 117.3 (CN), 71.5 (OCH_2Ph), 68.7 (CHOBn), 62.3 (CH_2NCH_2) ppm. IR: vmax = 3060, 3040, 2955, 2875, 2207, 1457, 1258, 1121, 745, 700 cm^{-1}. HRMS (TOF MSES positive mode) *m/z* calcd for $C_{11}H_{13}N_2O$ $[MH]^+$: 189.1028; not found.
26 Colourless oil (18%); Rf= 0.58 (PE/EtOAc : 75/25); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.42-7.28 (m, 15H, Ar), 5.38 (s, 1H, NC*H*Ph_2), ~4.73 (appt. d, A part of AB syst., 1H, *J*=12.0 Hz, OC*H*$_2$Ph), ~4.61 (appt. d, B part of AB syst., 1H, *J*=12.0 Hz, OC*H*$_2$Ph), 4.02-3.95 (m, 1H, C*H*OBn), 3.55-3.47 (m, AB part of ABX syst., 2H, C*H*$_2$Br), ~3.44 (appt. dd, AB part of ABX syst., 1H, NC*H*$_2$), ~3.30 (appt. dd, AB part of ABX syst., 1H, NC*H*$_2$) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 137.8, 137.6, 137.1 (C_q), 128.8, 128.7, 128.5, 128.4, 128.3, 128.1, 128.0 (CH_{Ar}), 116.4 (CN), 76.2 (CHOBn), 72.3 (OCH_2Ph), 69.2 ($CH(Ph)_2$), 53.5 (NCH_2), 31.0 ($BrCH_2$) ppm. IR: vmax = 3062, 3032, 2945, 2867, 2205, 1493, 1453, 1064, 734, 694 cm^{-1}. HRMS (TOF MSES positive mode) *m/z* calcd for $C_{24}H_{24}N_2OBr$ $[MH]^+$: 435.1072; found : 435.1064.

(1*S*,2*S*,3*R*)-*N*-methyl-(3-bromo-3-cyano-1-methyl-2-phenyl-propyl)-cyanamide 27

White solid (90%); Mp= 92°C; Rf= 0.23 (PE/EtOAc : 75/25); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.46-7.43 (m, 3H, Ar), 7.40-7.36 (m, 2H, Ar), 5.05 (d, 1H, *J*=3.9 Hz, C*H*BrCN), 3.55-3.45 (m, 1H, NC*H*CH3), ~3.23 (appt. dd, 1H, *J*=10.8 Hz, *J*=3.9 Hz, C*H*Ph), 3.07 (s, 3H, NC*H*$_3$), 1.19 (d, 3H, *J*=6.3 Hz, CHC*H3*) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 133.6 (C_q), 129.3, 129.0 (CH_{Ar}), 115.9, (CH*C*NBr), 115.6 (NCN), 59.0 (NCH), 52.1 (CHPh), 39.0 (NCH_3), 32.0 (*CH*BrCN), 15.4 (CH_3) ppm. IR: vmax = 3026, 3000, 2979, 2959, 2923, 2196, 1497, 1449, 1378, 1251, 770, 703, 600 cm^{-1}. HRMS (TOF MSES positive mode) *m/z* calcd for $C_{13}H_{14}N_3BrNa$ $[MNa]^+$: 314.0269; found : 314.0269. $[\alpha]_{578}^{20}$: - 19 (*c* 1.0, CH_2Cl_2).

(1*S*,2*S*,3*S*)-*N*-methyl-(3-bromo-3-cyano-1-methyl-2-phenyl-propyl)-cyanamide 28

White solid (75%); Mp= 92°C; Rf= 0.71 (PE/EtOAc : 75/25); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.43-7.40 (m, 3H, Ar), 7.35-7.32 (m, 2H, Ar), 5.01 (d, 1H, *J*=5.1 Hz, C*H*BrCN), 3.51-3.45 (m, 1H, NC*H*CH_3), ~3.23 (appt. dd, 1H, *J*=11.1 Hz, *J*=4.8 Hz, C*H*Ph), 3.06 (s, 3H, NC*H*$_3$), 1.15 (d, 3H, *J*=6.3

Hz, CHC*H*$_3$) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 135.1 (C_q), 129.1, 128.8 (CH_{Ar}), 116.1, (CH*C*NBr), 115.4 (NCN), 60.7 (NCH), 53.8 (CHPh), 39.3 (NCH_3), 29.4 (*CH*BrCN), 16.1 (CH_3) ppm. IR: vmax = 3070, 3026, 2987, 2971, 2943, 2196, 1490, 1453, 1374, 782, 702 cm^{-1}. HRMS (TOF MSES positive mode) *m/z* calcd for $C_{13}H_{15}N_3Br$ $[MH]^+$: 292.0449; found : 292.0443. $[\alpha]_{578}^{20}$: - 47 (*c* 0.5, CH_2Cl_2).

