Synthesis of 1,4-benzodiazepin-3-ones and 1,5-benzodiazocin-4-ones by addition of Grignard reagents to derivatives of *o*-aminobenzonitrile

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Addition of organometallics to *N*-(α-haloacyl)-*o*-aminobenzonitrile resulted in the formation of 2,5-disubstituted 1,4-benzodiazepin-3-ones, whereas *N*-(β-haloacyl)-*o*-aminobenzonitrile gave 2,6-disubstituted 1,5-benzodiazocin-4-ones under similar conditions. Initial cylization of *N*-(β-haloacyl)-*o*-aminobenzonitrile to obtain the corresponding lactam (*e.g.* α,α-dimethyl-*N*-(2-cyanophenyl)-β-lactam) increased the yield of 1,5-benzodiazocin-4-ones significantly. Somewhat surprisingly, addition of lithium reagents to *N*-(β-haloacyl)-*o*-aminobenzonitrile gave 4,4-disubstituted quinazolines *via* Grob fragmentation.

Introduction

Several 1,4-benzodiazepines have during a long period of time been used as drugs. The psychoactive drugs Librium (**A**), Valium (**B**), Ativan (**C**) and Xanax (**D**) are perhaps the most well known (Fig. 1). Further extensive investigations of this class of seven-membered *N*-heterocycles have also led to development of a number of pharmacologically active agents directed against other diseases such as cancer, HIV and cardio-arrhythmia in addition to the well-known anxiolytic and sedative effects.[1,2]

Moreover, alkaloids containing the 1,4-benzodiazepine moiety have been found among secondary metabolites derived from anthranilic acid. Most of the naturally occurring benzodiazepines are biologically active; however, molecules with tranquilizing properties have not been found.[3]

Despite the number and immense diversity of synthetic 1,4-benzodiazepines, especially the 1,4-benzodiazepin-2-ones, there are only a few studies available concerning 1,4-benzodiazepin-3-ones with the general formulas **1** and **2** (Fig. 2).[4] 1,4-Benzodiazepin-3-ones have lately attracted attention as peptidomimetics, thus a few synthetic methods have appeared during the last decade, usually involving intermolecular nucleophilic aromatic substitution.[5,6] It should be noted that these rare 1,4-benzodiazepin-3-ones also have biological activities. The potent antithrombotic agent Lotrafiban (**E**) provides an example (Fig. 2).[6]

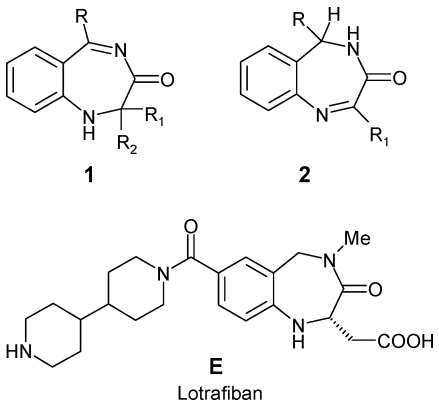

Fig. 2

Previous studies have shown that treatment of *o*-aminobenzonitrile (**3**), or its *N*-acylated derivatives (**4**), with Grignard reagents can result in the formation of the unusual 1,4-benzodiazepin-3-ones (**1** and **2**) often formed together with the quinazolines **5** (Scheme 1).[7a,b] Initially, the organometallic reagent

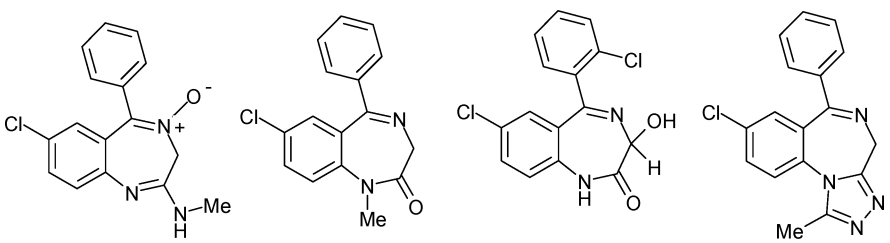

Fig. 1

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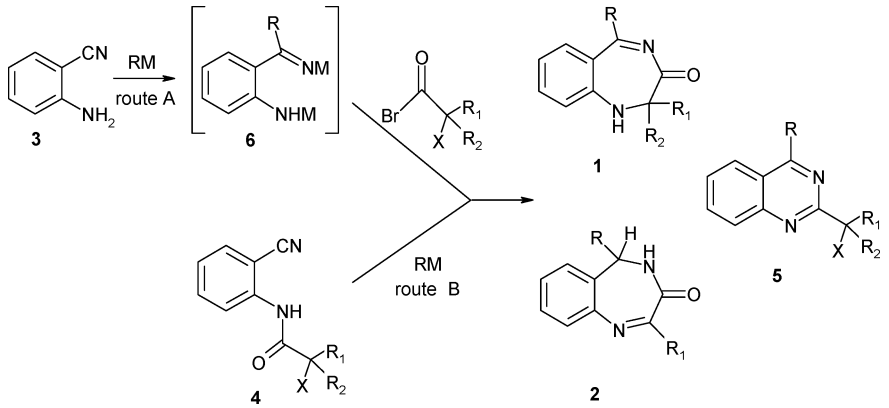
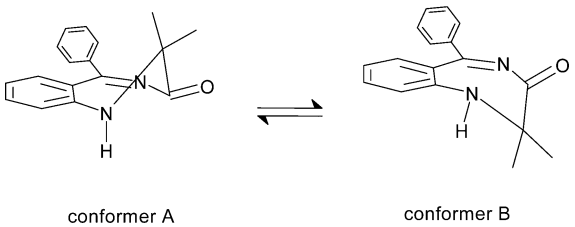


Scheme 1 Overview of Routes A and B toward 1,4-benzodiazepines **1** and **2**. M = MgBr, R = aryl, R_1 = alkyl, R_2 = alkyl or H, X = Br.

adds to the nitrile function, leading to the formation of an imine dianion **6**, which in some cases can be isolated. The reactivity of these anions and Route A to yield 1,4-benzodiazepine-3-ones **1** has recently been investigated in our group.[8] Compound **1** (R = Ph, R_1 = R_2 = Me) could also be separated into two crystalline conformers (A and B), whose structures (Fig. 3) have been determined by X-ray crystallography.[7b]



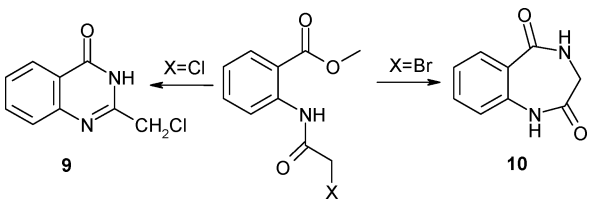
conformer A conformer B

Fig. 3 The two isolable conformers (A and B) of 1,2-dihydro-2,2-dimethyl-5-phenyl-3*H*-1,4-benzodiazepin-3-one (**1**)[7b].

Herein, we will take a closer look at Route B toward these intriguing products (Scheme 1) starting from *N*-(α-haloacyl)-*o*-anthranilonitrile (**4**). Furthermore, the methodology was also applied to obtain a higher homologue of 1,4-benzodiazepine-3-ones **1** and **2**, namely the 1,5-benzodiazocin-4-one **7** from *N*-(β-haloacyl)-*o*-aminobenzonitrile **8** (Scheme 5).

