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Ring forming reactions of imines of 2-aminobenzaldehyde and related compounds

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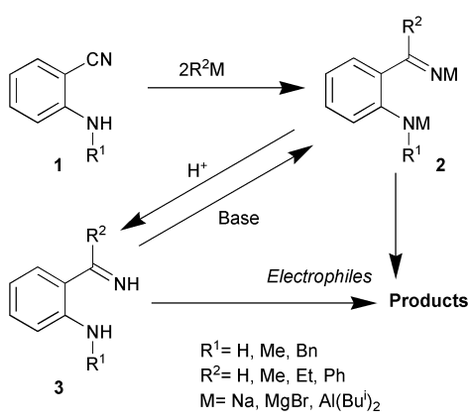
By addition of organometallic reagents to 2-aminobenzonitriles followed by quenching with suitable electrophiles (acyl halides, aldehydes and ketones), several types of 6-membered benzofused aromatic and non-aromatic nitrogen heterocycles could be obtained. Rearrangements leading to 1,2-dihydro-3*H*-1,4-benzodiazepin-3-ones and preparation of various quinazolines are described.

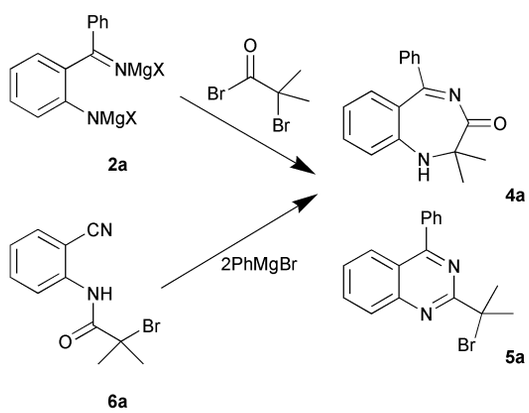
Introduction

In this paper we report a study on the reactivity and synthetic usefulness of the dianions **2** and the corresponding acids **3** (Scheme 1). When treated with certain electrophiles, these gave a variety of benzofused 6- and 7-membered cyclic products.



Scheme 1

It has previously been shown that compound **4a**, a rare example of a 1,4-benzodiazepine-3-one (isolated as two separate solid state conformers, the structures of which were determined by X-ray crystallography), together with the quinazoline **5a**, can result from treatment of anthranilonitrile (2-aminobenzonitrile) with two equivalents of a Grignard reagent, followed by addition of 2-bromoisobutyryl bromide (Scheme 2).[1] Alternatively, the preformed amide **6a** could be treated with a Grignard reagent to give similar results.



Scheme 2

These intriguing products combined with the potential synthetic usefulness of the difunctional structures **2** and **3**, has prompted us to investigate these systems and their reactions in more detail.

Results and discussion

As a starting point in the investigation of the nucleophilic properties of species of type **2** and **3**, the dianion **2a** and the corresponding 2-aminobenzophenone imine **3a** [2-(iminophenylmethyl)benzene amine] were reacted with various electrophiles. These specific derivatives were chosen because 2-aminobenzophenone imine (**3a**) is readily available and described in the literature.[2] In general, imines which have a hydrogen atom on the nitrogen are very susceptible to hydrolysis to the corresponding ketone and are therefore not easy to isolate. Thorough studies on the rate of such hydrolyses have been published.[3,4]

Dianions of type **2** are formed after addition of two equivalents of a metalating reagent to the corresponding anthranilonitrile in THF or diethyl ether solution. In some cases the imine anion can be carefully protonated to the imine and isolated as such (*vide supra*). Addition of PhMgBr to the nitrile functionality is preferably performed in THF, whereas addition of metal alkyls works best in ether. Attempts to add MeMgI or MeLi to anthranilonitriles invariably failed, *i.e.* after addition of an electrophile the nitrile function was always intact. Copper (I) is known to catalyse the addition of Grignard reagents to nitriles,[5] but addition of CuBr did not change the outcome. As Couture *et al.* have reported, other metal alkyl reagents readily add to N-substituted anthranilonitriles.[6]

Reactions with acylating agents

The initial reaction of the dianions **2** with acyl halides is of course very fast because of the high intrinsic reactivity of the reagents. Due to the difunctional nature of **2**, this initial reaction seems inevitably to be followed by a favoured ring-closure (6-*exo*-trig) to the six-membered ring of the intermediate anion **7** (Scheme 3). It does not matter which nitrogen atom reacts first as both reaction paths will lead to the same charged intermediate. It seems reasonable to assume that the charge resides to a significant degree on the exocyclic oxygen, rather that on the nitrogen (even/also when R^1 = H), because of the much lower basicity of the aliphatic alkoxide compared with the anilinic amine anion. This reasoning is based on our collected experience with these systems, and serves as a working model to explain the outcome of the reactions. The fate of the