(1*S*,2*S*,3*R*)-*N*-benzyl-(3-bromo-3-cyano-1-methyl-2-phenyl-propyl)-cyanamide 29

Pale yellow viscous oil (29%); Rf= 0.18 (PE/EtOAc : 85/15); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.49-7.34 (m, 10H, Ar), 5.04 (d, 1H, *J*=3.9 Hz, C*H*BrCN), 4.36 (s, 2H, NC*H*$_2$Ph), 3.67-3.57 (m, 1H, NC*H*CH3), 3.28 (dd, 1H, *J*=10.5 Hz, *J*=3.6 Hz, C*H*Ph), 1.11 (d, 3H, *J*=6.3 Hz, C*H*$_3$) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 134.1, 133.6 (C_q), 129.4, 129.3, 128.9 (CH_{Ar}), 115.9 (CH*C*NBr), 114.7 (NCN), 57.5 (NCH), 56.9 (NCH_2Ph), 52.4 (CHPh), 32.1 (*C*HBrCN), 16.4 (CH_3) ppm. IR: vmax = 3061, 3030, 2971, 2935, 2872, 1499, 1456, 1381, 1140, 730, 702 cm^{-1}. HRMS (TOF MSES positive mode) *m/z* calcd for $C_{19}H_{19}N_3Br$ $[MH]^+$: 368.0762; found : 368.0756. $[\alpha]_{578}^{20}$: +6 (*c* 2.9, CH_2Cl_2).

***N*-benzyl-(3-bromo-1-cyano-propyl)-cyanamide 30**

Yellow oil (43%); Rf= 0.55 (PE/EtOAc : 75/25); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.45-7.37 (m, 5H, Ar), 4.45 (d, *J*=13.6 Hz, 1H, NC*H*HPh), 4.31 (d, *J*=13.7 Hz, 1H, NCH*H*Ph), 4.15-4.10 (m, 1H, C*H*CN), 3.55-3.42 (m, 2H, CH_2Br), 2.59-2.36 (m, 2H, CH_2) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 132.0 (Cq_{Ar}), 129.5, 129.3, 129.0 (CH_{Ar}), 115.2 (CH*C*N), 113.0 (NCN), 56.4 (NCH_2Ph), 48.8 (*C*HCN), 33.8 (CH_2), 26.7 (CH_2Br) ppm. IR: vmax = 3031, 2949, 2212, 1496, 1462, 1348, 1316, 1255, 1218, 1164, 1153, 1115, 1068, 1029, 953, 925, 852, 763, 734, 707, 601 cm^{-1}. HRMS (TOF MSES positive mode) *m/z* calcd for $C_{12}H_{13}N_3Br$ $[MH]^+$: 278.0293; not found.

***N*-benzyl-(3-bromo-3-cyano-propyl)-cyanamide 31**

Colourless oil (49%); Rf= 0.32 (PE/EtOAc : 75/25); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.46-7.34 (m, 5H, Ar), 4.40 (t, *J*=7.4 Hz, 1H, C*H*BrCN), 4.23 (s, 2H, NC*H*$_2$Ph), 3.22 (t, *J*=6.5 Hz, 2H, NC*H*$_2$CH$_2$), 2.48-2.30 (m, 2H, NCH_2CH_2) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 133.8 (Cq_{Ar}), 129.1, 129.0, 128.5 (CH_{Ar}), 116.5, 116.3 (CH*C*NBr, N*C*N), 56.7 (NCH_2Ph), 47.2 (NCH_2CH_2), 34.0 (NCH_2CH_2), 23.4 (*C*HBrCN) ppm. IR: vmax = 3031, 2949, 2212, 1496, 1456, 1349, 1316, 1255, 1218, 1164, 1153, 1115, 1068, 1008, 953, 925, 868, 763, 734, 707 cm^{-1}. HRMS (TOF MSES positive mode) *m/z* calcd for $C_{12}H_{13}N_3Br$ $[MH]^+$: 278.0293; found : 278.0287.