Results and discussion

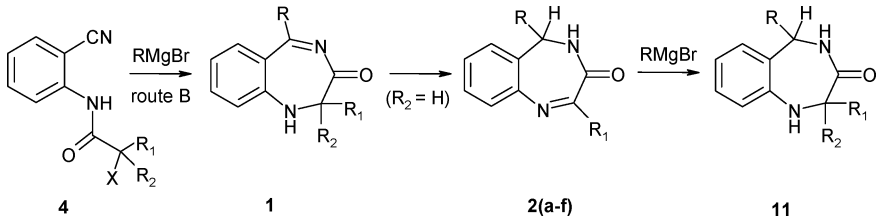
In this study a few factors were observed to affect the course of the reaction when organometallics, RM, reacted with *N*-haloacyl-*o*-aminobenzonitrile **4** (Scheme 1, Route B). These factors are: the nature of the halide (X) in the starting material (**4**), the organometallic reagent (RM) and the substituents at the α-position (R_1, R_2). The nature of the halide (X) has turned out to influence the size of the ring formed in the reaction. Thus, in some cases, quinazolines were obtained from the reaction *via* intramolecular attack on the amide anion. This should be disfavoured because of the low electrophilicity of the carbonyl functionality, but in the case where X = Cl, this was nevertheless the preferred outcome of the reaction. A similar precedent has previously been reported[9] by Párkányi, who found that methyl *N*-chloroacetylanthranilate cyclized to *N*-chloromethyl-4-quinazolinone (**9**) when treated with ammonia, while methyl *N*-bromoacetylanthranilate gave 1,4-benzodiazepin-2,5-dione (**10**) under the same reaction conditions (Scheme 2). In order to favour the formation of the desired benzodiazepine **1** we used the bromo-substituted starting material **4**.



Scheme 2 The influence of the substituent on the cyclization.[9]

Addition of alkyl Grignard reagents and lithium regents (BuLi, PhLi) to **4** failed to give benzodiazepines, and instead 4-amino-2-quinolinones were formed, *via* halogen-metal exchange at the α-carbon as previously reported by Bergman *et al.*[10] Addition of LiCl or TMEDA did not change the outcome of this reaction.

A side reaction in the synthesis of 1,4-benzodiazepin-3-ones is the addition of a second equivalent of the Grignard reagent which occurred when isomerisation of **1** was possible, *i.e.* R_2 = H (Scheme 3). It is reasonable to assume that 2,3-dihydro-1*H*-1,4-benzodiazepin-3-one is initially formed, which thereafter rapidly undergoes intramolecular hydride transfer to 4,5-dihydro-1,4-benzodiazepin-3-one **2**. In fact when such an isomerisation was possible (R_2 = H), only the 4,5-dihydro compound **2a–f**, and in some cases the 2,2,5-trisubstituted derivative **11**, could be isolated. It is known that the imine bond is susceptible to nucleophiles, and accordingly we have observed hydrolytic ring opening and also addition of phenylmagnesium bromide to 2-phenyl-1,4-benzodiazepin-5-one.[11] The proposed mechanism is also supported by the fact that **2a** could be converted to **11** by addition of phenylmagnesium bromide (the structures of **2** (R_1 = Et) and **11**(R_1 = Et, R_2 = Ph) have been confirmed by X-ray crystallography).[12] It is noteworthy that the addition of a second equivalent of the Grignard reagent did not occur in any cases except when R_1 = Et, R_2 = H. For example, when R_1 = *i*-propyl or *i*-butyl only the 2,5-disubstituted 1,4-benzodiazepin-3-ones (**2**) could be isolated, probably due to steric hindrance exerted by the R_1 group. The 1,4-benzodiazepin-3-ones prepared *via* Route B are summarised in Table 1.



Scheme 3 *Reagents and conditions*: Compound **1**: PhMgBr (2 eq), THF, reflux 12 h; General procedure for compound **2a–f**: a) RMgBr (2 eq), THF, reflux, 3 h; Compound **11**: PhMgBr (4,5 eq), THF, reflux.

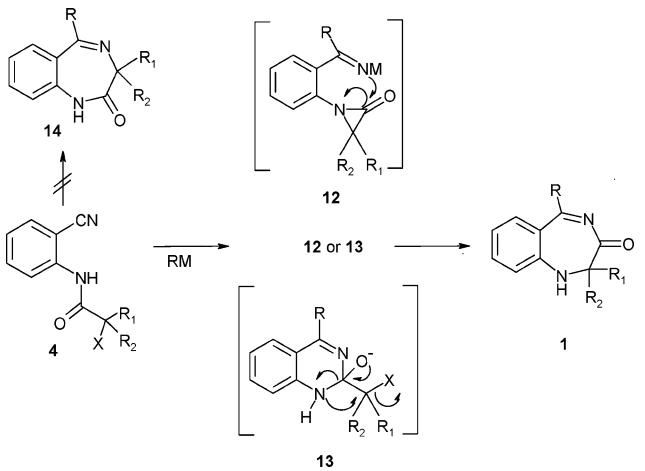
Table 1 1,4-Benzodiazepin-3-ones obtained *via* Route B, Scheme 3

Compound	R	R_1	R_2	Yield (%)
1	Ph	Me	Me	83
11	Ph	Et	Ph	80
2a	Ph	Et	H	68
2b	Ph	*i*-Pr	H	65
2c	Ph	*i*-Bu	H	69
2d	2-Thienyl	Et	H	74
2e	2-Thienyl	*i*-Pr	H	61
2f	2-Thienyl	*i*-Bu	H	63

Obviously, formation of 1,4-benzodiazepin-3-ones of type **1**, **2** and **11** proceeds *via* a rearrangement. One might speculate that the mechanism could involve an intermediate aziridinone (**12**). This hypothesis is however not supported by the fact that *N*-methyl-1,4-benzodiazepin-3-ones has been isolated from the reaction of *N*-methylated *o*-aminobenzonitrile **3** *via* Route A (Scheme 1). Another suggested mechanism, which also is supported by the formation of quinazolines **5**, involves the intermediate **13** (Scheme 1).[8] It is noteworthy that the non-rearranged isomer of **1**, *i.e.* 1,4-benzodiazepin-2-one **14**, was never observed (Scheme 4).

Although the 3-membered intermediate **12** does not seem to be on the reaction pathway to **1**, we became interested in the following question: can the 4-membered molecule **15** be transformed into the next higher homologue of 1,4-benzodiazocin-3-one, *i.e.* 1,5-benzodiazocin-4-one **7** (Scheme 5)? A similar ring expansion reaction of *N*-arylated β-lactams recently has been reported by Buchwald *et al.* using a copper-mediated coupling reaction.[13] Moreover, this is a convenient strategy for obtaining these rather unfavoured rings, as a nitrogen nucleophile is formed *in situ* which induces an intramolecular cyclization with a neighboring electrophile. These 8-membered heterocycles (**7a–g**) crystallized nicely, and the structure of **7f** has previously been determined in detail by X-ray methods.[14]