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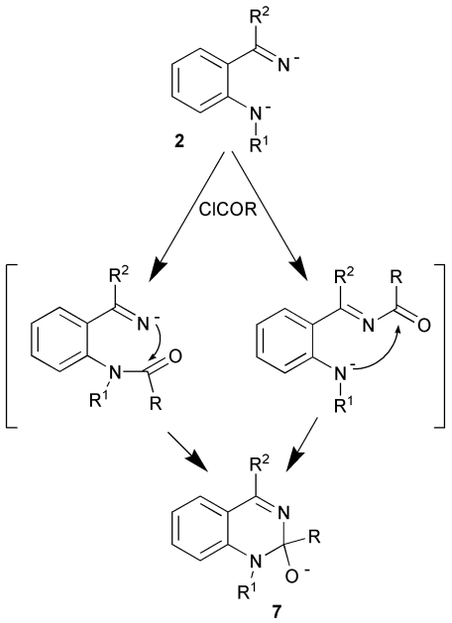


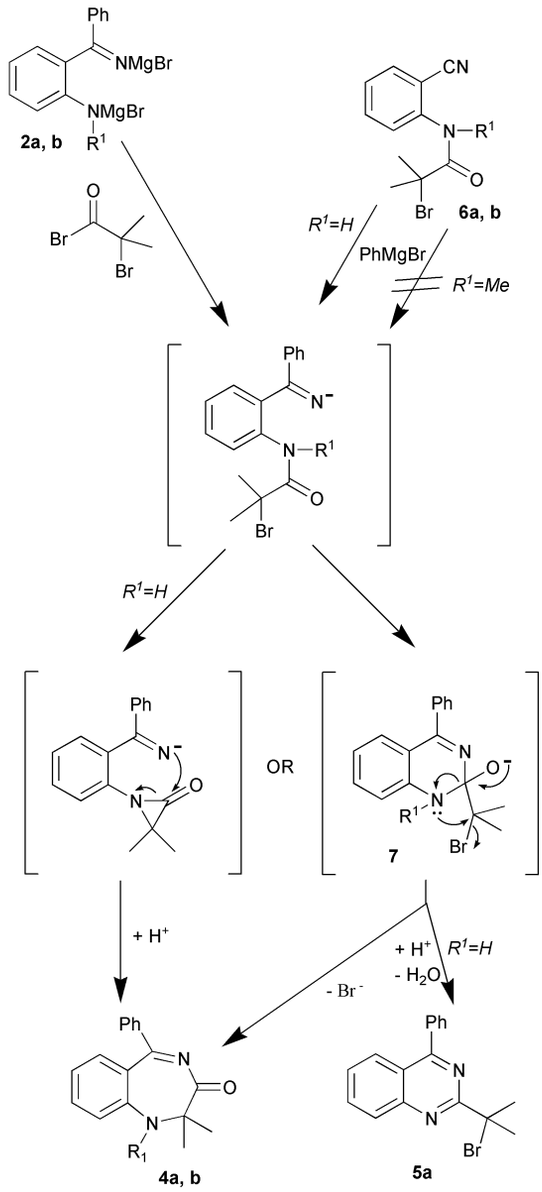
Scheme 3

intermediate **7** depends on the nature of the exocyclic substituent R and the reaction conditions at large. If R^1 = H, protonation and elimination of water will lead to formation of an aromatic quinazoline. There are several recent reports on synthesis of various quinazolines and quinazolinones from anthranilonitrile. Among these are 4-aminoquinazolines,[7–10] 3,4-dihydro-4-thioxo-2(1*H*)-quinazolinones (2-hydroxy-4-mercaptoquinazolines),[11–13] 2,4(1*H*,3*H*)-quinazolinediones (2,4-dihydroxyquinazolines) and 4-bromo-2-(chloromethyl)-quinazoline.[14]

Reactions with 2-haloacyl halides

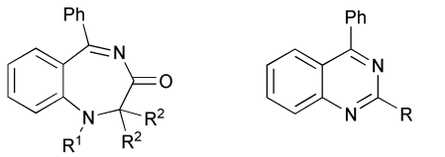
The reaction of **2a** with 2-bromoisobutyryl bromide has been reported.[1] This reaction, for which a full preparative procedure appears in this paper, yields 1,2-dihydro-2,2-dimethyl-5-phenyl-3*H*-1,4-benzodiazepin-3-one (**4a**) and a small amount of 2-(1-bromo-1-methylethyl)-4-phenylquinazoline (**5a**) (Scheme 2). The former is to our knowledge the only 1,4-benzodiazepine-3-one for which a synthesis has been reported. It has the rather unusual property of having two distinguishable and reasonably stable solid-state ring-conformers (structural elucidation of these were performed by X-ray crystallography).[1]

It was initially discovered that **6a** when treated with PhMgBr gave **4a**. In this case it is apparent that a rearrangement must be involved because the acyl function appears next to the imino nitrogen of the product. Later it was found that the same product arose if anthranilonitrile was first treated with PhMgBr, and then with the acyl bromide (Scheme 4). It is reasonable to assume that this unusual product is not formed through two completely different mechanisms, and that a common intermediate of type **7** (Scheme 3) is involved. In the original paper a possible rearrangement mechanism was put forth involving formation of an aziridinone which would be nucleophilically opened to form the product. We now propose another mechanism in which a six-membered ring expands to form the seven-membered ring of the product (Scheme 4). The latter mechanism would also explain the formation of the halomethylquinazoline **5a** by protonation and elimination of water. Therefore, according to the principle of Occam's razor, one should choose the second proposal. Could a rearranged product be isolated from a reaction with a dianion derived from *N*-methylanthranilonitrile, it would certainly be more tangible evidence that this assumed mechanism is correct. In that case, intermediate formation of a three-membered ring (with a