***N*-benzyl-(1-benzyloxymethyl-3-bromo-propyl)-cyanamide 32** and ***N*-benzyl-(3-benzyloxymethyl-3-bromo-propyl)-cyanamide 33**

Compounds **32**/**33** were obtained as an inseparable mixture of regioisomers; yellow oil (99%); Rf= 0.41 (PE/EtOAc : 60/40); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.42-7.33 (m, 10H, Ar), 4.61-4.51 (m, 2H, OC*H*$_2$Ph), 4.40-4.20 (m, 2H, CHC*H*$_2$O), 3.64-3.32 (m, 5H, C*H*N, NC*H*$_2$Ph, C*H*$_2$Br), 2.27-2.18 (m, 1H, C*H*HCH$_2$Br), 2.08-1.96 (m, 1H, CH*H*CH$_2$Br) ppm. Major regioisomer: ^{13}C NMR (75 MHz, $CDCl_3$): δ = 137.5, 134.8 (Cq_{Ar}), 128.9, 128.8, 128.6, 127.8, 127.6 (CH_{Ar}), 115.6 (NCN), 73.4 (OCH_2Ph), 70.8 ($CHCH_2O$), 57.8 (CHN), 56.8 (NCH_2Ph), 32.6 (CH_2CH_2Br), 29.3 (CH_2Br) ppm. IR: vmax = 3030, 2863, 2206, 1496, 1454, 1362, 1252, 1111, 1076, 953, 734, 697 cm^{-1}. HRMS (TOF MSES positive mode) *m/z* calcd for $C_{19}H_{22}N_2OBr$ $[MH]^+$: 373.0915; found : 373.0918.

***N*-benzyl-(1-acetoxymethyl-3-bromo-propyl)-cyanamide 34**

Yellow oil (75%); Rf= 0.29 (PE/EtOAc : 75/25); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.40-7.36 (m, 5H, Ar), 4.38-4.24 (m, 3H, NC*H*$_2$Ph, C*H*HOAc), 4.08-4.02 (m, 1H, CH*H*OAc), 3.54-3.34 (m, 3H, C*H*N, C*H*$_2$Br), 2.34-2.23 (m, 1H, C*H*HCH$_2$Br), 2.10-1.98 (m, 4H, CH*H*CH$_2$Br, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.4 (CO), 134.4 (Cq_{Ar}), 129.0, 128.9 (CH_{Ar}), 115.1 (NCN), 63.7 (CH_2O), 56.5 (CHN), 56.4 (NCH_2Ph), 32.6 (CH_2CH_2Br), 28.9 (CH_2Br), 20.6 (CH_3) ppm. IR: vmax = 3031, 2948, 2211, 1740, 1496, 1456, 1349, 1316, 1218, 1153, 1114, 1067, 1008, 868, 763, 706 cm^{-1}. HRMS (TOF MSES positive mode) *m/z* calcd. for $C_{14}H_{18}N_2O_2Br$ $[MH]^+$: 325.0552; found : 325.0555.

(1*S*,2*R*)-*N*-benzyl-(3-bromo-1-cyano-2-phenyl-propyl)-cyanamide (*S*,*R*)-36 and **(2*S*,3*R*)-*N*-(benzyl)-(3-bromo-3-cyano-2-phenyl-propyl)-cyanamide (*S*,*R*)-37**

Reaction of azetidine **18** with BrCN at 0°C for 8 days gave compound (*S*,*R*)-**36** as a single epimer (clear needles, 43%) and compound (*S*,*R*)-**37** as a single epimer (white crystals, 15%).

(*S*,*R*)-**36** Mp= 116°C; Rf =0.25 (PE/EtOAc : 50/50); ^{1}H RMN (300 MHz, $CDCl_3$) : δ (ppm) = 7.52-7.43 (m, 8H, Ar), 7.35-7.30 (m, 2H, Ar), ~4.44 (d, A part of AB syst., 1H, *J*=13.2 Hz, NC*H*$_2$Ph), 4.42 (d, 1H, *J*=10.2 Hz, C*H*CN), ~4.35 (d, B part of AB syst., 1H, *J*=13.2 Hz, NC*H*$_2$Ph), 3.80 (dd, A part of ABX syst., 1H, *J*=11.1 Hz, C*H*$_2$Br), 3.72 (dd, B part of ABX syst., 1H, *J*=10.8 Hz, C*H*$_2$Br), 3.66-3.59 (m, 1H, C*H*Ph) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 134.7, 132.0 (C_q), 129.6, 129.3, 129.1, 128.2 (CH_{Ar}), 114.3 (CH*C*N), 113.2 (NCN), 56.8 (NCH_2Ph), 54.0 (N*C*HCN), 47.6 (CHPh), 33.4 ($BrCH_2$) ppm. IR: vmax = 3066, 3033, 2969, 2890, 2208, 1495, 1457, 1124, 1078, 751, 702 cm^{-1}. HRMS (TOF MSES positive mode) *m/z* calcd for $C_{18}H_{17}N_3Br$ $[MH]^+$: 354.0606; found : 354.0613. $[\alpha]_{578}^{20}$: + 3 (*c* 1.3, CH_2Cl_2).