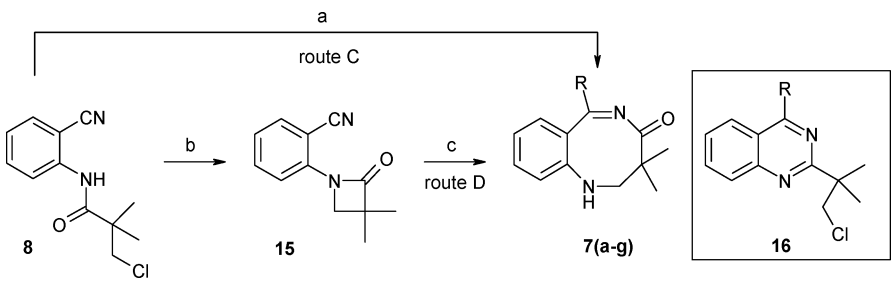
Compound **7** could also be obtained directly from the *N*-acylacetanilide **8** (Scheme 5, Route C), albeit in lower yields,



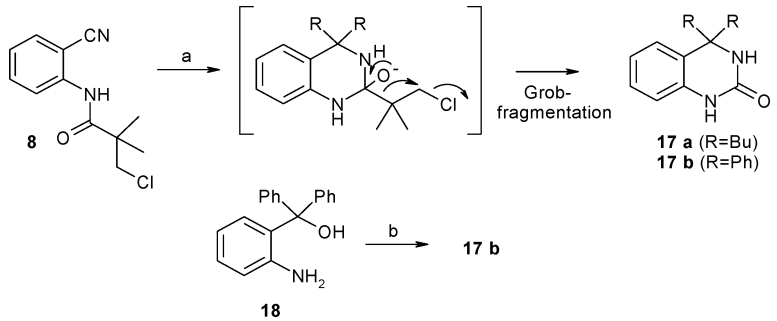
Scheme 4 Proposed mechanisms involved in the formation of benzodiazepine-3-ones **1**, **2a–f** and **11**. R = aryl, R_1 = alkyl or H, R_2 = alkyl, M = MgBr, X = Br.

primarily due to the formation of quinazolines **16**, which were isolated in two cases, namely 2-(2-chloro-1,1-dimethylethyl)-4-butylquinazoline (**16a**) and 2-(2-chloro-1,1-dimethylethyl)-4-isopropylylquinazoline (**16b**) (25–33%, Scheme 5). Obviously, Route B is much more favourable and convenient; most products were isolated directly after work-up, without further purification (Table 2).

Although it is known that organometal reagents such as RLi and $RCeCl_2$ can add twice to nitriles, the outcome of the reaction between **8** and RLi was unexpected, as outlined in Scheme 6.[15,16] The proposed mechanism involves a Grob fragmentation that results in the formation of the previously unknown quinazolinones **17**.[17] The 3,3,6-trisubstituted benzodiazocines **7a** and **7c** were also isolated from this reaction, but in low yields (≤30%). Molecule **17b** (R = Ph) could be independently prepared from reaction of *o*-aminotriphenylcarbinol **18** (readily available from



Scheme 5 *Reagents and conditions*: a) RMgBr (2 eq), THF, reflux, 3 h; b) NaH, DMF, 70 °C, 3.5 h; c) RMgBr (2 eq), THF, reflux, 3 h.



Scheme 6 Grob fragmentation.[17] *Reagents and conditions*: a) PhLi or BuLi (5 eq), THF, 1.5 h, –78 °C to RT; b) NaOCN, AcOH/H_2O (2:1), 3 h, 60 °C.

Table 2 1,5-Benzodiazocin-4-ones **7a–g** obtained *via* Routes C and D

		Yield (%)	
Compound	R	Route C	Route D
7a	Ph	44	91
7b	2-Thienyl	35	70
7c	Bu	46	74
7d	*i*-Pr	40	70
7e	Pr	42	73
7f	Et	42	85
7g	Me	28	39

o-aminobenzoic acid methyl ester) and NaOCN under acidic conditions (Scheme 6).[18]

Conclusions

The addition of organometallics to derivatives of *o*-aminobenzonitrile was investigated. This resulted in a convenient route toward several unusual 1,4-benzodiazepine-3-ones (Table 1) by addition of Grignard reagents to *N*-(α-haloacyl) derivatives of readily available anthranilonitrile. The methodology was also successfully applied to obtain the next higher homologue 1,5-benzodiazocine-4-one (Table 2) in high yields.

Experimental

All starting materials and solvents were obtained from commercial sources and used without further purification. THF was distilled from sodium and benzophenone. Chromatography was performed using silica gel (40–63 μm). Melting points were determined in open capillary tubes on a Büchi-B545 melting point apparatus. IR spectra were recorded on Thermo Nicolet Avatar 330 FT-IR instrument. NMR spectra were recorded on a Bruker DPX 300 operating at 300.1 MHz for ^{1}H and 75.5 MHz for ^{13}C in DMSO-D_6. Chemical shifts are reported in ppm downfield to TMS. The elemental analyses was performed by H. Kolbe Mikroanalytisches Laboratorium, Mülheim an der Ruhr, Germany.

N-(α-Bromoisobutyryl)-2-cyanoanilide (4a)

To a CH_2Cl_2 (50 mL) solution of *o*-aminobenzonitrile (3.54 g, 30 mmol) and pyridine (3.6 mL, 45 mmol), α-bromoisobutyryl bromide (36 mmol, 4.4 mL) was added dropwise at room temperature. After stirring for 20 h, the reaction mixture was washed with water several times, dried ($MgSO_4$) and evaporated to give an colourless oil. Addition of hexane gave 7.21 g (27 mmol, 90%) of **4a** as a white crystalline material after several hours, mp 68–69 °C (lit.[10] mp 61 °C); IR ν_{max}: 3350, 2205, 1690, 1580, 1530, 1450, 1300, 1160 and 760 cm^{-1}; δ_H: 2.01 (6H, s), 7.43 (2H, m), 7.77 (1H, m), 7.86 (1H, m), 10.26 (1H, s); δ_C: 30.9 (q), 59.6 (s), 109.7 (s), 116.6 (s), 126.8 (d), 127.1 (d), 133.2 (d), 133.8 (d), 139.8 (s), 170.2 (s).

N-(α-Bromobutyryl)-2-cyanoanilide (4b) (general procedure for *N*-(α-bromoalkyl)-2-cyanoanilides 4b–d)

To a well-stirred 2-phase system composed of K_2CO_3 (7.00 g, 50 mmol) in H_2O (50 mL) and *o*-aminobenzonitrile (5.90 g, 50 mmol) in CH_2Cl_2 (50 mL)) α-bromobutyryl bromide (5.9 mL, 50 mmol) in CH_2Cl_2 (25 mL) was added dropwise at 0–5 °C. After stirring for 20 h at room temperature the water phase was extracted with CH_2Cl_2. The combined organic phases were washed with aqueous $NaHCO_3$ (10%), dried ($MgSO_4$) and concentrated *in vacuo* to give 12.2 g (46 mmol, 91%) of **4b** as a white solid, mp: 104 °C (lit.[10] 105 °C); IR ν_{max}: 3240, 2970, 2230, 1670, 1580, 1535, 1450, 1300, 1170 and 770 cm^{-1}; δ_H: 1.00 (3H, t, *J 14.6* and 7.3), 1.97 (1H, m), 2.08 (1H, m), 4.57 (1H, t, *J* 14.6, 7.3), 7.41 (1H, m), 7.56 (1H, m), 7.72 (1H, m), 7.86 (1H, m), 10.56 (1H, s); δ_C: 11.8 (q), 28.0 (t), 50.2 (d), 107.8 (s), 116.5 (s), 125.7 (d), 126.4 (d), 133.4 (d), 133.9 (d), 139.3 (s), 167.7 (s).