Scheme 4

neutral nitrogen) is not possible. Methylation of anthranilonitrile was performed according to the literature,[15] and the subsequent reaction did indeed give 1,2,2-trimethyl-5-phenyl-3*H*-1,4-benzodiazepin-3-one (**4b**) (the structure was confirmed by methylation of **4a**). Hence the conclusion that ring-expansion is part of the mechanism. Formation of an intermediate oxirane can of course not be ruled out. This picture is somewhat clouded by the fact that treatment of the N-methylated preformed amide **6b** with PhMgBr failed to give the benzodiazepine, possibly because of attack on the amide followed by degradation of the system. Curiously it also appears that only tertiary haloacyl halides will give the 7-membered ring, possibly an indication that the ring-expanding substitution must be preceded by ionisation (S_N1). A hypothetical intermediate oxirane would also be more stabilised were it more heavily substituted. This reasoning is based on the fact that **4a** was isolated in high yield, whereas no 7-membered ring could be identified in the complex reaction mixture after reaction of **2a** with 2-bromopropionyl bromide (a methyl group less). In contrast, the *gem*-diethyl substituted compound **4c** could prepared in low yield, showing more generality of the reaction with tertiary haloacyl halides (Fig. 1). The IR-spectra of the *gem*-dimethyl compound **4a** and that of the *gem*-diethyl compound **4c** are almost identical with absorption peaks at 3299/3299, 1682/1684, 1612/1624 cm^{-1} respectively.



4a R^1=H, R^2=Me
b R^1, R^2=Me
c R^1=H, R^2=Et

5a R=$CBr(CH_3)_2$
b R=CH_2Cl
c R=$CHCl_2$

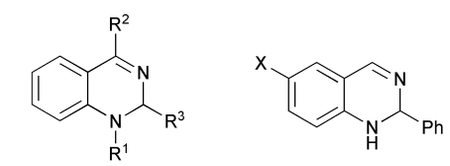
Fig. 1 Products from reactions with acyl halides.

Reaction of **2a** with chloroacetyl chloride gave the chloromethylquinazoline **5b**, a better yield of which was isolated after addition of solid NH_4Cl prior to addition of the acid chloride. The dichloromethyl compound **5c** could be prepared similarly. A two-step procedure to such compounds, which is in principle the same reaction, has been reported.[16] A very clean reaction leading to **5b** is deprotonation of the imine **3a** with sodium hydride in THF, followed by treatment with chloroacetyl chloride. Reaction of these two substrates without any added base, or under acidic conditions (dioxane saturated with HCl), also led to the same product, demonstrating the great stability of the six-membered intermediate and product. The dichloromethyl quinazoline **5c** showed a remarkable resilience to hydrolysis and the corresponding formylquinazoline could not be obtained.

In reactions of N1-blocked/protected **2** with haloacyl halides, there is as we have seen no possibility for formation of the usual 6-membered aromatic product. However, metalation of *N*-methyl- or *N*-benzylanthranilonitrile, followed by treatment with acetyl chloride, gave very complex reaction mixtures.

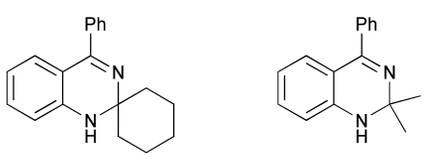
Reactions with aldehydes and ketones

In reactions of amino dianions **2** with aldehydes, 1,2-dihydroquinazolines are formed *via* a presumed initial formation of an imine, exemplified by compounds **8a** and **8b** (Fig. 2). The



8a R^1=H, R^2=Ph, R^3=Et
8b R^1=Bn, R^2=Et, R^3=Me

9a X=H
9b X=Br



10a

10b

Fig. 2 Products from reactions with aldehydes and ketones.

corresponding stepwise reaction, involving isolation of the 2-iminobenzonitrile followed by addition to the nitrile, has been described[16] and debated.[17] The precursor of **8b**, *i.e.* N-benzylated anthranilonitrile, 2-[(phenylmethyl)amino]-benzonitrile (**1a**), could be prepared in a fast one-pot procedure by reductive alkylation in 95% yield.

Treatment of anthranilonitrile with two equivalents of DIBAL-H reduces the nitrile functionality to an imine anion. Capture with benzaldehyde led to the formation of 1,2-dihydroquinazolines **9**. The highest yields were obtained when two equivalents of DIBAL-H were used, the assumption being that the first equivalent functions as base. Both less and more DIBAL-H diminished the yield drastically. In work-up of these reactions there were initially problems due to formation of strong aluminium complexes, but it was subsequently discovered that aqueous base could dissolve these. After extraction with an organic solvent, it also proved possible to extract the products with aqueous acid (HCl), leaving unwanted organic matter in the organic phase. Neutralisation of the acidic solutions afforded the products. This procedure does not give excellent yields, but its simplicity and the fact that it does give access to an unusual set of compounds, speaks in its favour. After attempted recrystallisation of **9a** in hot hexane, the known[18,19] fully aromatic 2-phenylquinazoline was recovered, demonstrating the ease of oxidation (dehydrogenation) of these compounds.