(*S*,*R*)-**37** Mp= 85°C; Rf =0.17 (PE/EtOAc : 50/50); ^{1}H RMN (300 MHz, $CDCl_3$) : δ (ppm) = 7.48-7.40 (m, 6H, Ar), 7.35-7.30 (m, 2H, Ar), 7.27-7.24 (m, 2H, Ar), 4.63 (pd, 1H, *J*=4.2 Hz, C*H*BrCN), ~4.18 (d, A part of AB syst., 1H, *J*=14.1 Hz, NC*H*$_2$Ph),~4.05 (d, B part of AB syst., 1H, *J*=14.4 Hz, NC*H*$_2$Ph), 3.77-3.65 (m, A part of ABX syst., 1H, C*H*$_2$N), 3.55-3.44 (m, B part of ABX syst., 1H, C*H*$_2$N and 1H, C*H*Ph) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 134.5, 133.8 (C_q), 129.4, 129.3, 129.1, 129.0, 128.6, 128.4 (CH_{Ar}), 116.7 (NCN), 115.5 (CH*C*NBr), 56.9 (NCH_2Ph), 51.3 (NCH_2), 48.0 (CHPh), 29.8 (BrCHCN) ppm. IR: vmax = 3065, 3032, 2969, 2889, 2207, 1495, 1456, 1124, 1078, 751, 703 cm^{-1}. HRMS (TOF MSES positive mode) *m/z* calcd for $C_{18}H_{17}N_3Br$ $[MH]^+$: 354.0606; found : 354.0606. $[\alpha]_{578}^{20}$: - 16 (*c* 1.3, CH_2Cl_2).

(1*R*,2*R*)-*N*-(benzyl)-(3-bromo-1-cyano-2-phenyl-propyl)-cyanamide (*R*,*R*)-36 and **(2*S*,3*S*)-*N*-benzyl-(3-bromo-3-cyano-2-phenyl-propyl)-cyanamide (*S*,*S*)-37**

Reaction of azetidine **19** with BrCN at -18°C for 12 days gave compound (*R*,*R*)-**36** (white solid, 17%) and compound (*S*,*S*)-**37** (white crystals, 62%).

(*R*,*R*)-**36** Mp= 116°C; Rf =0.30 (PE/EtOAc : 50/50); ^{1}H RMN (300 MHz, $CDCl_3$) : δ (ppm) = 7.44-7.31 (m, 6H, Ar), 7.18-7.14 (m, 2H, Ar), 7.06-7.02 (m, 2H, Ar), ~4.23 (d, A part of AB syst., 1H, *J*=13.8 Hz, NC*H*$_2$Ph), ~4.17 (d, B part of AB syst., 1H, *J*=14.7 Hz, NC*H*$_2$Ph), 4.13 (d, 1H, *J*=10.5 Hz, C*H*CN), 3.86-3.75 (m, AB part of ABX syst., 2H, C*H*$_2$Br), 3.67-3.62 (m, 1H, C*H*Ph) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 134.5, 131.6 (C_q), 129.4, 129.1, 129.0, 128.9, 128.0 (CH_{Ar}), 114.7 (CH*C*N), 113.3 (NCN), 56.5 (NCH_2Ph), 53.6 (N*C*HCN), 47.7 (CHPh), 33.5 ($BrCH_2$) ppm. IR : vmax = 3066, 3033, 2969, 2890, 2207, 1495, 1456, 1239, 1124, 1078, 751, 703 cm^{-1}. HRMS (TOF MSES positive mode) *m/z* calcd for $C_{18}H_{17}N_3Br$ $[MH]^+$: 354.0606; found : 354.0614. $[\alpha]_{578}^{20}$: + 35 (*c* 1.3, CH_2Cl_2).

(*S*,*S*)-**37** Mp= 97°C; Rf =0.15 (PE/EtOAc : 50/50); ^{1}H RMN (300 MHz, $CDCl_3$) : δ (ppm) = 7.48-7.39 (m, 6H, Ar), 7.35-7.30 (m, 2H, Ar), 7.28-7.25 (m, 2H, Ar), 4.65 (d, 1H, *J*=6.6 Hz, C*H*BrCN), ~4.16 (d, A part of AB syst., 1H, *J*=14.1 Hz, NCH_2Ph),~4.10 (d, B part of AB syst., 1H, *J*=14.4 Hz, NCH_2Ph), ~3.63 (dd, A part of ABX syst., 1H, *J*=12.3 Hz, CH_2N), 3.52 (m, 1H, C*H*Ph), ~3.41 (dd, B part of ABX syst., 1H, *J*=12.3 Hz, CH_2N) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 134.5, 133.6 (C_q), 129.2, 129.1, 129.0, 128.9, 128.5, 128.3 (CH_{Ar}), 116.6 (NCN), 115.4 (CHCNBr), 56.7 (NCH_2Ph), 52.4 (NCH_2), 48.4 (CHPh), 29.3 (BrCHCN) ppm. IR: vmax = 3066, 3033, 2969, 2890, 2207, 1495, 1456, 1124, 1078, 751, 703 cm^{-1}. HRMS (TOF MSES positive mode) *m/z* calcd for $C_{18}H_{16}N_3BrNa$ $[MNa]^+$: 378.0405; found : 378.0413. $[\alpha]_{578}^{20}$: - 69 (*c* 1.3, CH_2Cl_2). X-Ray data: see supplementary material.

