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3-Bromo *N*-Alkyl Cyanamides as Versatile Building Blocks

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

Abstract: 3-Bromo *N*-alkyl cyanamides are accessible in one simple synthetic operation from *N*-alkyl azetidines reacting with cyanogen bromide. These unexplored building blocks combine two extremely useful electrophilic moieties: an alkyl bromide and a cyanamide. We demonstrate here that they can be transformed into a range of nitrogen-containing molecules, and especially cyclic guanidines, accessible in enantiomerically pure form. Considering the large structural diversity of available azetidines, this contribution complements the use of these strained heterocycles in diversity-oriented synthesis.

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They can be easily fitted with additional functional groups such as a nitrile (R^2 or R^4), and can be produced in enantiomerically pure form, starting from an azetidine derived from a β -amino-alcohol.^{2f,9} This article aims to explore the reactivity of these original building blocks, in order to generate structural diversity.

Introduction

The search for available, flexible, and bench-stable new building blocks allowing the simple generation of molecular diversity is a key topic in the context of diversity-oriented synthesis (DOS), which has recently emerged as a useful tool for the discovery of new small bioactive molecules.¹ Azetidines, as reactive yet available² and bench-stable nitrogen heterocycles, have emerged as promising candidates to generate new libraries with high levels of structural diversity,³ from which new drug candidates have emerged.⁴ We recently reported⁵ that *N*-alkyl azetidines **1** efficiently react with cyanogen bromide, leading to regioisomeric 3-bromo *N*-alkyl cyanamides **2-3** through the von Braun reaction.⁶ These compounds are produced with predictable and usually high regioselectivity in the ring-opening step, and they can be decorated with diverse substituents or functional groups starting from the required azetidines, which are very easy to prepare (Scheme 1).

Scheme 1. Reaction of azetidines with cyanogen bromide (von Braun reaction).

These 3-bromo *N*-alkyl cyanamides combine two useful electrophilic moieties: the cyanamide⁷ and an alkyl bromide.

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Results and Discussion

We first focused on the synthesis of 6-membered cyclic guanidines through the reaction of a 3-bromo *N*-cyanamide **4**, easily prepared from commercially available *N*-benzhydryl azetidine, with primary amines⁵ (Scheme 2, Table 1). Such reactions were first described by Hageman⁸ in the early fifties and by us⁵ in a single example, but its scope remained to be established. Interest in guanidines has recently been growing, especially in the field of organocatalysis,⁹ and the combination of these simple reactions, together with the potential structural diversity brought by the two reaction partners, would represent a convenient entry to these heterocycles.

Our initial attempts at guanidine synthesis, based on Hageman's conditions (refluxing ethanol), needed however protracted reaction times to reach completion, and gave low yields in the case of hindered amines. An optimisation study was therefore carried out with the sterically hindered 1-adamantylamine and cyclohexylamine, and it was found that a spectacular shortening of reaction time was possible upon microwave irradiation. Optimal conditions were found with isopropanol as solvent at 120°C (Table 1). Solvent effects were less obvious, and the use of HFIP, reported to be a solvent promoting the addition of

Scheme 2. Synthesis of cyclic guanidines by reaction of 3-bromo *N*-alkyl cyanamide **4** with amines.

amines to cyanamides¹⁰ was not beneficial here. From a practical viewpoint, this reaction directly affords guanidinium hydrobromides conveniently isolated as crystalline salts.

Amine	Conditions	Time	Yield	Product
R = Cy	80°C, EtOH	10 days	84%	5 , R = Cy
R = Cy	110°C, Toluene	4 days	71%	5 , R = Cy
R = Cy	110°C, BuOH	<i>n</i> - 4 days	82%	5 , R = Cy
R = Cy	μ w, 80°C EtOH	4 h	73%	5 , R = Cy
R = Cy	μ w, 80°C PrOH	<i>i</i> - 4 h	85%	5 , R = Cy
R = Cy	μ w, 120°C PrOH	<i>i</i> - 1 h	82%	5 , R = Cy
R = Adamantyl	80°C, EtOH	10 days	16%	6 , R = Adamantyl
R = Adamantyl	110°C, BuOH	<i>n</i> - 4 days	71%	6 , R = Adamantyl
R = Adamantyl	μ w, 120°C <i>i</i> -PrOH	3 h	75%	6 , R = Adamantyl
R = Adamantyl	μ w, 140°C <i>i</i> -PrOH	1 h	74%	6 , R = Adamantyl

Table 1: Optimization of reaction conditions for hindered amines.

The reaction scope was next examined with other amines in either refluxing ethanol (80°C, 7 days: *conditions A*) or under 1:

Amine scope. a) Stoichiometry of 1:2 for (1*R*,2*R*)-cyclohexyl-1,2-diamine : **4** was used.