Synthesis of the interesting spiro compound **10a** has been published,[16] but without experimental details and a very low yield. It was discovered that for reaction of **2a** with ketones it is beneficial to treat the dianion with two equivalents of ammonium chloride (added as a solid to the THF-solution), protonating the amine and the imine, prior to addition of the ketone. Using this new procedure in conjunction with the acidic extraction used for purification of the compounds **9**, it proved possible to isolate **10a** in 70% yield without need for any chromatography after reaction with cyclohexanone. Similarly, reaction with acetone afforded the *gem*-dimethyl compound **10b**. The ease of protonation of the compounds **10** was somewhat surprising as 5% citric acid could be used for the extraction.

There is a published stepwise procedure from anthranilonitrile to 2,2-diaryl substituted 1,2-dihydroquinazolines,[20] as well as a mass spectrometric study of these compounds.[21] These products can formally be derived from a dianion of type **2** and an appropriate ketone. However, benzophenone was found to be too unreactive (hindered) to be used in this context.

Conclusions

Addition of organometallic reagents to 2-aminobenzonitriles, followed by capture of the dianion with electrophiles (acyl halides, aldehydes and ketones), is a preparatively useful route to various quinazolines. The quinazoline skeleton appears in alkaloids[22–25] and in medicinal derivatives such as prazozin (antihypertensive α_1-adrenoreceptor antagonist)[26,27] and methaqualone (sedative).[28]

Using variants on the synthetic scheme described in this paper, quinazolines or 1,2-dihydroquinazolines substituted in position 2 with alkyl or aryl groups can be obtained. Earlier work has shown that other electrophiles can be utilized to gain access to *e.g.* 2-quinazolinones.[16] Because of the apparent inability for addition of alkyl metal reagents to N-unsubstituted anthranilonitriles, direct access to aromatic quinazolines is limited to those with an aryl substituent at position 4. However, treatment of anthranilonitriles with DIBAL-H, followed by capture of the dianion with an aldehyde, provides access to 4-unsubstituted quinazolines after oxidation to the aromatic system. We have also shown that addition of alkyl metal reagents to N-substituted anthranilonitriles, followed by reaction with aldehydes, is a feasible route to the corresponding 1,2-dihydroquinazolines. This provides a route to 4-alkyl-1,2-dihydroquinazolines, and opens access to the aromatic systems by deprotection of N1.

When tertiary haloacyl halides were added to the 2-aminobenzophenone dianions **2**, 1,2-dihydro-3*H*-1,4-benzodiazepin-3-ones were formed. These compounds are unusual,[29] despite the close structural similarity with the common 1,2-dihydro-3*H*-1,4-benzodiazepin-2-ones. The mechanism of formation appears to involve ring-expansion from a 6-membered ring.

Experimental

All starting materials and solvents (PA grade) are commercially available and used without further purification. THF was dried over sodium.

NMR spectra were recorded on a Bruker DPX 300 (^{1}H 300 MHz, ^{13}C 75 MHz) in DMSO-D_6, using the solvent peak as reference (^{1}H 2.50 ppm, ^{13}C 39.51 ppm). Coupling constants (J) are given in Hz. IR spectra were recorded on a Perkin–Elmer 1600 FT-IR on KBr-tablets. HRMS-determinations (FAB) were performed by Einar Nilsson, University of Lund, Sweden. Elemental analyses were performed by H. Kolbe Mikroanalytisches Laboratorium, Mülheim an der Ruhr, Germany. Melting points were determined on a Reichert Kofler hot stage.

2-[(Phenylmethyl)amino]benzonitrile (1a)

Anthranilonitrile (5.90 g, 50.0 mmol) was dissolved in 50 mL AcOH. Benzaldehyde (6.5 mL, 64 mmol) was added and the reaction stirred at rt for 30 min. The reaction flask was immersed in ice and $NaBH_4$ (2.0 g, 52 mmol) was added in portions. A vigorous exothermic reaction followed on each addition. On cooling a thick precipitate formed. After addition of 100 mL water, the product was filtered off and dried to yield 9.89 g (47.5 mmol, 95%) white powder, mp 118 °C (lit.[30] mp 117–118 °C).

General procedure for preparation of 5.0 mmol 2-amino-benzoimine dianions 2

To a slowly stirred solution of 10.8 mmol Grignard reagent in 10–20 mL THF or Et_2O (THF for aryl reagents, Et_2O for alkyl reagents) the nitrile (5.0 mmol) was added in portions as a solid (the condenser removed). CAUTION! May react violently! The dianion was allowed to fully form during 15 min of reflux. To form **2a**, anthranilonitrile (0.59 g, 5.00 mmol) was treated with 10.8 mmol PhMgBr in 10–20 mL THF.

2-Aminobenzophenone imine (3a)

Dianion **2a** (40 mmol from 4.72 g anthranilonitrile and PhMgBr) in 45 mL THF at 25 °C was quenched with 50 mL sat. NH_4Cl. The phases were separated and the aqueous phase extracted with 2 × 50 mL Et_2O. The combined organic phases were washed with 2 × 20 mL water, 20 mL brine and dried (Na_2SO_4). Evaporation of the solvent yielded an oil which slowly solidified over several days at −15 °C. Hexane was added and the solid cake crushed to small pieces. The solid material was filtered off and washed with two portions of hexane to give 6.08 g (31 mmol, 77%) yellow crystalline material, mp. 45 °C (lit.[2] mp 48 °C from diisopropylether).