N-(α-Bromo-3-methylbutanoyl)-2-cyanoanilide (4c)

Compound **4c** as prepared according to the procedure given for **4b** on a 50 mmol scale, using 6.8 mL (50 mmol) α-bromo-3-methylbutanoyl bromide. After evaporation **4c** was collected as a off white solid. Yield: 13.5 g (48 mmol, 96%), mp 125 °C (from 2-propanol); Ir ν_{max}: 3241, 2973, 2231, 1666, 1521, 1490, 1439, 1189, 753, 713 cm^{-1}; δ_H: 1.04 (3H, d, *J* 6.1), 1.11 (3H, d, *J* 6.1), 2.24 (1H, m), 4.43 (1H, d, *J* 8.6), 7.42 (1H, m), 7.53 (1H, m), 7.77 (1H, m), 7.85 (1H, m), 10.54 (1H, s); δ_C: 19.5 (q), 20.19 (q), 31.9 (d), 57.0 (d), 107.9 (s), 116.6 (s), 125.8 (d), 126.5 (d), 133.4 (d), 134.0 (d), 139.2 (s), 167.5 (s).

N-(α-Bromohexanoyl)-2-cyanoanilide (4d)

Compound **4d** was prepared according to the procedure given for **4b** on a 50 mmol scale, using 7.6 mL (50 mmol) of α-bromohexanoyl bromide. After evaporation **4d** was collected as a white solid. Yield: 13.3 g (90%), mp 107 °C (from 2-propanol); Ir ν_{max}: 3241, 2965, 2228, 1669, 1523, 1334, 1174, 960, 757, 670 cm^{-1}; δ_H : 0.91 (3H, d, *J* 6.6), 0.96 (3H, d, *J* 6.6), 1.73 (1H, m),

1.92 (2H, m), 4.75 (1H, t, *J* 15.2 and 7.6), 7.41 (1H, m), 7.59 (1H, m), 7.72(1H, m), 7.85 (1H, m), 10.56 (1H, s); δ_C : 21.7 (q), 22.0 (q), 26.05 (d), 42.9 (t), 47.1 (d), 107.4 (s), 116.4 (s), 125.5 (d), 126.3 (d), 133.4 (d), 133.9 (d), 139.2 (s), 167.8 (s).

1,2-Dihydro-2,2-dimethyl-5-phenyl-3*H*-1,4-benzodiazepin-3-one (1) and 2-(1-bromo-1-methylethyl)-4-phenylquinazoline (5)

N-(α-Bromoisobutyryl)-2-cyanoanilide **4a** (1.33 g, 5 mmol) was dissolved in THF (10 mL) and added dropwise to a stirred THF (10 mL) solution of phenylmagnesium bromide (11 mmol, prepared by general procedure). After 12h at reflux, aqueous NH_4Cl (20 mL, 20%) was added cautiously and the mixture was stirred for 1h. The aqueous layer was extracted with EtOAc and the combined organic layers were washed (water and brine) and dried ($NaSO_4$). Evaporation of the solvent gave a yellow solid material which was recrystallised from ethanol to give 1.10 g (83%) of **1**, as a yellow fine powder, mp 197 °C (lit.[8] 197°C). Ir υ_{max}: 3300, 3000, 2940, 1685, 1575, 1450, 1255, 1105, 770, 700 cm^{-1}; δ_H: 1.29 (6H, s), 6.72 (1H, t, *J* 7.4), 6.74–7.20 (2 H, m), 7.28 (1H, s), 7.38 (1H, t, *J* 7.4), 7.50–7.60 (5H, m); δ_C: 24.1 (q), 62.4(s), 116.7 (d), 117.8 (s), 120.1 (d), 128.4 (d), 129.4 (d), 130.7 (d), 132.6 (d), 132.8 (d), 138.9 (s), 147.0 (s), 166.2 (s), 173.7 (s).

The structure has been established by X-ray crystallography and separated into two crystalline conformers.[7b]

Compound **5** was collected as white needles 65.4 mg (4%) from the filtrate, mp 136 °C (lit.[8] mp 136 °C); IR υ_{max}: 1609, 1561, 1540, 1485, 1464, 1390, 1164, 782, 621, 596, 522 cm^{-1}; δ_H: 2.23 (6H, s), 7.63–7.69 (3H, m), 7.74–7.80 (1H, m), 7.82–7.86 (2H, m), 8.03–8.14 (3H, m); δ_C: 32.4 (q), 66.1 (s), 120.7 (s), 126.8 (d), 128.8 (d), 128.8 (d), 130.1 (d), 130.3 (d), 134.6 (d), 135.6 (s), 150.3 (s), 166.0 (s), 168.0 (s).

2-Ethyl-5-phenyl-4,5-dihydro-[3*H*]-1,4-benzodiazepin-3-one (2a)

N-(α-Bromobutyryl)-2-cyanoanilide **4b** (2.67 g, 10 mmol) was dissolved in 20 mL dry THF and added dropwise to a THF-solution of phenylmagnesium bromide (22 mmol in 20 mL). After 4h at reflux aqueous NH_4Cl (30 mL, 20%) was added and the mixture was stirred for one hour. The organic layer was separated off and the water phase was extracted several times with EtOAc. The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo.* The residue crystallized from ethanol to give 1.82 g (68%) of **2a** as a yellow crystalline solid, mp 183–185 °C; Ir ν_{max}: 3167, 3032, 1662, 1630, 1479, 1447, 1132, 771, 733, 695 cm^{-1}; δ_H 348 K: 0.71 (3H, t, *J* 7.5), 2.34–2.57 (2H, m) (appear in $CDCl_3$ at 2.73 (2H, brs)), 5.46 (1H, d, *J* 7.4), 7.09–7.11 (2H, m,), 7.25–7.33 (6H, m), 7.41–7.46 (1H, m), 10.59 (s, 1H); δ_C: 9.36 (s), 29.31 (t), 55.49 (d), 126.18 (d), 127.2 (d), 128.1 (d), 128.8 (d), 145.38 (s), 163.4 (s), 168.3 (s). The structure of this compound has previously been determined by X-ray crystallography.[12]

2-Phenyl-2-isopropyl-4,5-dihydro-[3*H*]-1,4-benzodiazepin-3-one (2b)

N-(α-Bromo-3-methylbutanoyl)-2-cyanoanilide **4c** (1.4 g, 5 mmol) was dissolved in THF (20 mL) and added dropwise to a THF solution (10 mL) of phenylmagnesium bromide (11.5 mmol). After 20h at reflux aqueous NH_4Cl (20 mL, 20%) was added and the reaction mixture was stirred for one hour. The organic layer was separated off and the water phase was extracted several times with EtOAc. The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo.* Purification by column chromatography (EtOAc/heptane, 1:4) gave a off-white solid **2b**, 0.90 g (65%) which could be recrystallised from 2-propanol to give white prisms, mp 142 °C, (Found C, 77.78; H, 6.44; N, 10.12. $C_{18}H_{18}N_2O$ requires C, 77.67; H, 6.52; N, 10.06%); Ir ν_{max}: 3215, 2969, 1651, 1623, 1589, 1449, 1050, 761, 725, 697 cm^{-1}; δ_H (353 K): 0.60 (3H, d, *J* 6.8), 1.04 (3H, d, *J* 6.8), 2.92–3.03 (1H, m), 5.39 (1H, d, *J* 7.6), 7.11–7.25 (2H, m), 7.28–7.34 (6H, m), 7.42–7.47 (1H, m), 9.14 (1H, d, J 7.5); δ_C (353 K): 19.0 (q), 19.8 (q), 33.7 (d), 56.0 (d), 126.1 (d), 126.9 (d), 127.2 (d), 127.2 (d), 128.1 (d), 128.3 (d), 128.7 (d), 132.5 (s), 138.6 (s), 145.8 (s), 163.4 (s), 171.4 (s).