2-(benzyl-cyano-amino)-4-bromo-2-methyl-butyric acid *tert*-butyl ester 38

Clear oil (75%); Rf= 0.28 (PE/EtOAc : 90/10); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.46-7.30 (m, 5H, Ar), 4.20 (d, A part of AB syst., 1H, *J*=13.8 Hz, NCH_2Ph),~4.13 (d, A part of AB syst., 1H, *J*=14.1 Hz, NCH_2Ph), 3.49-3.32 (m, 2H, CH_2Br), 2.63-2.46 (m, 2H, CH_2CH$_2$Br), 1.58 (s, 3H, CH_3), 1.55 (s, 9H, C(CH_3)$_3$) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.1 (COO), 134.6 (C_q), 129.0, 128.8, 128.7 (CH_{Ar}), 115.2 (NCN), 83.7 (COOC(CH_3)$_3$), 65.8 (NC$_q$COO), 52.4 (NCH_2Ph), 39.6 (BrCH$_2$CH_2), 28.0 (C(CH_3)$_3$), 25.3 (BrCH$_2$), 21.4 (CH3) ppm. IR: vmax = 3015, 2979, 2931, 2212, 1724, 1497, 1457, 1391, 1370, 1144, 1116, 754, 695, 663 cm^{-1}. HRMS (TOF MSES positive mode) *m/z* calcd for $C_{17}H_{23}N_2O_2BrNa$ $[MNa]^+$: 389.0841; found : 389.0850.

(*1S, 1'R*) *N*-(1'-phenyl-ethyl)-(3-bromo-1-cyano-propyl)-cyanamide 39 and **(*1'R, 3R*) *N*-(1'-phenyl-ethyl)-(3-bromo-3-cyano-propyl)-cyanamide 40**

From azetidine **7,** compounds **39** (39%) and (*1'R, 3R*)-**40** (36%) were obtained.

39 White solid (39%); Mp= 63-65°C; Rf= 0.28 (PE/EtOAc : 80/20); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.52-7.42 (m, 5H, Ar), 4.38 (q, 1H, *J*=6.9 Hz, NC*H*CH$_3$Ph), 4.19-4.14 (m, 1H, NC*H*CN), 3.59-3.47 (m, 2H, CH_2Br), 2.59-2.34 (m, 2H, CH_2CH$_2$Br), 1.79 (d, 3H, *J*=7.5 Hz, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 138.2 (C_q), 129.6, 129.5, 126.9 (CH_{Ar}), 115.5 (CHCN), 112.1 (NCN), 62.1 (NCHPh), 48.9 (NCHCN), 34.5 (CHCH_2), 27.2 ($BrCH_2$), 20.6 CH_3 ppm. IR : vmax = 3061, 3030, 2978, 2935, 2209, 1495, 1456, 1239, 1117, 766, 702 cm^{-1}. HRMS (TOF MSES positive mode) *m/z* calcd for $C_{13}H_{14}N_3BrNa$ $[MNa]^+$: 314.0269; not detected. $[\alpha]_{578}^{20}$: - 60 (*c* 1.0, CH_2Cl_2).

(*1'R, 3R*)-40 Clear oil (36%); Rf= 0.17 (PE/EtOAc : 80/20); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.47-7.36 (m, 5H, Ar), 4.43-4.38 (m, 1H, C*H*CNBr), 4.15 (q, 1H, *J*=7.1 Hz, NC*H*CH$_3$), 3.22-3.07 (m, 2H, NCH_2), 2.42-2.35 (m, 2H, NCH$_2$CH_2), 1.71 (d, 3H, *J*=6.9 Hz, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 139.8 (C_q), 129.3, 128.9, 126.5 (CH_{Ar}), 116.5 (CHCNBr), 115.3 (NCN), 60.6, (NCH), 47.2, 34.1 (CH2), 23.6 (BrCHCN), 20.9 (CH_3) ppm. IR : vmax = 3061, 3026, 2974, 2923, 2872, 2205, 1495, 1452, 1377, 1124, 766, 695 cm^{-1}. HRMS (TOF MSES positive mode) *m/z* calcd for $C_{13}H_{14}N_3BrNa$ $[MNa]^+$: 314.0269; found : 314.0274. $[\alpha]_{578}^{20}$: - 50 (*c* 1.0, CH_2Cl_2).