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

To a 20 mL THF-solution of 5.0 mmol **2a**, 2-bromoisobutyryl bromide (0.94 mL, 7.5 mmol) was added in portions. The reaction mixture was refluxed for 3 h and then poured into 25 mL 10% NH_4Cl. The organic layer was separated off and the aqueous layer extracted with 2 × 50 mL Et_2O. The combined organic layers were capped and left overnight, after which fine needles could be filtered off. More material precipitated from the filtrate on addition of hexane to a total of 0.93 g **4a** (3.5 mmol, 70%) yellow fine needles, mp 197 °C. This compound exists as two different conformers in the solid state, the structure of which have previously been determined by X-ray crystallography;[1] IR ν_{max}: 3299, 2991, 1682, 1612, 1596, 1571, 1449, 1324, 1252, 1161, 1102, 954, 918, 769, 696, 640 cm^{-1}; δ_H: 1.29 (6 H, s), 6.72 (1 H, t, J 7.4), 6.74–7.19 (2 H, m), 7.28 (1 H, br s), 7.38 (1 H, t, J 7.4), 7.50–7.61 (5 H, 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 remaining filtrate was filtered through a short silica plug and concentrated. On addition of more hexane, a precipitate of **5a** formed and was filtered off. Yield 0.120 g (0.37 mmol, 3.4%) powder, mp 136 °C. The material could be recrystallised from EtOH to yield white needles, mp 137 °C (Found C, 62.51; H, 4.57; N, 8.53. $C_{17}H_{15}BrN_2$ requires C, 62.40; H, 4.62; N, 8.56%); IR ν_{max}: 1608, 1561, 1541, 1485, 1464, 1390, 1332, 1164, 1096, 782, 701, 622, 596, 522 cm^{-1}; δ_H: 2.23 (6 H, s), 7.63–7.68 (3 H, m), 7.74–7.79 (1 H, m), 7.82–7.86 (2 H, m), 8.03–8.14 (3 H, 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)

1,2-Dihydro-1,2,2-trimethyl-5-phenyl-3*H*-1,4-benzodiazepin-3-one (4b)

To a 20 mL THF-solution of 5.0 mmol **2b** (from *N*-methyl-anthranilonitrile and PhMgBr according to the general procedure) cooled to 0 °C, 2-bromoisobutyryl bromide (0.94 mL, 7.5 mmol) was added during 5 min. The colour changed from deep black–brown to yellowish orange. On stirring for 1 h at 0 °C a precipitate (of salt) was formed. The reaction mixture was poured into 25 mL 10% NH_4Cl. The organic layer was separated off and the aqueous layer extracted with 3 × 50 mL Et_2O. The combined organic layers were washed with 3 × 25 mL water, 25 mL brine, dried (Na_2SO_4) and the solvent evaporated. The main component (on TLC) of the residue was purified on a silica column by elution with 0–15% Et_2O in hexane to afford 0.75 g (2.7 mmol, 54%) light yellow solid, mp 112 °C (from Et_2O) (Found C, 77.76; H, 6.46; N, 10.02. $C_{18}H_{18}N_2O$ requires C, 77.67; H, 6.52; N, 10.06 %); IR ν_{max}: 3045–2819, 1708, 1618, 1576, 1565, 1476, 1458, 1446, 1322, 1241, 1094, 778, 702, 574 cm^{-1}; δ_H: 1.32 (6 H, s), 2.74 (3 H, s), 7.15–7.17 (2 H, m), 7.30 (1 H, d, J 7.9), 7.48–7.55 (3H, m), 7.59–7.61 (3H, m); δ_C: 20.5 (q), 32.9 (q), 76.7 (s), 122.8 (d), 128.7 (d), 129.4 (d), 129.4 (d), 131.6 (d), 131.8 (s), 132.1 (d), 135.9 (s), 151.1 (s), 167.2 (s), 191.7 (s).

Compound **4b** was also obtained by methylation of **4a**: compound **4a** (1.32 g, 5.00 mmol) in 15 mL DMF was treated with 60% NaH (0.21 g, 5.3 mmol). To the dark orange solution (formed after a few minutes) MeI (0.47 mL, 7.5 mmol) was added, and the reaction mixture stirred for 30 min. The yellow solution was poured into 60 mL water and left overnight, followed by extraction with 3 × 50 mL Et_2O. The combined ether layers were washed with 3 × 25 mL water, 25 mL brine, dried (Na_2SO_4) and the solvent evaporated to yield a yellow oil. The oil was dissolved in 25 mL Et_2O and filtered through a plug of silica. Slow evaporation of the solvent left 0.49 g (1.8 mmol, 35%) light yellow crystalline material, which was identified as **4b** (IR and TLC).