2-Phenyl-2-isobutyl-4,5-dihydro-[3*H*]-1,4-benzodiazepin-3-one (2c)

Compound **2c** was prepared according to the procedure given for **2b** on a 5 mmol scale using *N*-(α-bromo-3-hexanoyl)-2-cyanoanilide **4d**. The crude product was purified by column chromatography (EtOAc/heptane, 1:4) to afford 1.01 g (69%) of **2c** as a yellow solid. The product could be recrystallised from 2-propanol to afford a yellow powder solid, mp 156–157 °C, (Found C, 78.05; H, 6.89; N, 9.58. $C_{19}H_{20}N_2O$ requires C, 78.05; H, 6.89; N, 9.58%); Ir ν_{max}: 3203, 3062, 2957, 1656, 1626, 1449, 1384, 749, 724, 696 cm^{-1}; δ_H (353 K): 0.65 (d, 3H, *J* 6.61), 0.73 (d, 3H, *J* 6.61), 1.84–1.93 (1H, m), 2.19–2.26 (1H, m), 2.50–2.57 (1H, m; appear in $CDCl_3$ at 2.8 (1H, brs)), 5.39 (1H, d, *J* 7.0), 7.13–7.15 (m, 2H), 7.24–7.32 (6H, m), 7.41–7.46 (1H, m), 9.90 (1H, m, *J* 6.5); δ_H (353 K): 21.7 (q), 21.9 (q), 24.3 (d), 44.7 (t), 55.5(d), 125.7 (d), 125.9 (d), 126.8 (d), 126.9 (d), 127.8 (d), 127.8 (d), 128.2 (d), 132.6 (s), 138.3 (s), 145.2 (s), 163.0 (s), 166.1 (s).

2-Ethyl-5-(2-thienyl)-4,5-dihydro-[3*H*]-1,4-benzodiazepin-3-one (2d)

Compound **2d** was prepared according to the procedure given for **2b** on a 5 mmol scale using *N*-(α-bromo-butyryl)-2-cyanoanilide **4b**. The crude product was purified by column chromatography (EtOAc/heptane, 1:3) to afford 1.01 g (74%) of **2d** as a pale yellow solid, 168–169 °C (from 2-propanol); Ir ν_{max}: 3169, 2980, 1661, 1629, 1450, 1229, 1119, 769, 708 cm^{-1}; δ_H (353 K): 0.82 (3H, t, *J* 7.4), 2.39–2.73 (2H, m; appear in $CDCl_3$ at 2.77–2.81 (2H, m)), 5.56 (1H, d, *J* 6.8), 6.64 (1H, brs), 6.90–6.93 (1H, m), 7.25–7.32 (2H, m), 7.37–7.38 (1H, m), 7.41–7.48 (2H, m), 9.25 (1H, brs); δ_C: 9.5 (q), 29.5 (t), 53.0 (d), 125.2 (d), 125.3 (d), 126.3 (d), 126.8 (d), 127.5 (d), 128.3 (d), 129.2 (d), 132.9 (s), 144.1 (s), 145.4 (s), 163.4 (s), 168.2 (s).

2-Isopropyl-5-(2-thienyl)-4,5-dihydro-[1*H*]-1,4-benzodiazepin-3-one (2e)

Compound **2e** was prepared according to the procedure given for **2b** on a 5 mmol scale using *N*-(α-bromo-3-methylbutanoyl)-2-cyanoanilide **4c**. The crude product was purified by column chromatography (EtOAc/heptane, 1:3) to afford 0.87 g (61%) of **2e** as a yellow solid. The product could be recrystallised from 2-propanol to afford of a pale yellow crystalline solid, mp 135–137 °C; (Found C, 67.68; H, 5.58; N, 9.92. $C_{16}H_{16}N_2OS$ requires C, 67.58; H, 5.67; N, 9.85%); Ir ν_{max}: 3172, 2966, 1651, 1623, 1287, 1027, 841, 799, 760, 703 cm^{-1}; δ_H (353 K): 0.71 (3H, d, *J* 6.8),

1.09 (3H, d, *J* 6.8), 2.97–3.06 (1H, m), 5.55 (1H, d, *J* 7.4), 6.63 (1H, brs), 6.90–6.92 (1H, m), 7.26–7.33 (2H, m), 7.37–7.40 (2H, m), 7.43–7.45 (1H, m), 9.20 (1H, d, 7.1); δ_C (353 K): 19.0 (q), 20.0 (q), 33.6 (d), 52.8 (d), 125.3 (d), 125.5 (d), 126.3 (d), 126.6 (d), 127.5 (d), 128.3 (d), 129.1 (d), 132.1(s), 143.6 (s), 145.3 (s), 163.3 (s), 171.1 (s).

2-Isobutyl-5-(2-thienyl)-4,5-dihydro-[1*H*]-1,4-benzodiazepin-3-one (2f)

Compound **2f** was prepared according to the procedure given for **2b** on a 5 mmol scale using *N*-(α-bromo-3-hexanoyl)-2-cyanoanilide **4d**. The product was purified by column chromatography (EtOAc/heptane, 1:3) to afford 0.94 g (63%) of **2f** as a pale yellow solid. The product could be recrystallised from 2-propanol to give white needles, mp 179–180 °C; (Found C, 68.54; H, 6.12; N, 9.45. $C_{17}H_{18}N_2OS$ requires C, 68.43; H, 6.08; N, 9.39%); Ir ν_{max}: 3161, 3044, 2866, 1663, 1627, 1428, 1286, 1176, 1094, 759, 719, 710 cm^{-1}; δ_H (353 K): 0.71 (3H, d, *J* 6.6), 0.78 (3H, d, *J* 6.6), 1.91–2.04 (1H, m), 2.25–2.32 (1H, m), 2.49–2.59 (1H, m; appear in $CDCl_3$ at 2.82–2.89 (1H, m)), 5.54 (1H, d, *J* 6.0), 6.65 (1H, brs), 6.90–6.93 (1H, m), 7.24–7.32 (2H, m), 7.35–7.42 (2H, m), 7.43–7.48 (1H, m), 9.18 (1H, brs); δ_C (353K): 22.1 (q), 22.4 (q), 24.4 (d), 45.1 (t), 53.1 (d), 124.9 (d), 125.3 (d), 126.5 (d), 127.0 (d), 127.8 (d), 128.4 (d), 129.3 (d), 132.7 (s), 144.5 (s), 145.3 (s), 163.4 (s), 166.2 (s).