μ wave irradiation in *i*-PrOH (120°C, 1-3 h, 200 W: *conditions B*). The structures of the produced guanidines **7-14** are shown in Figure 1, demonstrating a wide scope for this reaction, including for aliphatic amines and anilines, as well as for functionalized amines and diamines. In this last case, the crystalline *bis*- Figure guanidines **13** and **14** were isolated in average to good yields, thus demonstrating that the initial alkylation step is probably more rapid than the cyclisation step leading to the 6-membered guanidine.¹¹ The structure of the C2-symmetric chiral guanidine **14**, obtained from enantiomerically pure (1*R*, 2*R*)-cyclohexyl-1,2-diamine was determined by X-ray crystallography.¹² It should be mentioned here that beta amino alcohols, amino esters, or other 1,2-diamines such as (*R,R*)-1,2-diphenylethane-1,2-diamine failed to produce the expected guanidines under conditions A or B. Only (*S*)-phenylglycine derived amino ester **15** gave bicyclic guanidine **16** in low isolated yield. This compound displayed no optical activity, probably due to complete epimerization. Noteworthy also is the formation of the 7-membered [1,2,4] triazepane **17** when phenylhydrazine was used under conditions B. The structure of this rarely reported heterocyclic scaffold¹³ was determined by X-ray crystallography, and its NMR spectra display two distinct conformers.¹² The position of the *N*-Ph moiety in **17** can be explained by the known propensity of hydrazines to undergo alkylation at their more substituted nitrogen atom.¹⁴ *N*-phenyl-*N*-methylhydrazine only gave a complex mixture of products under conditions B (Scheme 3).

Finally, the scope of the reacting 3-bromocyanamide was briefly examined. Thus the 3-bromo cyanamides substituted at C-1 **18** and **19**⁵ gave good yields of substituted guanidines **21** and **22**. Notably, no competing reactivity of the cyano group in **19** was observed, but *t*-butyl ester **20** behaved differently, since only low yields of the expected guanidine **23** could be isolated under conditions A. The major isolated product resulted in this case from an intramolecular cyclization involving the *t*-butyl ester acting as the nucleophile, yielding lactone **24** in 58% yield upon μ wave irradiation in EtOH at 80°C. This lactone could also be obtained by simply heating in HFIP (50°C, 7 days) without added amine. Finally, the 1,2-disubstituted 3-bromo cyanamide **25** was evaluated under conditions B with 4-methylbenzylamine, but the expected guanidine was not produced. Instead, cyclopropane **26**

therefore benefit from the progress made in azetidine chemistry, and appear, as demonstrated here, as innovative tools for DOS strategies.

Scheme 3. Reaction with other functionalized amines and hydrazines.

was isolated from the reaction mixture, in which the relative stereochemistry of the substituents was determined by X-ray crystallography.¹² This demonstrates that C-2 substitution in the starting cyanamide is detrimental to guanidine formation, probably by lowering the electrophilic character of the alkyl bromide. Thus, the amine acts in this case as a base, able to deprotonate the position alpha to the nitrile, leading to intramolecular alkylation. A further experiment was performed to confirm this, by treatment of **25** with LiHMDS (a non-nucleophilic base) in THF at -78°C. In this case, the cyclopropanes **26** and **27** were isolated in 55 and 31% yield respectively (Scheme 4).

Conclusions

This work demonstrates that 3-bromo-*N*-alkyl cyanamides are versatile building blocks able to generate in a single step various heterocyclic structures. Such building blocks are very easy to prepare from azetidines, for which synthetic access has widened only recently, allowing the introduction of a vast array of substituents and solving the issues of diastereoselectivity and enantioselectivity.² The production of libraries of 3-bromo-*N*-alkyl-cyanamides may

Scope of the 3-bromo-cyanamide reactant

Experimental Section

General information: ¹H and ¹³C NMR spectra were recorded at 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), quintuplet (quint.), multiplet (m), broad (br), or a combination of these. Solvents were used as internal standard when assigning NMR spectra (δ H: CDCl₃ 7.27 ppm; δ C: CDCl₃ 77.0 ppm; δ H: CD₃OD 3.34 ppm, δ C: CD₃OD 49.86 ppm). Assignments for signals from ¹H and ¹³C in the NMR spectra were validated by two-dimensional correlated spectroscopy (2D COSY and HSQC) and Heteronuclear Multiple Bond Correlation (HMBC). High-resolution mass spectra (HR-MS) were obtained on a Q-TOF mass spectrometer. IR data were collected with an ATR-FT-IR spectrometer. THF was distilled from sodium/benzophenone ketyl. Column chromatography was performed on

silica gel (230–400 mesh) with use of various mixtures of EtOAc, petroleum ether (35–60°C fraction) (PE) and methanol. TLC was performed on Merck Kieselgel 60 F254 plates. Melting points are uncorrected. All reactions under microwave irradiation were performed in a 10 mL sealed tube in a commercially available monomode reactor (CEM Discover) with IR monitoring and non-invasive pressure transducer.

General procedure for the synthesis of guanidines: A solution of the required *N*-(3-bromopropyl)cyanamide (1 or 2 equiv.) and of the required amine (1 equiv., concentration: 0.2 M) was heated either at 80°C in abs. EtOH (3–5 mL) under argon for 3–7 days (*conditions A*) or under microwave irradiation (200 W) at 120°C in iPrOH (4–5 mL) for 1–3 hours (*conditions B*). The progress of the reaction was monitored by TLC analysis. The solution was concentrated under reduced pressure, and the residue was triturated with small portions of diethyl ether. The resulting solid was washed with EtOAc and dried under reduced pressure.