(*1R, 1'R*) *N*-(1'-phenyl-ethyl)-(3-bromo-1-cyano-propyl)-cyanamide 41 and 40.

From azetidine **9,** compound **41** (32%) and **40** (39%, 95:5 mixture of epimers) were obtained.

41 Clear oil (32%); Rf= 0.39 (PE/EtOAc : 80/20); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.50-7.37 (m, 5H, Ar), 4.45-4.39 (q, 1H, *J*=6.6 Hz, NC*H*CH$_3$Ph), 3.98-3.93 (m, 1H, NC*H*CN), 3.53-3.40 (m, 2H, CH_2Br), 2.62-2.38 (m, 2H, CH_2CH$_2$Br), 1.79 (d, 3H, *J*=6.9 Hz, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 137.9 (C_q), 129.6, 127.4, 127.0 (CH_{Ar}), 115.6 (CHCN), 111.9 (NCN), 60.9 (NC*H*Ph), 48.3 (NC*H*CN), 34.2 (CHCH_2), 26.6 ($BrCH_2$), 21.3 CH_3 ppm. IR: vmax = 3065, 3026, 2978, 2935, 2876, 2213, 1495, 1456, 1235, 1097, 766, 695 cm^{-1}. HRMS (TOF MSES positive mode) *m/z* calcd for $C_{13}H_{14}N_3BrNa$ $[MNa]^+$: 314.0269; not detected. $[\alpha]_{578}^{20}$: +42 (*c* 1.0, CH_2Cl_2).

40 Clear oil (39%, 95:5 mixture of epimers) Rf= 0.17 (PE/EtOAc 80/20); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.47-7.36 (m, 5H, Ar), 4.42-4.38 (m, 1H, C*H*CNBr), 4.15 (q, 1H, *J*=7.1 Hz, NC*H*CH$_3$), 3.21-3.06 (m, 2H, NCH_2), 2.47-2.27 (m, 2H, NCH$_2$CH_2), 1.71 (d, 3H, *J*=6.9 Hz, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 139.8 (C_q), 129.3, 128.8, 126.5 (CH_{Ar}), 116.5 (CHCNBr), 115.3 (NCN), 60.8, (NCH), 47.2, 34.1 (CH2), 23.7, (BrCHCN), 20.9 (CH_3) ppm.

[2(1'*R*),2*S*]-2-[cyano-(1'-phenyl-ethyl)-amino]-4-bromo-butyric acid *tert*-butyl ester 42 and **[(2*R* and 2*S*) 4(1'*R*)]-4-[cyano-(1'-phenyl-ethyl)-amino]-2-bromo-butyric acid *tert*-butyl ester 43**

From azetidine **8**, compounds **42** (23%) and **43** (inseparable mixture of epimers, 79:21 ratio, 26%) were obtained.

42 Yellow oil (23%); Rf= 0.51 (PE/EtOAc : 90/10); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.42-7.28 (m, 5H, Ar), 4.26-4.19 (q, 1H, *J*=6.0 Hz, NC*H*CH$_3$Ph), 3.49-3.42 (m, 2H, CH_2Br), 3.29-3.21 (m, 1H, NC*H*CN), 2.44-2.23 (m, 2H, CH_2CH$_2$Br), 1.71 (d, 3H, *J*=6.0 Hz, CH_3), 1.50 (s, 9H, C(CH_3)$_3$) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 168.7 (COO), 139.6 (C_q), 129.0, 128.7, 126.9 (CH_{Ar}), 113.7 (NCN), 83.2 (COOC), 60.3 (NCHPh), 59.1 (NCHCOO), 33.2 (CHCH_2), 28.5 ($BrCH_2$), 27.9 (C(CH_3)$_3$), 21.4 (CH_3) ppm. IR: vmax = 3042, 3022, 2977, 2936, 2211, 1729, 1457, 1394, 1368, 1248, 1153, 767, 703 cm^{-1}. HRMS (TOF MSES positive mode) *m/z* calcd for $C_{17}H_{24}O_2N_2Br$ $[MH]^+$: 367.1021; found : 367.1032. $[\alpha]_{578}^{20}$: - 2 (*c* 1.2, CH_2Cl_2).