2,5-Diphenyl-2-ethyl-1,2,4,5-tetrahydro-[3*H*]-1,4-benzodiazepin-3-one (11)

N-(α-Bromobutyryl)-2-cyanoanilide **4b** (5.9 g, 22 mmol) was dissolved in THF (100 mL) and added dropwise to a stirred solution of phenylmagnesium bromide (0.1 mol) in THF (100 mL). The reaction mixture was refluxed overnight and thereafter quenched by addition of aqueous NH_4Cl (100 mL). The layers were separated and the water phase was extracted with EtOAc. The combined organic phases were washed with water and brine, dried ($MgSO_4$) and concentrated *in vacuo.* The residue was recrystallised from 2-propanol to give 6.02 g (80%) of **11** as a yellow crystalline solid, mp 198–199 °C; Ir ν_{max}: 3180, 3050, 2980, 1650, 1600, 1495, 1450, 1415, 745, 725, 715 cm^{-1}; δ_H: 0.85 (3H, t, *J* 7.4), 1.82–1.89 (1H, m), 2.24–2.33 (1H, m), 5.10 (1H, s), 5.42 (1H, d, *J* 6.5), 6.91–6.95 (2H, m), 7.06–7.08 (2H, m), 7.01–7.16 (5H, m), 7.02–7.23 (5H, m), 8.40 (1H, d, *J* 6.5); δ_C: 8.2 (q), 31.5 (t), 57.9 (d), 70.2 (s), 121.1 (d), 123.2 (d), 126.3 (d), 126.4 (d), 126.5 (d), 127.2 (d), 127.5 (d), 127.6 (d), 128.3 (d), 128.7 (d), 133.6 (s), 142.4 (s), 142.6 (s), 145.6 (s), 174.3 (s). The structure of this compound has previously been determined by X-ray crystallography.[11]

3-Chloro-*N*-(2-cyanophenyl)-2,2-dimethylpropananamide (8)

To a CH_2Cl_2 suspension (50 mL) of anthranilonitrile (5.9 g, 50 mmol) and pyridine (4.9 mL, 60 mmol) β-chloropivaloyl chloride (5 mL, 60 mmol) was slowly added at 0 °C. After 20 h stirring at room temperature, the reaction mixture was washed with water several times and dried (Na_2SO_4). Crystalline material appeared after a few minutes and the mixture was capped and left over night in room temperature. The crystals was filtered off and carefully washed with cold CH_2Cl_2 to give 9.6 g (81%) of **8** as pale pink needles, mp: 97–98 °C (Found C, 60.89; H, 5.54; N, 11.83. $C_{12}H_{13}ClN_2O$ requires C, 60.89; H, 5.54; N, 11.83%); Ir ν_{max}: 3310, 2980, 2229, 1662, 1509, 1448, 1301, 1189, 926, 757, 719cm^{-1}; δ_H 1.31 (s, 6H), 3.85 (s, 2H), 7.42 (m, 2H), 7.68 (m, 1H), 7.83 (m, 1H), 9.78 (m, 1H); δ_C: 23.0 (q), 44.4 (t), 52.2 (s), 109.5 (s), 116.6 (s), 126.3 (d), 127.1 (d), 132.9 (d), 133.6 (d), 140.2 (s), 173.5 (s).

α,α-Dimethyl-*N*-(2-cyanophenyl)-β-lactam (15)

3-Chloro-*N*-(2-cyanophenyl)-2,2-dimethylpropanamide **8** (7.8 g, 33 mmol) was dissolved in DMF (20 mL) and added at to a suspension of NaH (0.79 g, 33 mmol) in DMF (30 mL) under nitrogen atmosphere in room temperature. After ~30 min, when H_2 ceased to evolve, the mixture was heated to 70 °C and left for 3.5 h with stirring. The reaction mixture was cooled room temperature and then poured into cold water. A white precipitate was formed and collected by filtration after a few minutes. Washing with several portions of water gave 6.01 g (91%) of **15** as a white solid material, mp: 86–87 °C (found C, 71.79; H, 6.10; N, 13.92. $C_{12}H_{12}N_2O$ required C, 71.98; H, 6.04; N, 13.99%); Ir ν_{max}: 2968, 2217, 1735, 1488, 1449, 1358, 1151, 1074, 756 cm^{-1}; δ_H: 1.33 (s, 6H), 3.92 (s, 2H), 7.24 (m, 1H), 7.68 (m, 1H), 7.76 (m, 1H), 8.05 (m, 1H); δ_C: 20.8 (q), 50.7 (s), 55.5 (t), 98.7 (s), 117.3 (s), 120.2 (d), 124.0 (d), 134.1 (d), 134.2 (d), 140.4 (s), 172.0 (s).

6-Phenyl-3, 3-dimethyl-1,2,3,4-tetrahydro-1, 5-benzodiazocin-4-one (7a). General procedure for compound 7a–7g (Routes C and D)

Route D. A THF solution (20 mL) of lactam **15** (1.3 g, 6.5 mmol) was added to phenyl magnesium bromide (13 mmol) in THF (10 mL). After 3 h at reflux, the reaction was quenched by addition of NH_4Cl (20 mL, 20%). Solid material was filtered off and the phases were separated. The water phase was washed with EtOAc and the combined organic layers were washed with water and brine and dried (Na_2SO_4). Evaporation of the solvent *in vacuo* gave a yellow solid which was recrystallised from ethanol to afford 1.65 g (91%) of **7a** as a fine yellow powder solid, mp 197–199 °C; (Found C, 77.78; H, 6.44; N, 10.12. $C_{18}H_{18}N_2O$ required C, 77.67; H, 6.52; N, 10.06%); Ir ν_{max}: 3374, 2923, 1661, 1626, 1485, 1303, 1178, 934, 751, 698, 626 cm^{-1}; δ_H: 7.64 (m, 2H), 7.52 (m, 3H), 7.10 (m, 1H), 6.91 (m, 1H), 6.69 (m, 2H), 6.41 (m, 1H), 3.61 (dd, 1H, $J = 14.7$, 6.9 Hz), 2.90 (dd, 1H, $J = 14.7$, 6.9 Hz), 1.19 (s, 3H), 1.09 (s, 3H); δ_C: 21.8 (q), 26.0 (q), 38.2 (t),. 52.1 (s), 114.3 (d), 114.7 (s), 117.5 (d), 128.4 (d), 129.4 (d), 139.0 (s), 132.2 (d), 131.3 (d), 130.9 (d), 146.3 (s), 164.4 (s).

Route C. 3-Chloro-*N*-(2-cyanophenyl)-2-methanbutanamide **8** (2.36 g, 10 mmol) was dissolved in THF (30 mL) and added to a THF solution (20 mL) of phenyl magnesium bromide (25 mmol). After 3h at reflux NH_4Cl (20 mL, 20%) was added and followed by the work-up described above (for **7a** from lactam **15**) The organic layer was evaporated to afford a yellow oil which was purified by column chromatography (EtOAc/heptane, 1:4) which gave 1.22 g (44%) of **7a** as a yellow crystalline solid.

6-(2-Thienyl)-3,3-dimethyl-1,2,3,4-tetrahydro-1,5-benzodiazocin-4-one (7b)

Compound **7b** was prepared by the same procedure as described for **7a** (Route D) on a 10 mmol scale using α,α-dimethyl-*N*-(2-cyanophenyl)-β-lactam (**15**) and thienyl magnesium bromide (20 mmol) to give 1.99 g (70%) of **7b** as a yellow powder

solid, mp 228–230 °C (2-propanol), (Found C, 67.52; H, 5.62; N, 9.78. $C_{16}H_{16}N_2OS$ required C, 67.58; H, 5.67; N, 9.85%); Ir ν_{max}: 3370, 3333, 2965, 1654, 1632, 1600, 1486, 1231, 1160, 1045, 849, 727 cm^{-1}; δ_H: 1.12 (s, 3H), 1.16 (s, 3H), 2.72–2.98 (m, 1H), 3.57–3.79 (m, 1H), 6.34–6.59 (m, 1H), 6.60–6.74 (m, 1H), 6.76–6.95 (m, 1H), 7.28–6.98 (m, 2H), 7.33–7.36 (m, 1H), 7.75–7.93 (m, 1H); δ_C: 21.4 (q), 26.1 (q), 38.9 (t), 51.7 (s), 114.3 (d), 117.5 (d), 128.2 (d), 131.4 (d), 131.6 (d), 132.3 (d), 133.5 (d), 143.9 (s), 145.3 (s), 158.4 (s), 191.52 (s). Alternatively, **7b** could be obtained *via* Route C according to the procedure described for **7a** on a 10 mmol scale using 3-chloro-*N*-(2-cyanophenyl)-2-methanbutanamide 8 and thienyl magnesium bromide (25 mmol). Evaporation gave a yellow oil which was purified by column chromatography (EtOAc/heptane, 1:4) to give 0.99 g (35%) of **7b** as a yellow crystalline solid.