1-Benzhydryl-3-cyclohexyl-3,4,5,6-tetrahydropyrimidin-2(1*H*)-ylideneamine hydrobromide 5

White solid; Mp: 225–228°C; R_f: 0.23 (DCM/MeOH/aq. 30% NH₄OH 95/5/1); ¹H NMR (300 MHz, CD₃OD): δ = 7.47–7.37 (m, 6H, ArH), 7.25–7.22 (m, 4H, ArH), 6.56 (s, 1H, NCHPh₂), 3.89–3.79 (m, 1H, CHN), 3.36 (t, *J*=5.9 Hz, 2H, CH₂N), 3.10 (t, *J*=5.8 Hz, 2H, CH₂N), 1.91–1.83 (m, 6H, CH₂, CH₂cyc), 1.71–1.63 (m, 3H, CH₂cyc), 1.54–1.42 (m, 2H, CH₂cyc), 1.26–1.13 (m, 1H, CH₂cyc) ppm. ¹³C NMR (75 MHz, CD₃OD): δ = 155.4 (C=NH), 138.6 (C_qAr), 130.2, 130.0, 129.7 (CH_{Ar}), 67.0 (CHPh₂), 59.6 (CHN), 44.6, 41.3 (CH₂N), 30.9, 26.5, 26.3, 22.9 (CH₂) ppm. IR: ν_{max} = 3282(b), 3108(b), 2939, 2860, 1637, 1558, 1530, 1444, 1313, 1151, 1073, 1025, 774, 726, 698 cm⁻¹. HRMS (TOF MSES positive mode) *m/z* calcd. for C₂₃H₃₀N₃ [M]⁺: 348.2440; found: 348.2431.

1-Adamantan-1-yl-3-benzhydryl-3,4,5,6-tetrahydropyrimidin-2(1*H*)-ylideneamine hydrobromide 6

White solid; Mp: 209–211°C; R_f: 0.45 (DCM/MeOH/aq. 30% NH₄OH 90/10/1); ¹H NMR (300 MHz, CD₃OD): δ = 7.51–7.41 (m, 6H, Ar), 7.30–7.28 (m, 4H, Ar), 6.57 (s, 1H, NCHPh₂), 3.41 (appt t, *J*= 5.9 Hz, 2H, CH₂N), 3.27 (appt t, *J*=5.8 Hz, 2H, CH₂N), 2.27–2.15 (m, 7H, CH₂, CH₂cyc, CH₂cyc), 1.95–1.91 (m, 2H, CH₂cyc), 1.86–1.72 (m, 8H, CH₂cyc) ppm. ¹³C NMR (75 MHz, CD₃OD): δ = 159.2 (C=NH), 139.8, 139.1 (C_qAr), 130.4, 130.3, 129.9, 129.8, 129.6 (CH_{Ar}), 67.0 (NCHPh₂), 62.3 (C_qcycN), 43.3 (CH₂N), 41.8 (CH₂N), 41.7, 41.6, 39.6, 36.8, 36.7, 36.6 (CH₂), 31.7 (CH), 30.7 (CH), 30.6 (CH), 28.4 (CH₂) ppm. IR: ν_{max} = 3270, 3061, 2895, 2848, 2205, 1633, 1526, 1495, 1451, 1361, 1065, 730, 694 cm⁻¹. HRMS (TOF MSES positive mode) *m/z* calcd. for C₂₇H₃₄N₃ [M]⁺: 400.2753; found: 400.2750.

1-Benzhydryl-3-(4-methylbenzyl)-3,4,5,6-tetrahydropyrimidin-2(1*H*)-ylideneamine hydrobromide 7

White solid (72%, conditions A); Mp: 228°C; R_f: 0.25 (EtOAc/MeOH/40% aq. NH₃: 94/5/1); ¹H NMR (300 MHz, CD₃OD): δ = 7.51–7.20 (m, 14H, ArH), 6.63 (s, 1H, NCHPh₂), 4.72 (s, 2H, NCH₂Ph), 3.41 (appt t, 2H, *J*=6.0 Hz, CH₂N), 3.20 (appt t, 2H, *J*=6.0 Hz, CH₂N), 2.37 (s, 3H, CH₃), 1.91 (appt quint., 2H, *J*=6.0 Hz, CH₂) ppm. ¹³C NMR (75 MHz, CD₃OD): δ = 156.0 (C=NH), 139.2, 138.3 (C_qAr), 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 (CH₂), 21.2 (CH₃) ppm. IR: ν_{max} = 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 C₂₅H₂₈N₃ [M]⁺: 370.2283; found: 370.2273.