43 Inseparable mixture of epimers (79:21 ratio); yellow oil (26%); Rf= 0.46 (PE/EtOAc 90/10); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.40-7.29 (m, 5H, Ar), 4.23-4.18 (m, 1H, C*H*COOBr), 4.10 (q, 1H, *J*=6.0 Hz, NC*H*CH$_3$), 3.13-2.91 (m, 2H, NCH_2), 2.38-2.25 (m, A part of ABX syst., 1H, NCH$_2$CH_2), 2.23-2.08 (m, B part of ABX syst., 1H, NCH$_2$CH_2), 1.65 (d, 3H, *J*=6.0 Hz, CH_3), 1.44 (s, 9H, C(CH_3)$_3$) ppm. 13C NMR (75 MHz, CDCl3): δ = 167.7 (COO), 140.2 M, 140.0 m (Cq), 128.9, 128.4, 126.9, 126.4, 126.2 (CH_{Ar}), 115.6 m, 115.6 M, 115.30 (NCN), 82.8 (COOC), 60.2 M, 59.7 m (NCH), 47.7 M, 47.6 m (NCH_2), 44.0 (BrCHCOO), 32.3 m, 32.2 M (CHCH_2), 27.5 (C(CH_3)$_3$), 20.9 M, 20.8 m (CH_3) ppm. IR: vmax = 3042, 3022, 2980, 2936, 2207, 1729, 1457, 1394, 1368, 1280, 1147, 767, 703 cm^{-1}. HRMS (TOF MSES positive mode) *m/z* calcd for $C_{17}H_{23}O_2N_2BrNa$ $[MNa]^+$: 389.0840; found : 389.0838.

(*2R* and *2S*) *N*-[(1'*R*)-phenyl-ethyl)]-(2-benzyloxy-3-bromo-propyl)-cyanamide 44

From azetidine **15**, compounds **44** were obtained as an inseparable mixture of epimers (70:30); white solid (98%); Rf= 0.67 (PE/EtOAc 75/25); ^{1}H RMN (300 MHz, $CDCl_3$) : δ (ppm) = 7.41-7.28 (m, 10H^M and 10H^m, Ar), ~4.68 (appt. d, A part of AB syst., 1H^m, *J*=11.1 Hz, OCH_2Ph), ~4.67 (appt. d, A part of AB syst., 1H^M, *J*=11.4 Hz, OCH_2Ph), ~4.58 (appt. d, B part of AB syst., 1H^m, *J*=12.6 Hz, OCH_2Ph), ~4.54 (appt. d, B part of AB syst., 1H^M, *J*=11.7 Hz, OCH_2Ph), 4.19 (q, 1H^m, *J*=7.2Hz, NC*H*CH$_3$), 4.10 (q, 1H^M, *J*=6.9Hz, NC*H*CH$_3$), 3.89-3.82 (m, 1H^m, C*H*OPh), 3.82-3.75 (m, 1H^M, C*H*OPh), ~3.50 (dd, AB part of ABX syst., 1H^M, *J*=11.1Hz, BrCH_2), ~3.44 (dd, AB part of ABX syst., 1H^M, *J*=11.1Hz, BrCH_2), ~3.36 (appt. d, AB part of ABX syst., 2H^m, BrCH_2), ~3.25 (dd, AB part of ABX syst., 1H^m, *J*=14.1Hz, NCH_2), ~3.18 (dd, AB part of ABX syst., 1H^M, *J*=14.7Hz, NCH_2), ~3.12 (dd, AB part of ABX syst., 1H^M, *J*=14.7Hz, NCH_2), ~3.01 (dd, AB part of ABX syst., 1H^m, *J*=14.1Hz,

NC*H*$_2$), 1.63 (d, 3H^m, *J*=6.9Hz, CHC*H*$_3$), 1.62 (d, 3H^M, *J*=6.9Hz, CHC*H*$_3$) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 140.5, 140.1, 137.1, 137.0 (C_q), 128.9, 128.5, 128.4, 128.1, 128.0, 127.9, 126.4 (CH_{Ar}), 116.4, 116.2 (CN), 76.3, 75.5 (CHOPh), 72.4, 72.1 (OCH_2Ph), 60.7, 59.9 (*C*HCH$_3$), 52.9, 52.0 (NCH_2), 31.1, 31.0 ($BrCH_2$), 21.1, 21.0 (CH*C*H$_3$) ppm. IR: vmax = 3069, 3031, 2977, 2933, 2869, 2211, 1495, 1457, 1090, 1068, 742, 700 cm^{-1}. HRMS (TOF MSES positive mode) *m/z* calcd for $C_{19}H_{22}N_2OBr$ $[MH]^+$: 373.0915; found : 373.0917.