6-Butyl-3, 3-dimethyl-1,2,3,4-tetrahydro-1, 5-benzodiazocin-4-one (7c) and 2-(2-chloro-1,1-dimethylethyl)-4-butylquinazoline (16a)

Compound **7c** was prepared by the same procedure as described for **7a** (Route D) on a 10 mmol scale using α,α-dimethyl-*N*-(2-cyanophenyl)-β-lactam (**15**) and butyl magnesium bromide (20 mmol) to give 1.91 g (74%) of a colourless crystalline material, mp: 118–119 °C (2-propanol), (Found C, 74.44; H, 8.53; N, 10.88 $C_{16}H_{22}N_2O$ required C, 74.38; H, 8.58; N, 10.84%); Ir ν_{max}: 3316, 2926, 2866, 1655, 1604, 1491, 1337, 1191, 1148, 970, 746, 736 cm^{-1}; δ_H: 0.92 (3H, m), 1.13 (6H, s), 1.38–1.45 (2H, m), 1.64–1.57 (2H, m), 2.77–2.89 (3H, m), 3.47 (1H, dd, *J* 14.4 and 6.9), 6.48–6.53 (1H, m), 6.58–6.61 (1H, m), 6.66–6.68 (1H, m), 7.02–7.07 (1H, m), 7.23–7.26 (1H, m); δ_C: 13.8 (q), 21.8 (q), 21.9 (t), 28.7 (t), 25.7 (q), 37.8 (t), 38.0 (t), 52.3(s), 115.2 (d), 116.7 (s), 117.5 (d), 129.6 (d), 130.9 (d), 145.0 (s), 167.0 (s), 191.1 (s) Alternatively, **7c** could be obtained *via* Route C according to the procedure described for **7a** on a 10 mmol scale using 3-chloro-*N*-(2-cyanophenyl)-2-methanbutanamide **8** and butyl magnesium bromide (25 mmol). Evaporation gave a yellow oil which was purified by column chromatography (EtOAc/heptane, 1:4) to give 1.19 g (46%) **7c** as a yellow crystalline solid.

16a was also isolated from the column as white needles. Yield: 0.91 g (33%), mp 45 °C, (Found C, 69.56; H, 7.61; N, 10.09 $C_{15}H_{21}ClN_2$ required C, 69.43; H, 7.65; N, 10.12%); Ir ν_{max}: 2954, 2869, 1615, 1552, 1416, 1397, 1383, 1186, 934, 791, 760, 622 cm^{-1}; δ_H: 0.93 (3H, t, *J* 7.3), 1.36–1.46 (2H, m), 1.48 (6H, s), 1.78–1.83 (2H, m), 3.27 (2H, t, *J* 7.6), 4.11 (2H, s), 7.64–7.70 (1H, m), 7.92–7.94 (2H, m), 8.25–8.28 (1H, m); δ_C: 13.8 (q), 21.8 (t), 25.0 (q), 29.8 (t), 33.0 (t), 44.3 (t), 54.8 (s), 121.4 (s), 125.0 (d), 127.2 (d), 128.4 (d), 133.7 (d), 149.2 (s), 167.9 (s), 171.0 (s).

6-Isopropyl-3,3-dimethyl-1,2,3,4-tetrahydro-1, 5-benzodiazocin-4-one (7d) and 2-(2-chloro-1,1-dimethylethyl)-4-isopropylylquinazoline (16b)

Compound **7d** was prepared by the same procedure as described for **7a** (Route D) on a 10 mmol scale using α,α-dimethyl-*N*-(2-cyanophenyl)-β-lactam (**15**) and isopropyl magnesium bromide (20 mmol) to give 1.71 g (70%) of **7d** as a crystalline solid, mp 117–118 °C, Ir ν_{max}: 3318, 2973, 2935, 1660, 1529, 1486, 1196, 1162, 973, 736 cm^{-1}; δ_H: 1.14 (6H, s), 1.16–1.22 (6H, m), 2.69 (1H, dd, *J* 14.7 and 7.3), 3.26 (1H, m), 3.47 (1H, dd, *J* 14.7 and 7.3), 7.02–7.08 (1H, m)), 6.66–6.68 (1H, m), 6.59–6.64 (1H, m), 6.49–6.53 (1H, m), 7.20–7.23 (1H, m); δ_C: 20.0 (q), 21.7 (q), 22.2 (q), 25.8 (q), 35.5 (d), 38.0 (t), 52.1 (s), 115.1 (d), 116.5 (s), 117.4 (d), 129.1 (d), 130.8 (d), 145.0 (s), 171.7 (s), 191.4 (s).

Alternatively, **7d** could be obtained *via* Route C according to the procedure described for **7a** on a 5 mmol scale using 3-chloro-*N*-(2-cyanophenyl)-2-methanbutanamide **8** and isopropyl magnesium bromide (12.5 mmol). Evaporation gave a yellow oil which was purified by flushing through a short silica plug, EtOAc:heptane (1:4), gave 0.49 g (40%) of **7d** as a yellow crystalline solid. **16b** was also isolated as a pale yellow oil. Yield: 0.33 g (25%); Ir ν_{max}: 2968, 2864, 1614, 1556, 1494, 1389, 1336, 1188, 1108, 926, 762 cm^{-1}; δ_H: 1.33 (6H, d, *J 6.8*), 1.48 (6H, s), 3.94–4.03 (1H, m), 4.11 (2H, s), 7.65–7.70 (1H, m), 7.92–7.94 (2H, m), 8.30–8.33 (1H, m); δ_C: 21.6 (q), 25.0 (q), 30.2 (d), 44.4 (t), 54.8 (s), 120.5 (s), 124.4 (d), 128.6 (d), 127.1 (d), 133.5 (d), 149.6 (s), 168.0 (s), 175.0 (s).

6-Propyl-3,3-dimethyl-1,2,3,4-tetrahydro-1, 5-benzodiazocin-4-one (7e)

Compound **7e** was prepared by the same procedure as described for **7a** (Route D) on a 10 mmol scale using α,α-dimethyl-*N*-(2-cyanophenyl)-β-lactam (**15**) and propyl magnesium bromide (20 mmol) to give 1.78 g (73%) of **7e** as a colourless crystalline solid, mp 111–112 °C; Ir ν_{max}: 3323, 2923, 2866, 1655, 1598, 1491, 1334, 1197, 1154, 978, 836, 762, 744 cm^{-1}; δ_H: 0.97–1.02 (3H, m), 1.13 (6H, s), 1.25–1.06 (m, 1H), 1.59–1.69 (2H, m),2.73–2.28 (3H, m), 3.45 (1H, dd, *J* 14.62 and 6.92), 6.48–6.53 (1H, m), 6.58–6.61 (1H, m), 6.68–6.71 (1H, m), 7.01–7.08 (1H, m), 7.23 (1H, m); δ_C:13.7 (q), 19.86 (t), 21.8 (q), 25.7 (q), 37.8 (t), 40.3 (t), 52.3 (s), 115.2 (d), 116.8 (s), 117.5 (d), 129.6 (d), 130.9 (d), 144.9 (s), 166.9 (s), 191.1 (s).