(*S*)-1-Benzhydryl-3-(1-phenylethyl)-3,4,5,6-tetrahydropyrimidin-2(1*H*)-ylideneamine hydrobromide 8

White powder (67%, conditions A); Mp: 162°C; R_f: 0.25 (EtOAc/MeOH/40% aq. NH₃: 94/5/1); ¹H NMR (300 MHz, CD₃OD): δ = 7.52–7.28 (m, 15H, ArH), 6.65 (s, 1H, NCHPh₂), 5.47 (q, 1H, *J*=6.9 Hz,

*CHCH*₃Ph), 3.32–3.25 (m, 1H, CH₂N), 3.11 (appt t, 2H, *J*=6.6 Hz, CH₂N), 3.03–2.95 (m, 1H, CH₂N), 1.92–1.68 (m, 2H, CH₂), 1.73 (d, 3H, *J*=6.9 Hz, CH₃) ppm. ¹³C NMR (75 MHz, CD₃OD): δ = 156.5 (C=NH), 140.3, 139.2, 139.1 (C_qAr), 131.0, 130.5, 130.4, 130.3, 129.1 (CH_{Ar}), 67.7 (NCHPh₂), 58.6 (NCHCH₃), 45.8, 42.4 (NCH₂), 23.3 (CH₂), 17.6 (CH₃) ppm. IR: ν_{max} = 3301, 3120, 3057, 3025, 2974, 2935, 2872, 1637, 1557, 1529, 1444, 1380, 1321, 1069, 1026, 753, 695 cm⁻¹. HRMS (TOF MSES positive mode) *m/z* calcd. for C₂₅H₂₈N₃ [M]⁺: 370.2283; found: 370.2275. [α]_D²⁰: -44 (c 1.8, MeOH).

1-Benzhydryl-3-(4-methoxyphenyl)-3,4,5,6-tetrahydropyrimidin-2(1*H*)-ylideneamine hydrobromide 9

Purple brown solid (61%, conditions A); Mp: 135°C; R_f: 0.30 (EtOAc/MeOH/40% aq. NH₃: 93/5/2); ¹H NMR (300 MHz, CD₃OD): δ = 7.53–7.33 (m, 12H, ArH), 7.13–7.08 (m, 2H, ArH), 6.62 (s, 1H, NCHPh₂), 3.86 (s, 3H, CH₃OPh), 3.69 (appt t, 2H, *J*=6.0 Hz, CH₂N), 3.34–3.31 (m, 2H, CH₂N), 2.15 (appt quint., 2H, *J*=6.0 Hz, CH₂) ppm. ¹³C NMR (75 MHz, CD₃OD): δ = 162.5 (C=NH), 156.7, 139.0, 135.4 (C_qAr), 130.9, 130.7, 130.5, 117.7 (CH_{Ar}), 67.5 (NCHPh₂), 57.0 (OCH₃), 52.5, 45.4 (NCH₂), 23.3 (CH₂) ppm. IR: ν_{max} = 3444, 3361, 3258, 3180, 3132, 1622, 1590, 1503, 1448, 1322, 1239, 1164, 1030, 837, 730, 698 cm⁻¹. HRMS (TOF MSES positive mode) *m/z* calcd. for C₂₄H₂₆N₃O [M]⁺: 372.2076; found: 372.2077.

1-Allyl-3-benzhydryl-3,4,5,6-tetrahydropyrimidin-2(1*H*)-ylideneamine hydrobromide 10

Light brown solid (88%, conditions B); Mp: 146°C; R_f: 0.25 (EtOAc/MeOH/40% aq. NH₃: 93/5/2); ¹H NMR (300 MHz, CD₃OD): δ = 7.17–7.06 (m, 6H, ArH), 6.96–6.94 (m, 4H, ArH), 6.28 (s, 1H, NCHPh₂), 5.66–5.53 (ddt, 1H, 10.5, 17.4 Hz, *J*=6.0, CH₂CH=CH₂), 5.03–5.00 (bd, 1H, *J*=9.9 Hz, CH₂CH=CH₂), 5.00–4.95 (bd, 1H, *J*=16.8 Hz, CH₂CH=CH₂), 3.82 (appt d, 2H, *J*=5.1 Hz, CH₂CH=CH₂), 3.13 (appt t, 2H, *J*=6.1 Hz, NCH₂), 2.88 (appt t, 2H, *J*=5.7 Hz, NCH₂), 1.61 (appt quint., 2H, *J*=5.9 Hz, CH₂) ppm. ¹³C NMR (75 MHz, CD₃OD): δ = 156.4 (C=NH), 139.2 (C_qAr), 132.7, 130.9, 130.6 (CH_{Ar}), 130.4 (CH=CH₂), 118.8 (CH=CH₂), 67.4 (NCHPh₂), 55.1, 48.6, 45.1 (NCH₂), 23.1 (CH₂) ppm. IR: ν_{max} = 3282, 3132, 3077, 3026, 2959, 2205, 1633, 1574, 1539, 1444, 1330, 1073, 935, 750, 695 cm⁻¹. HRMS (TOF MSES positive mode) *m/z* calcd. for C₂₀H₂₄N₃ [M]⁺: 306.1970; found: 306.1971.