1-Benzhydryl-3-(4-methyl-benzyl)-tetrahydro-pyrimidin-2-ylideneamine hydrobromide 45

A solution of 3-bromo cyanamide **24** (1 mmol) and of 4-methylbenzylamine (1 mmol) was heated at 80° in abs. EtOH (4 mL) for 5 days. The solution was concentrated under reduced pressure, and the residue was triturated with small portions of diethyl ether until crystallization to give **45** as a white solid (235 mg, 72%); Mp= 228°C; Rf= 0.25 (EtOAc/MeOH/40% aq. NH_3 : 94/5/1); ^{1}H NMR (300 MHz, CD_3OD): δ = 7.51-7.20 (m, 14H, Ar), 6.63 (s, 1H, N*H*Ph$_2$), 4.88 (bs, 2H, $^+NH_2$), 4.72 (s, 2H, NCH_2Ar), 3.41 (appt. t, 2H, *J*=6.0 Hz, C*H*$_2$N), 3.30 (t, 2H, *J*=6.0 Hz, C*H*$_2$N), 3.41 (appt. t, 2H, *J*=6.0 Hz, CH_2), 3.20 (appt. t, 2H, *J*=6.0 Hz, CH_2), 2.37 (s, 3H, CH_3), 1.91 (appt. quint., 2H, *J*=6.0 Hz, CH_2) ppm. ^{13}C NMR (75 MHz, CD_3OD): δ = 156.0 ($C_{guanidine}$), 139.2, 138.3 (Cq_{Ar}), 133.0, 130.8, 130.1, 129.9, 129.7, 129.4, 128.2 (CH_{Ar}), 66.8 (CH), 54.9, 47.7, 44.4, 22.4 (CH_2), 21.2 (CH_3) ppm. IR: vmax = 3346, 3269, 3124, 2918, 2202, 1643, 1590, 1574, 1545, 1451, 1328, 1180, 1075, 1030, 789, 722, 694 cm-1. HRMS (TOF MSES positive mode) *m/z* calcd for $C_{25}H_{28}N_3$ $[MH]^+$: 370.2283; found : 370.2273.

4-benzhydryl-4,5,6,7-tetrahydro-tetrazolo[1,5-α]pyrimidine 46

The bromide **24** (66 mg, 0.2 mmol) was dissolved in DMF (1 mL), and sodium azide (13 mg, 0.2 mmol) was added. The solution was then heated in a sealed tube at 140 °C for 48h. The solution was allowed to cool, concentrated under reduced pressure, and the residue obtained was purified by column chromatography to give **46** as a white solid (33 mg, 57%); Mp= 152-154°C; Rf= 0.22 (PE/EtOAc 75/25); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.35-7.24 (m, 10H, Ar), 6.79 (s, 1H, C*H*Ph), 4.23 (t, *J*=6.1 Hz, 2H, C*H*$_2$N), 3.17 (t, *J*=5.5 Hz, 2H, C*H*$_2$N), 2.22-2.14 (m, 2H, C*H*$_2$) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 154.8 (CqN), 137.8 (Cq_{Ar}), 128.5, 128.4, 127.8 (CH_{Ar}), 65.0 (*C*HPh), 42.8 (CH_2N), 40.8 (CH_2N), 20.9 (CH_2) ppm. IR: vmax = 3140, 3060, 2961, 2866, 1612, 1488, 1448, 1331, 1302, 1104, 1078, 1041, 975, 925, 786, 744, 733, 712, 699, 642, 619 cm-1. HRMS (TOF MSES positive mode) *m/z* calcd. for $C_{17}H_{18}N_5$ $[MH]^+$: 292.1562; found : 292.1564.

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Keywords: azetidines, von Braun reaction • guanidines

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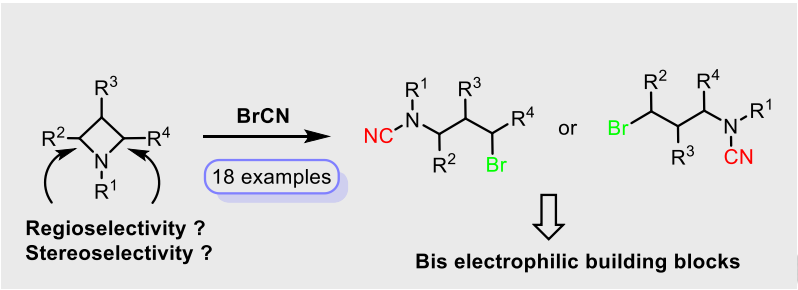

Azetidines, von Braun reaction.

*Karen Wright, Bruno Drouillat, Laurence Menguy, Jérôme Marrot and François Couty **

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The von Braun Reaction Applied to Azetidines

The regio- and stereoselectivity of ring cleavage of *N*-alkyl azetidines induced by reaction with cyanogen bromide (the von Braun reaction) was studied in depth. The produced 3-bromo *N*-alkyl cyanamides were used as original building blocks for the synthesis of nitrogen heterocycles.