1,2-Dihydro-2,2-diethyl-5-phenyl-3*H*-1,4-benzodiazepin-3-one (4c)

To a 20 mL THF-solution of 5.0 mmol **2a**, 2-bromo-2-ethylbutyryl bromide (1.15 mL, 7.5 mmol) was added. The reaction mixture was refluxed for 3 h and then poured into 25 mL 10% NH_4Cl. The organic layer was separated off and the aqueous layer extracted with 2 × 50 mL Et_2O. The combined organic layers were washed with 50 mL water, 50 mL brine, dried (Na_2SO_4) and evaporated to a yellow oil, which was purified through a short silica column with hexane, hexane–diisopropyl ether and finally Et_2O. The final eluent portion contained the product. Evaporation of the solvent afforded the product which was recrystallised from diisopropyl ether to yield 0.16 g (0.55 mmol, 11%) yellow needles, mp 170 °C (Found C, 78.12; H, 6.85; N, 9.53. $C_{19}H_{20}N_2O$ requires C, 78.05; H 6.89; N 9.58%); IR ν_{max}: 3299, 2964, 2934, 1685, 1624, 1575, 1558, 1475, 1456, 1326, 1244, 756, 694, 637 cm^{-1}; δ_H: 0.84 (6 H, t, J 7.3), 1.63 (4 H, m), 6.71 (1 H, dt, J 0.7, 7.5), 6.93 (1 H, br s), 7.16 (2 H, m), 7.36 (1 H, dt, J 1.3, 7.7), 7.46–7.60 (5 H, m); δ_C: 7.6 (q), 25.0 (t), 69.8

(s), 116.7 (d), 118.1 (s), 120.4 (d), 128.4 (d), 129.4 (d), 130.7 (d), 132.5 (d), 132.7 (d), 138.7 (s), 147.3 (s), 165.7 (s), 174.1 (s).

2-(Chloromethyl)-4-phenylquinazoline (5b)

To a 10 mL THF solution of 5.0 mmol **2a**, solid NH_4Cl (0.27 g, 5.0 mmol) was added. The mixture was refluxed 5 min. The flask was raised from the oil-bath and chloroacetyl chloride (0.60 mL, 7.5 mmol) was added dropwise. After yet another reflux period of 15 min, 50 mL water was added. After a few minutes the liquid was decanted off and extracted with 2 × 20 mL EtOAc which was then added to the solid residue. The solvent was evaporated. The red residue was recrystallised from 95% EtOH to yield 0.78 g (3.2 mmol, 64%) beige needles, mp 128 °C (Found C, 70.59; H, 4.30; N, 10.88. $C_{15}H_{11}ClN_2$ requires C, 70.73; H, 4.35; N, 11.00%); IR ν_{max}: 3026, 2966, 1611, 1561, 1539, 1486, 1442, 1383, 1347, 1270, 840, 772, 700, 622 cm^{-1}; δ_H: 5.00 (2 H, s), 7.52–7.65 (3 H, m), 7.78–7.81 (3 H, m), 8.08–8.11 (3 H, m); δ_C: 47.8 (t), 121.0 (s), 126.9 (d), 128.3 (d), 128.7 (d), 128.8 (d), 130.0 (d), 130.3 (d), 134.7 (d), 136.3 (s), 150.7 (s) 160.9 (s), 168.7 (s).

2-(Dichloromethyl)-4-phenylquinazoline (5c)

To a 20 mL THF solution of 5.0 mmol **2a**, solid NH_4Cl (0.54 g, 10 mmol) was added. The mixture was refluxed 5 min. The flask was raised from the oil-bath and dichloroacetyl chloride (0.72 mL, 7.5 mmol) was added dropwise. After 30 min. the solvent was evaporated *in vacuo*. The residue was dissolved in 10 mL water and 40 mL 95% EtOH by heating. On slow cooling fine needles formed and was filtered off to yield 0.46 g (1.6 mmol, 32%) off-white needles, mp 185 °C (lit.[31] mp 185 °C); IR ν_{max}: 2997, 1611, 1567, 1537, 1487, 1385, 793, 771, 702, 685, 626 cm^{-1}; δ_H: 7.55 (1 H, s), 7.66–7.68 (3 H, m), 7.84–7.86 (3 H, m), 8.15–8.17 (3 H, m); δ_C: 72.1 (d), 121.5 (s), 127.1 (d), 128.6 (d), 128.7 (d), 129.7 (d), 130.1 (d), 130.5 (d), 135.2 (d), 136.0 (s), 150.2 (s), 160.1 (s), 169.6 (s).

2-Bromo-*N*-methyl-*N*-(2-cyanophenyl)-2-methylpropanamide (6b)