[2-(3-Benzhydryl-3,4,5,6-tetrahydropyrimidin-2(1*H*)-ylidenamino)-ethyl] carbamic acid tert-butyl ester hydrobromide 11

Beige solid (78%, conditions A); Mp: 203–204°C; R_f: 0.20 (DCM/MeOH/aq. 30% NH₄OH 90/10/1); ¹H NMR (300 MHz, CD₃OD): δ = 7.46–7.40 (m, 6H, ArH), 7.27–7.25 (m, 4H, ArH), 6.55 (s, 1H, NCHPh₂), 3.56 (t, 2H, *J*=6.1 Hz, NCH₂), 3.48 (t, 2H, *J*=6.1 Hz, NCH₂), 3.36 (m, 2H, NHCH₂), 3.12 (t, 2H, *J*=5.7 Hz, NCH₂), 1.96–1.89 (m, 2H, CH₂), 1.45 (s, 9H, CH₃) ppm. ¹³C NMR (75 MHz, CD₃OD): δ = 159.0 (C=O), 155.8 (C=NH), 138.4 (C_qAr), 130.2, 130.0, 129.7 (CH_{Ar}), 80.7 (CO), 66.6 (NCHPh₂), 52.2, 49.2, 44.4 (NCH₂), 38.9 (NHCH₂), 28.9 (CH₃), 22.4 (CH₂) ppm. IR: ν_{max} = 3321, 3156, 2962, 1708, 1637, 1593, 1542, 1511, 1361, 1333, 1242, 1167, 1132, 1089, 856, 749, 698 cm⁻¹. HRMS (TOF MSES positive mode) *m/z* calcd. for C₂₄H₃₃N₄O₂ [M]⁺: 409.2604; found: 409.2586.

(1*R*,2*R*)-[2-(3-Benzhydryl-3,4,5,6-tetrahydropyrimidin-2(1*H*)-ylidenamino)-cyclohexyl] carbamic acid tert-butyl ester hydrobromide 12

White solid (88%, conditions A); Mp: 223–225°C; R_f: 0.71 (EtOH/DCM/Acetone 20/10/10); ¹H NMR (300 MHz, CD₃OD): δ = 7.47–7.38 (m, 6H, ArH), 7.25–7.21 (m, 4H, ArH), 6.57 (s, 1H, NCHPh₂), 3.81–3.64 (m, 2H, NHCH, NCH), 3.57–3.34 (m, 2H, NCH₂), 3.16–3.03 (m, 2H, NCH₂), 1.98–1.72 (m, 7H, CH₂), 1.51–1.32 (m, 12H, CH₃, CH₂) ppm. ¹³C NMR (75 MHz, CD₃OD): δ = 157.9 (C=O), 155.6 (C=NH), 138.4 (C_qAr), 130.3, 130.2, 129.7 (CH_{Ar}), 80.6 (CO), 67.0 (NCHPh₂), 63.6 (NCH), 51.4 (NHCH), 44.6, 41.3 (NCH₂), 34.0, 30.6 (CH₂), 29.0 (CH₃), 26.1, 25.9, 22.9 (CH₂) ppm. IR: ν_{max} = 3305, 3191, 2927, 2864, 2205, 1684, 1645, 1562, 1511, 1444, 1317, 1156, 1077, 1018, 730, 698 cm⁻¹. HRMS (TOF

MSES positive mode) m/z calcd. for $C_{28}H_{39}N_4O_2$ $[MH]^+$: 463.3073; found : 463.3063. $[\alpha]_{578}^{20}$: +28 (c 0.5, MeOH).

1,3-Bis(3-benzhydryl-3,4,5,6-tetrahydropyrimidin-2(1*H*)-ylideneamino)propane dihydrobromide 13

White solid (87%, conditions A); Mp: 159°C; Rf: 0.10 (EtOAc/MeOH/30% aq. NH_3 : 48/50/2); 1H NMR (300 MHz, CD_3OD): δ = 7.51-7.26 (m, 20H, ArH), 6.60 (s, 2H, $NCHPh_2$), 3.64-3.42 (m, 8H, CH_2N), 3.21-3.15 (appt t, 4H, $J=5.7$ Hz, CH_2NCHPh_2), 2.19-2.04 (m, 2H, CH_2), 2.01-1.92 (appt quint., 4H, $J=5.4$ Hz, CH_2) ppm. ^{13}C NMR (75 MHz, CD_3OD): δ = 156.1 (C=NH), 139.1 (C_{qAr}), 130.9, 130.7, 130.5 (CH_{Ar}), 67.5 ($NCHPh_2$), 50.3, 48.9, 45.2 (NCH_2), 26.2, 23.2 (CH_2) ppm. IR : ν_{max} = 3306, 3148, 2935, 2880, 1641, 1578, 1535, 1448, 1322, 1077, 726, 698 cm^{-1} . HRMS (TOF MSES positive mode) m/z calcd for $C_{37}H_{44}N_6$ $[M]^{2+}$: 286.1813; not found.

(*R,R*)-1,2-Bis(3-benzhydryl-3,4,5,6-tetrahydropyrimidin-2(1*H*)-ylideneamino)cyclohexane dihydrobromide 14