Alternatively, **7e** could be obtained *via* Route C according to the procedure described for **7a** on a 5 mmol scale using 3-chloro-*N*-(2-cyanophenyl)-2-methanbutanamide **8** and propyl magnesium bromide (12.5 mmol). Evaporation gave a yellow oil which was purified by flushing through a short silica plug, EtOAc:heptane (1:4), gave 0.51 g (42%) of **7e** as a crystalline solid.

6-Ethyl-3,3-dimethyl-1,2,3,4-tetrahydro-1, 5-benzodiazocin-4-one (7f)

Compound **7f** was prepared by the same procedure as described for **7a** (Route D) on a 10 mmol scale using α,α-dimethyl-*N*-(2-cyanophenyl)-β-lactam (**15**) and ethyl magnesium bromide (20 mmol) to give 1.96 g (85%) of **7f** as a pale yellow crystalline solid, mp 166 °C; Ir ν_{max}: 3367, 2970, 1673, 1650, 1602, 1492, 1385, 1334, 1197, 1020, 955, 751 cm^{-1}; δ_H:1.13–1.18 (9H, m), 2.78–2.95 (3H, m), 3.46 (1H, dd, *J* 14.7 and 6.8), 6.50–6.54 (1H, m), 6.60–6.62 (1H, m), 6.67–6.72 (1H, m), 7.03–7.08 (1H, m), 7.24–7.27 (1H, m); δ_C:11.2 (q), 21.8 (q), 25.8 (q), 31.4 (t), 37.9 (t), 52.4 (s), 115.2 (d), 116.8 (s), 117.4 (d), 129.5 (d), 130.9 (d), 145.0 (s), 167.8 (s), 191.1 (s).

Alternatively, **7f** could be obtained *via* Route C according to the procedure described for **7a** on a 5 mmol scale using 3-chloro-*N*-(2-cyanophenyl)-2-methanbutanamide **8** and ethyl magnesium bromide (12.5 mmol). Evaporation gave a yellow oil which was purified by flushing through a short silica plug, EtOAc:heptane

(1:4), gave 0.48 g (42%) of **7f** as a pale yellow solid. The structure of this compound has been established by X-ray chrystallagrophy.[14]

6-Methyl-3,3-dimethyl-1,2,3,4-tetrahydro-1, 5-benzodiazocin-4-one (7g)

Compound **7g** was prepared by the same procedure as described for **7a** (Route D) on a 10 mmol scale using α,α-dimethyl-*N*-(2-cyanophenyl)-β-lactam (**15**) and methyl magnesium bromide (20 mmol) to give 0.84 g (39%) of **7g** as a solid, mp 218 °C, (Found C, 72.28; H, 7.42; N, 13.03 $C_{13}H_{16}N_2O$ required C, 72.19; H, 7.46; N, 12.95%); Ir ν_{max}: 3363, 2970, 1675, 1660, 1601, 1489, 1335, 1220, 1146, 962, 747 cm^{-1}; δ_H: 1.14 (6H, m), 2.24–2.05 (3H, m; appear at 2.55 in $CDCl_3$ (3H, s)), 2.86 (1H, dd, *J* 7.2), 3.52 (1H, dd, *J* 6.8), 6.49–6.54 (1H, m), 6.59–6.62 (1H, m), 6.71–6.75 (1H, m), 7.03–7.09 (1H, m), 7.38–7.31 (1H, m); δ_C : 22.0 (q), 25.6 (q), 26.7 (q), 37.7 (t), 52.5 (s), 115.2 (d), 116.8 (s), 117.4 (d), 130.0 (d), 131.1 (d), 145.1 (s), 163.5 (s), 190.4 (s).

Alternatively, **7g** could be obtained *via* Route C according to the procedure described for **7a** on a 5 mmol scale using 3-chloro-*N*-(2-cyanophenyl)-2-methanbutanamide **8** and methyl magnesium bromide (12.5 mmol). Evaporation gave a yellow oil which was purified by flushing through a short silica plug, EtOAc:heptane (1:4), gave 0.30 g (28%) of **7g** as a yellow crystalline solid.

4,4-Dibutyl-3,4-dihydroquinazoline (17a)

To a solution of 3-chloro-*N*-(2-cyanophenyl)-2-methanbutanamide **8** (1.36 g, 5.8 mmol) in THF (50 mL), BuLi (18.1 mL, 29 mmol) was added at −78 °C. The temperature was slowly allowed to rise until room temperature was reached (~30 min). After stirring for 1.5 h aqueous NH_4Cl (15 mL, 20%) was carefully added and a white solid appeared. The reaction mixture was allowed to stir for a few minutes and thereafter the solid material was filtered off to give of **17a**. Additional white material (**17a**) appeared in the filtrate, which was collected after a few hours to give a total of 0.91 g (61%) of **17a**. The product could be recrystallised from ethanol to give white needles, mp: 179 °C; IR ν_{max}: 3211, 3116, 3068, 2956, 2930, 2859, 1685 cm^{-1}; δ_H: 0.74–0.79 (6H, m), 0.88–0.90 (2H, m), 1.13–1.25 (6H, m), 1.52–155 (2H, m), 1.72–1.77 (2H, m), 6.62 (1H, s), 6.69–6.72 (1H, m), 6.81–6.85 (1H, m), 7.02–7.06 (2H, m), 8.89 (1H, s); δ_C: 14.0 (q), 22.3 (t), 25.7 (t), 43.1 (t), 60.5 (s), 113.4 (d), 120.9 (d), 122.6 (s), 124.7 (d), 127.3 (d), 138.0 (s), 153.2 (s).

4,4-Diphenyl-3,4-dihydroquinazoline (17b)

Compound **17b** was prepared according to the procedure described for **17a** on a 5 mmol scale using appropriate amount of reagents and solvents. 0.95 g (63%) of **17b** was filtered off as a white solid, mp 276 °C (ethanol), IR ν_{max}: 3335, 3191, 3055, 2969, 1669, 1599, 1446, 1416, 1262, 750, 696 cm^{-1}; δ_H: 6.46–6.47 (m, 1H), 6.82–6.90 (m, 2H), 7.11–7.21 (m, 5H), 7.27–7.35 (m, 6H), 8.14 (s, 1H), 9.38 (s, 1H); δ_C: 66.2 (s), 114.0 (d), 120.6 (d), 125.4 (s), 127.2 (d), 127.4 (d), 127.8 (d), 128.0 (d), 128.1 (d), 137.3 (s), 145.0 (s), 154.1 (s). Compound **17b** could be alternatively obtained from reaction of NaOCN with *o*-amino-triphenylcarbinol (**18**): NaOCN (0.65 g, 10 mmol) was dissolved in a hot solution of acetic acid and water (2:1) (20 mL) and added to *o*-amino-triphenylcarbinol (2.75 g, 10 mmol) in 100 mL acetic acid and water (2:1). After stirring at 60 °C for 3 h solid material was filtered off to afford **17b** as a white solid. Yield: 1.35 g (4.5 mmol, 45%).

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