2-Bromoisobutyryl bromide (3.0 mL, 24 mmol) was added dropwise to *N*-methylanthranilonitrile (1.32 g, 10.0 mmol) and 3.0 mL pyridine in 50 mL Et_2O. After stirring of the reaction mixture for 16 h, it was poured into 100 mL water. The layers were separated and the aqueous layer extracted with 50 mL Et_2O. The combined organic layers were washed with 3 × 25 mL water and 50 mL brine, dried (Na_2SO_4) and evaporated to yield an oil which crystallised several hours after addition of hexane. The solid was filtered off and washed with several portions of hexane to yield 2.09 g (7.46 mmol, 75%) of a crystalline material, mp 70 °C (from hexane–2-propanol) (Found C, 51.34; H, 4.73; N, 9.95. $C_{12}H_{13}BrN_2O$ requires C, 51.26; H, 4.66; N, 9.96%); IR ν_{max}: 3076–2925, 2230, 1644, 1596, 1486, 1449, 1359, 1092, 773, 749, 620, 553, 481 cm^{-1}; δ_H: 1.88 (6 H, s), 3.45 (3 H, s), 7.57 (1 H, t, *J* 7.8), 7.65 (1 H, d, *J* 7.9), 7.81 (1 H, dt, *J* 1.4 and 7.9), 7.94 (1 H, dd, *J* 1.2 and 7.8); δ_H: 32.1 (q), 40.7 (q, CH_3), 57.8 (s), 116.2 (s), 128.7 (d), 129.4 (d), 133.6 (d), 134.5 (d), 146.7 (s), 169.5 (s)

1,2-Dihydro-2-ethyl-4-phenylquinazoline (8a)

To 4.0 mmol of dianion **2a** in 10 mL THF, propionaldehyde (0.57 mL, 8.0 mmol) was added, and the reaction mixture was refluxed 2 h. After cooling to rt, 10 mL 10% NH_4Cl was added, followed by extraction with 3 × 20 mL Et_2O. The combined ethereal layers were washed with 3 × 10 mL water and 20 mL brine, dried (Na_2SO_4) and evaporated to a yellow oil. The yellow product was purified by column chromatography on silica with 0–25% Et_2O in hexane to yield 0.45 g semisolid material which could be crystallised from hexane to yield 0.30 g (1.3 mmol, 33%) yellow crystalline material, mp 99.5 °C (Found C, 81.33; H, 6.50; N, 11.78. $C_{16}H_{16}N_2$ requires C, 81.32; H, 6.82; N, 11.85%); IR ν_{max}: 3258, 3055, 2957–2870, 1619, 1563, 1487, 1341, 1315, 1262, 1129, 753, 701 cm^{-1}; δ_H: 1.03 (3 H, t, *J* 7.3), 1.79 (2 H, m), 4.70 (1 H, t, *J* 5.6), 6.34 (1 H, br s), 6.56 (1 H, t, *J* 7.9), 6.74 (1 H, d, *J* 7.9), 6.94 (1 H, d, *J* 7.6), 7.19 (1 H, t, *J* 7.6); δ_C: 9.0 (q), 28.7 (t), 70.0 (d), 114.0 (d), 116.2 (d), 116.3 (s), 127.6 (d), 128.0 (d), 128.7 (d), 129.0 (d), 132.3 (d), 138.2 (s), 148.3 (s), 163.9 (s).

1,2-Dihydro-1-benzyl-4-ethyl-2-methylquinazoline (8b)

The nitrile **1a** (1.04 g, 5.00 mmol) was added to 10.8 mmol EtMgBr in 20 mL Et_2O. The dianion was allowed to fully form during 15 min of reflux. The dianion solution was cooled to rt and acetaldehyde (0.56 mL, 10 mmol) was added dropwise. A yellow precipitate formed. The mixture was refluxed 15 min, and then quenched with 20 mL 10% NH_4Cl. The layers were separated and the aqueous layer extracted with 2 × 20 mL Et_2O. The combined organic layers were washed 2 × 20 mL water, 20 mL brine, dried (Na_2SO_4) and evaporated to give a yellow oil (1.56 g). The part soluble in 60 mL boiling hexane was put on a silica dry-flash column and eluted with 1 : 1 diisopropyl ether–hexane followed by diisopropyl ether, and finally a large volume of Et_2O from which the product was recovered by evaporation of the solvent. This yielded 0.59 g (2.2 mmol, 44%) yellow oil (pure on TLC); HRMS found: $[M + H]^+$, 265.1712 ($C_{18}H_{21}N_2$ requires 265.1705); δ_H: 1.02–1.12 (6 H, m), 2.57–2.67 (2 H, m), 4.37 (1 H, d, *J* 16.3), 4.49 (1 H, d, *J* 16.3), 5.15 (1 H, q, *J* 6.0), 6.55 (1 H, d, *J* 8.1), 6.61 (1 H, dt, *J* 0.9 and 7.5), 7.15 (1 H, dt, *J* 1.5 and 7.8), 7.23–7.38 (6 H, m); δ_C: 10.9 (q), 17.4 (q), 27.0 (t), 50.1 (t), 70.7 (d), 112.3 (d), 116.1 (d), 117.2 (s), 125.5 (d), 126.9 (d), 128.4 (d), 132.2 (d), 138.2 (s), 144.3 (s), 163.3 (s).