Light brown solid (67%, conditions A); Mp: 290°C; Rf: 0.15 (EtOAc/MeOH/40% aq. NH_3 : 40/58/2); 1H NMR (300 MHz, CD_3OD): δ = 7.52-7.23 (m, 20H, ArH), 6.63 (s, 2H, $NCHPh_2$), 4.33-4.30 (bm, 2H, CHN), 3.59-3.50 (m, 2H, CHN), 3.32-3.14 (m, 4H, CHN), 3.01-2.92 (m, 2H, CHN), 2.27-1.60 (m, 12H, CH_2) ppm. ^{13}C NMR (75 MHz, CD_3OD): δ = 156.4 (C=NH), 139.1, 138.5 (C_{qAr}), 131.1, 131.0, 130.8, 130.7, 130.6 (CH_{Ar}), 67.9 ($NCHPh_2$), 59.6 (NCH), 46.1, 42.2 (NCH_2), 30.9, 25.9, 23.4 (CH_2) ppm. IR : ν_{max} = 3440, 3305, 3191, 3061, 2924, 2880, 2860, 1633, 1554, 1526, 1452, 1322, 1073, 746, 698 cm^{-1} . HRMS (TOF MSES positive mode) m/z calcd for $C_{40}H_{47}N_6$ $[M]^+$: 611.3862; found : 611.3851. $[\alpha]_{578}^{20}$: + 62 (c 1.9, MeOH). A crystal suitable for X-ray analysis was obtained by recrystallisation from isopropanol (see Supporting Information).

8-Benzhydryl-3-phenyl-5,6,7,8-tetrahydro-imidazo[1,2,*a*]pyrimidin-2(4*H*)-one 16

Conditions A. After two hours at 120°C under microwave irradiation, the solution was concentrated under reduced pressure, giving one major product after trituration with small portions of diethyl ether. This residue was treated with aqueous K_2CO_3 , extracted with EtOAc and then purified by flash chromatography (EtOAc/MeOH : 100/0 to 90/10) to afford **16** as a viscous clear oil (23%); Rf: 0.50 (EtOAc); 1H NMR (300 MHz, $CDCl_3$): δ = 7.41-7.19 (m, 16H, ArH, $NCHPh_2$), 4.79 (s, 1H, $NCHPh$), 3.25-3.08 (m, 4H, NCH_2), 2.05 (appt quint., 2H, $J=5.7$ Hz, CH_2) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 184.9 (CO), 167.9 (C=NH), 137.7, 137.5, 134.2 (C_{qAr}), 128.9, 128.7, 128.5, 128.2, 128.1, 127.8, 127.6, 127.1 (CH_{Ar}), 69.7 (CHPh), 64.0 (CHPh₂), 40.6, 39.6, 21.1 (CH_2) ppm. IR : ν_{max} = 3089, 3061, 3026, 2967, 2939, 2872, 2237, 1696, 1570, 1499, 1460, 1381, 1318, 1278, 908, 722, 706 cm^{-1} . HRMS (TOF MSES positive mode) m/z calcd for $C_{25}H_{24}N_3O$ $[MH]^+$: 382.1919; found : 382.1916.

4-Benzhydryl-1-phenyl-1,2,4-triazepan-3-ylideneamine hydrobromide 17

Beige solid (64%, conditions B); Mp: 106°C; Rf: 0.30 (EtOAc/MeOH/40% aq. NH_3 : 93/5/2); 1H NMR (300 MHz, CD_3OD , major conformer 66%): δ = 7.55-6.90 (m, 15H, Ar), 6.36 (s, 1H, $NCHPh_2$), 3.76-3.58 (m, 2H, NCH_2), 3.45 (bs, 2H, NCH_2), 1.93 (bs, 2H, CH_2) ppm. 1H NMR (300 MHz, CD_3OD , minor conformer 33%): δ = 7.55-6.90 (m, 15H, Ar), 6.71 (s, 1H, $NCHPh_2$), 3.76-3.58 (m, 2H, NCH_2), 3.26 (appt t, 2H, $J=5.4$ Hz, NCH_2), 2.14 (appt quint, 2H, $J=5.4$ Hz, CH_2) ppm. ^{13}C NMR (75 MHz, CD_3OD , major and minor conformers): δ = 159.0, 150.7 (C=NH), 146.1, 139.0, 138.9 (C_{qAr}), 131.5, 131.0, 130.8, 130.6, 130.5, 130.4, 124.1, 122.6, 116.1, 115.6 (CH_{Ar}), 69.4, 67.7 (CHPh₂), 47.8, 45.0 (NCH_2), 22.9 (CH_2) ppm. IR : ν_{max} = 3239, 3077, 2963, 2868, 2300, 1633, 1592, 1491, 1444, 1322, 738, 691 cm^{-1} . HRMS (TOF MSES positive mode) m/z calcd for $C_{23}H_{25}N_4$ $[M]^+$: 357.2079; found: 357.2073. A crystal suitable for X-ray analysis was obtained by recrystallisation from EtOAc (see Supporting Information).

(*R*)-3-Benzyl-4-benzylloxymethyl-1-(1-phenylethyl)-3,4,5,6-tetrahydropyrimidin-2(1*H*)-ylideneamine hydrobromide 21

Beige solid (90%, conditions A); Rf: 0.39 (DCM/MeOH/aq. 30% NH_4OH 95/5/1); 1H NMR (300 MHz, CD_3OD , 1:1 diastereoisomeric mixture): δ = 7.43-7.27 (m, 15H, ArH), 5.37-5.28 (m, 1H, $NCH(CH_3)Ph$), 4.98-4.93 (m, 1H, $NCHHPh$), 4.71-4.64 (m, 1H, $NCHHPh$), 4.52-4.40 (m, 2H, OCH_2Ph), 3.72-3.53 (m, 3H, NCH , $CHCH_2O$), 3.42-3.33, 3.19-3.15, 3.01-2.87 (3m, 2H, NCH_2), 2.11-2.08, 1.97-1.83 (2m, 2H, CH_2), 1.65, 1.56 (2d, 3H, $J=6.9$ Hz, CH_3) ppm. ^{13}C NMR (75 MHz, CD_3OD): δ = 156.4, 156.3 (C=NH), 139.8, 139.4, 139.0, 136.6 (C_{qAr}), 130.2, 130.1, 130.0, 129.8, 129.7, 129.4, 129.3, 129.2, 128.8, 128.5, 128.1, 128.0, 127.4 (CH_{Ar}), 74.6, 74.5 (OCH_2Ph), 71.0, 70.4 ($CHCH_2O$), 57.5, 57.5 (NCH(CH_3)Ph), 56.8, 56.5 (NCH), 54.0, 54.0 (NCH_2Ph), 39.3, 39.3 (NCH_2), 26.2, 25.8 (CH_2), 16.8, 16.2 (CH_3) ppm. IR : ν_{max} = 3451, 3309, 3132, 3057, 2860, 2201, 1637, 1566, 1538, 1491, 1451, 1321, 1073, 734, 694 cm^{-1} . HRMS (TOF MSES positive mode) m/z calcd. for $C_{27}H_{32}N_3O$ $[M]^+$: 414.2545; found : 414.2539.

3-Benzyl-1-(4-methylbenzyl)-3,4,5,6-tetrahydropyrimidin-2(1*H*)-ylidenamino-4-carbonitrile hydrobromide 22

Beige solid (91%, conditions B); Mp: 81-83°C; Rf: 0.12 (DCM/MeOH/aq. 30% NH_4OH 95/5/1); 1H NMR (300 MHz, CD_3OD): δ = 7.48-7.13 (m, 9H, ArH), 4.96-4.64 (m, 5H, NCH_2Ph , NCH_2PhCH_3 , $CHCN$), 3.67-3.56 (m, 2H, NCH_2), 2.38-2.32 (m, 5H, CH_3 , CH_2) ppm. ^{13}C NMR (75 MHz, CD_3OD): δ = 155.5 (C=NH), 139.7, 134.9, 132.3 (C_{qAr}), 131.0, 130.4, 130.2, 128.5, 128.2 (CH_{Ar}), 117.7 (CN), 55.1, 54.9 (NCH_2PhCH_3 , NCH_2Ph), 48.3 (NCH), 45.0 (NCH_2), 26.0 (CH_2), 21.3 (CH_3) ppm. IR : ν_{max} = 3306, 3128, 3022, 2923, 2872, 2343, 1645, 1574, 1539, 1452, 1349, 805, 754, 702 cm^{-1} . HRMS (TOF MSES positive mode) m/z calcd. for $C_{20}H_{23}N_4$ $[M]^+$: 319.1923; found : 319.1929.

3-Benzyl-4-methyl-1-(4-methylbenzyl)-3,4,5,6-tetrahydro-2(1*H*)-pyrimidin-2(1*H*)-ylidenamino-4-carboxylic acid tert-butyl ester hydrobromide 23

White solid (25%, conditions A); Mp: 97°C; Rf: 0.25 (CH_2Cl_2 /MeOH : 90/10); 1H NMR (300 MHz, CD_3OD): δ = 7.45-7.18 (m, 9H, ArH), 4.91-4.53 (m, 4H, NCH_2Ph , NCH_2PhCH_3), 3.55-3.35 (m, 2H, NCH_2CH_2), 2.36-2.30 (m, 2H, NCH_2CH_2), 2.36 (s, 3H, CH_3Ph), 1.58 (s, 3H, $CCCH_3$), 1.49 (s, 9H, $C(CH_3)_3$) ppm. ^{13}C NMR (75 MHz, CD_3OD): δ = 173.1 (C=O), 157.3 (C=NH), 140.2, 138.0, 133.3 (C_{qAr}), 131.6, 130.8, 129.5, 129.1, 127.8 (CH_{Ar}), 85.7 ($COOC(CH_3)_3$), 66.5 ($NCqCH_3$), 55.8, 52.3 (NCH_2PhCH_3 , NCH_2Ph), 45.5 (NCH_2CH_2), 34.9 (NCH_2CH_2), 28.9 ($C(CH_3)_3$), 24.6 ($CqCH_3$), 22.0 ($PhCH_3$) ppm. IR : ν_{max} = 3308, 3126, 2975, 2927, 1727, 1636, 1588, 1536, 1449, 1374, 1353, 1148, 1127, 843, 750, 700 cm^{-1} . HRMS (TOF MSES positive mode) m/z calcd for $C_{25}H_{34}N_3O_2$ $[M]^+$: 408.2651; found : 408.2637.