1,2-Dihydro-2-phenylquinazoline (9a)

To anthranilonitrile (0.59 g, 5.0 mmol) in 10 mL Et_2O at 0 °C, 1 M DIBAL-H in toluene (10 mL, 10 mmol) was added under nitrogen atm. After addition the mixture was stirred 1 h 0–25 °C. Benzaldehyde (1.6 mL, 15 mmol) was added dropwise and stirring continued for 1 h. The reaction mixture, followed by a rinsing portion of 20 mL Et_2O, was poured into a separatory funnel and washed with 2 × 20 mL 4 M NaOH. The combined alkaline portions were in turn extracted with 20 mL Et_2O. The combined organic layers were washed with 20 mL water and extracted with 3 × 20 mL 2 M HCl. The combined HCl portions were washed with 20 mL hexane and then carefully made basic with about 40 mL sat. Na_2CO_3. The colour changed from red to pale yellow and the formed precipitate was filtered off and dried. This afforded 0.48 g (2.3 mmol, 48%) of a pale yellow solid, mp. 126 °C (lit.[32] mp 131–132 °C from benzene–diisopropyl ether); HRMS: found $[M + H]^+$, 209.1082 ($C_{14}H_{12}N_2$ requires 209.1079); IR ν_{max}: 3227, 3053, 1630, 1569, 1479, 1455, 1269, 909, 743, 698 cm^{-1}; δ_H: 5.99 (1 H, br s), 6.55–6.61 (2 H, m), 6.66 (1 H, s), 7.13–7.17 (2 H, m), 7.28–7.40 (3 H, m), 7.46–7.49 (2 H, m), 8.11 (1 H, br s); δ_C: 71.2 (d), 113.1 (d), 116.1 (s), 116.6 (d), 126.8 (d), 127.7 (d), 127.9 (d), 128.2 (d), 133.1 (d), 143.6 (s), 145.7 (s), 157.5 (d).

1,2-Dihydro-6-bromo-2-phenylquinazoline (9b)

2-Amino-5-bromobenzonitrile (0.99 g, 5.00 mmol; prepared by bromination of 2-aminobenzonitrile in AcOH)[33] treated with DIBAL-H according to the same procedure as reported for **10a**, yielded 0.54 g (1.9 mmol, 38%) yellow solid, mp. 129 °C; HRMS: found $[M + H]^+$, 287.0188 ($C_{14}H_{11}BrN_2$ requires 287.0184). IR ν_{max}: 3235, 1628, 1562, 1478, 1454, 1266, 1183, 820, 757, 700 cm^{-1}; δ_H: 6.05 (1 H, br s), 6.55 (1 H, d, *J* 8.3), 6.88 (1 H, s), 7.26–7.47 (7 H, m), 8.12 (1 H, br s); δ_C: 71.1 (d), 106.3 (s), 106.8 (s), 115.2 (d), 126.7 (d), 127.0 (d), 128.1 (d), 130.0 (d), 135.4 (d), 143.2 (s), 144.7 (s), 156.3 (d).

Spiro[cyclohexane-1,2′-(1*H*)-4′-phenylquinazoline] (10a)

To 5.0 mmol dianion **2a** in 20 mL THF, solid NH_4Cl (0.54 g, 10 mmol) was added, and the mixture was refluxed 5 min. Cyclohexanone (1.55 mL, 15 mmol) was added and the reflux continued for 19 h. 10 mL 10% NH_4Cl and 20 mL Et_2O was added and the phases separated. The aqueous phase was extracted with 2 × 20 mL Et_2O and the combined organic phases were washed with 4 × 20 mL water. The washed solution was in turn extracted with 4 × 20 mL 5% citric acid. After the combined acidic portions were neutralised with about 50 mL sat. Na_2CO_3, a solid slowly (20 h) formed and was filtered of. After washing with water and drying, 0.97 g (3.5 mmol, 70%) of a mustard coloured solid remained, mp 143 °C (lit.[16] 146 °C from diisopropyl ether); IR ν_{max}: 3288, 2927, 2846, 1610, 1559, 1474, 1444, 1325, 746, 700 cm^{-1}; δ_H: 1.47–1.87 (10 H, m), 6.30 (1 H, br s), 6.52 (1 H, t, *J* 7.3); δ_C: 21.1 (t), 25.4 (t), 37.2 (t), 69.3 (s), 114.3 (d), 115.5 (s), 115.7 (d), 127.4 (d), 128.0 (d), 128.7 (d), 128.9 (d), 132.3 (d), 138.5 (s), 146.4 (s), 161.7 (s).

1,2-Dihydro-2,2-dimethyl-4-phenylquinazoline (10b)

Following the procedure for compound **11a**, acetone (1.5 mL, 20 mmol) was added to 5.0 mmol **2a** and the reflux continued for 3 h. The same work-up procedure yielded 0.78 g (3.3 mmol, 66%) large yellow crystals, mp 115 °C (from heptane) (Found C, 81.31; H, 6.76; N, 11.91. $C_{16}H_{16}N_2$ requires C, 81.32; H, 6.82; N, 11.85%); IR ν_{max}: 3299, 2976, 1623, 1569, 1538, 1329, 1286, 1195, 1168, 958, 745, 696, 677 cm^{-1}; δ_H: 1.39 (6 H, s), 6.42 (1 H, br s), 6.50 (1 H, dt, *J* 0.8 and 7.5), 6.65 (1 H, dd, *J* 0.8 and 8.3), 6.90 (1 H, d, *J* 7.5), 7.16 (1 H, dt, *J* 1.5 and 7.5), 7.45 (5 H, m); δ_C: 28.6 (q), 68.6 (s), 114.0 (d), 114.8 (s), 115.7 (d), 127.4 (d), 128.0 (d), 128.6 (d), 128.9 (d), 132.4 (d), 138.2 (s), 146.7 (s), 161.6 (s).

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