Benzyl-(3-methyl-2-oxo-tetrahydrofuran-3-yl)cyanamide 24

Colourless oil; Rf: 0.31 (PE/EtOAc : 60/40); 1H NMR (300 MHz, $CDCl_3$): δ = 7.30-7.26 (m, 5H, Ar), 4.35-4.17 (m, 2H, OCH_2), -4.26 (d, A part of AB syst., 1H, $J=14.4$ Hz, $NCHHPh$), -4.16 (d, B part of AB syst., 1H, $J=13.8$ Hz, $NCHHPh$), 2.69-2.60 (m, 1H, OCH_2CHH), 2.27-2.18 (m, 1H, OCH_2CHH), 1.55 (s, 3H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 174.2 (C=O), 134.3 (C_{qAr}), 128.8, 128.7, 128.6 (CH_{Ar}), 114.3 (CN), 64.8 (OCH_2), 61.6 ($NCqCH_3$), 51.5 (NCH_2Ph), 34.7 (OCH_2CH_2), 20.6 ($CqCH_3$) ppm. IR : ν_{max} = 2991, 2916, 2887, 2212, 1776, 1723, 1497, 1453, 1385, 1219, 1191, 1099, 1024, 714 cm^{-1} . HRMS (TOF MSES positive mode) m/z calcd for $C_{13}H_{15}N_2O_2$ $[MH]^+$: 231.1135; found : 231.1134.

(1*S*,2*R*)-*N*-Benzyl-(1-cyano-2-phenylcyclopropyl)cyanamide 26 and (1*R*,2*R*)-*N*-Benzyl-(1-cyano-2-phenylcyclopropyl)cyanamide 27: To a solution of the 3-bromopropyl cyanamide **25** (64 mg, 0.18 mmol) in dry THF (2.5 mL) at -78°C was added dropwise a 1.3M solution of LiHMDS in THF (0.25 mL) under argon. The reaction mixture was then allowed to stir, with reaction progress monitored by TLC. After completion, the reaction was quenched with a saturated aqueous NH_4Cl solution and extracted with CH_2Cl_2 (3x10 mL). The combined organic extracts were

dried over magnesium sulfate, filtered and evaporated under reduced pressure. The residue was purified by thin layer chromatography (EP/EtOAc 75/25) to give **26** as white needles (55%) and **27** as a clear oil (31%).

26: Mp: 120°C; Rf: 0.41 (PE/EtOAc : 75/25); ¹H NMR (300 MHz, CDCl₃): δ = 7.47-7.39 (m, 5H, ArH), 7.36-7.31 (m, 3H, ArH), 7.04-7.01 (m, 2H, ArH), ~4.48 (d, A part of AB syst., 1H, J=13.5 Hz, NCHH), ~4.41 (d, B part of AB syst., 1H, J = 13.5 Hz, NCHH), 2.77 (appt. t, X part of ABX syst., 1H, CHPh), ~1.98 (dd, A part of ABX syst., 1H, J=8.6 Hz, CHH), ~1.86 (dd, B part of ABX syst., 1H, J=9.9 Hz, CHH) ppm. ¹³C NMR (75 MHz, CDCl₃): δ = 132.7, 132.1 (C_{qAr}), 129.4, 129.3, 129.2, 128.7, 128.5, 127.9 (CH_{Ar}), 115.4 (CN), 113.0 (NCN), 55.7 (CH₂Ph), 38.9 (Cq), 34.5 (CHPh), 21.4 (CH₂) ppm. IR: ν_{max} = 3101, 3065, 3033, 2921, 2215, 1604, 1498, 1455, 1392, 1275, 1217, 1176, 1079, 1027, 776, 766, 745 cm⁻¹. HRMS (TOF MSES positive mode) *m/z* calcd for C₁₈H₁₆N₃ [MH]⁺ : 274.1344; found : 274.1338. [α]_D²⁰₅₇₈ : + 80 (c 2.7, CH₂Cl₂).

27: Rf: 0.50 (EP/EtOAc : 75/25); ¹H NMR (300 MHz, CDCl₃): δ = 7.47-7.42 (m, 4H, ArH), 7.36-7.28 (m, 4H, ArH), 6.84-6.82 (m, 2H, ArH), ~4.03 (d, A part of AB syst., 1H, J=12.3 Hz, NCHH), ~3.64 (d, B part of AB syst., 1H, J = 12.3 Hz, NCHH), 3.10 (appt. t, X part of ABX syst., 1H, CHPh), 2.16-2.02 (m, AB part of ABX syst., 2H, CH₂) ppm. ¹³C NMR (75 MHz, CDCl₃): δ = 131.8, 130.3 (C_{qAr}), 129.4, 129.3, 129.2, 128.9, 128.7 (CH_{Ar}), 117.8 (CN), 113.7 (NCN), 55.0 (CH₂Ph), 36.3 (Cq), 34.6 (CHPh), 19.4 (CH₂) ppm. IR: ν_{max} = 3092, 3066, 3032, 2924, 2219, 1604, 1498, 1455, 1377, 1213, 1157, 1029, 778, 760, 744 cm⁻¹. HRMS (TOF MSES positive mode) *m/z* calcd for C₁₈H₁₆N₃ [MH]⁺ : 274.1344; found : 274.1333. [α]_D²⁰₅₇₈ : + 6 (c 2.5, CH₂Cl₂).

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Guanidines, Cyanamides, Azetidines

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3-Bromo *N*-Alkyl Cyanamides as Versatile Building Blocks

3-Bromo *N*-alkyl cyanamides, accessible in one step from azetidines, were used as original building blocks for the synthesis of nitrogen heterocycles and functionalized cyclopropanes.