HL
http://heteroletters.org

ISSN: 2231 – 3087(print)
ISSN: 2230 – 9632 (Online)
Coden HLEEAI
Vol. 4: (4), 2014, 481-486

ONE-POT SYNTHESIS OF DIHYDROQUINAZOLINES VIA CONDENSATION OF α-AMINONITRILES WITH 2-AMINOACETOPHENONE

Ahmad Q. Hussein*[a], and Eyad A. Younes[b]

[a] *Department of Chemistry, Faculty of Science, The University of Jordan, Amman, Jordan*
[b] *Department of Chemistry, Memorial University of Newfoundland, St. John's, NL A1B 3X7, Canada*
E-mail: *aqhussein@ju.edu.jo*

Abstract: The one-pot condensation reaction of α-aminonitriles with 2-aminoacetophenone afforded the corresponding 2,2-disubstituted-4-methyl-1,2-dihydoquinazoline derivatives**,** rather than the anticipated 2-amino-1,4-benzodiazepines**.**

Kewords: one-pot synthesis, 2-Aminoacetophenone, 2-amino-1,4-benzodiazepines, α-amino-nitriles, 1,2-dihydroquinazolines.

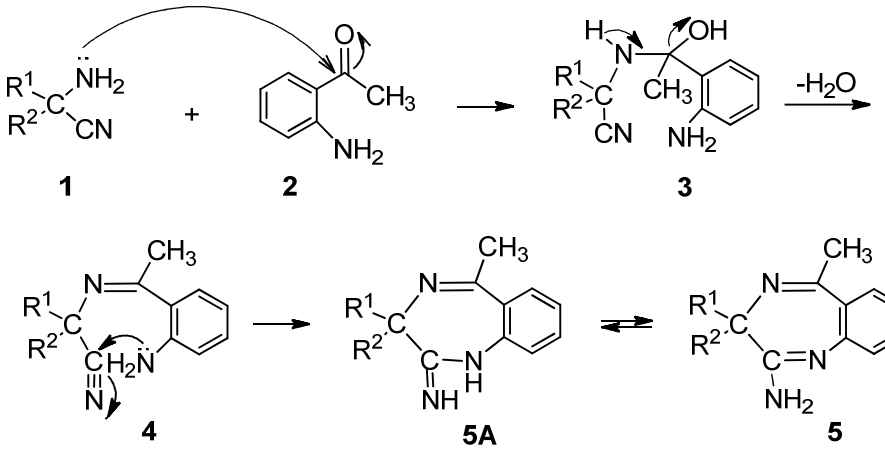
Introduction:

α-Aminonitriles (**1**) incorporate at the α-carbon atom both a nucleophilic terminus (the amino group) and a sufficiently reactive electrophilic center (the cyano group), which are suitably located to participate in ring forming transformations. These versatile synthons are easily accessible from readily available materials via simple chemical reactions, such as Strecker synthesis[i]. This renders these compounds favorable components for cyclization reactions in conjunction of appropriate reaction partners. Hence, they find wide application in the field of organic synthesis, particularly as starting materials for the synthesis of *aza*-heterocycles[ii-vii].

In this contest, we recently reported on the utilization of α-aminonitriles in the synthesis of 2-amino-1,4-benzodiazepines through condensation with *o*-nitrobenzoyl chloride and subsequent reduction of the nitro group[viii].

To further explore new synthetic applications of α-aminonitriles as scaffolds for *aza*-heterocyclic systems, we here investigate the condensation of α-aminonitriles with the commercially available 2-aminoacetophenone (**2**).

Based on simple successive electrophilic-nucleophilic interactions involving the reactive termini of the starting materials in the manner depicted in Scheme 1, we anticipated that such condensation would eventually lead to the corresponding 2-amino-1,4-benzodiazepines (**5**). Since the latter class of heterocycles are known to display wide range of biological activities[ix-xiv], the just mentioned reaction warrants investigation as a promising pathway towards the synthesis of latter compounds. Over a dozen of benzodiazepine derivatives are nowadays in medical use[xv,xvi], among which are chlorodiazepoxide (Librium), and diazepam (Valium).



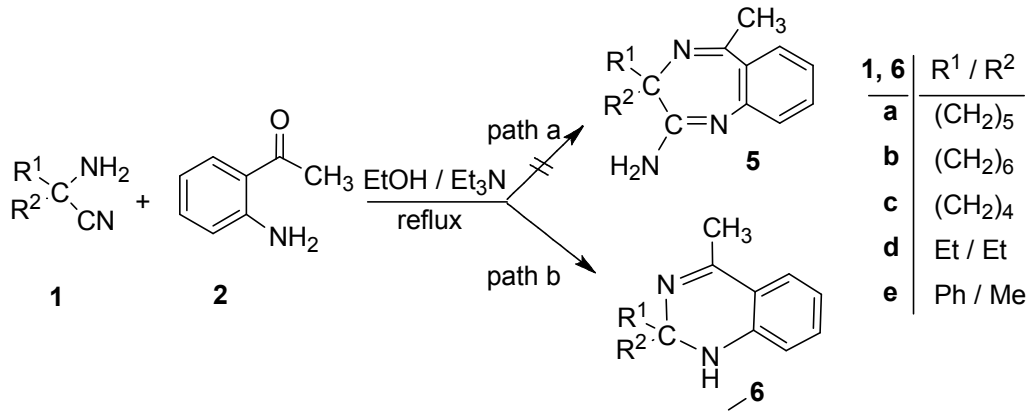
Scheme 1. Expected reaction pathway between α–aminonitriles and 2-aminoacetophenone leading to benzodiazepines.

Results and discussion:

Refluxing a mixture of 1-aminocyclohexanecarbonitrile (**1a**, $R^1+R^2 = (CH_2)_5$) with an equivalent amount of 2-aminoacetophenone in ethanol as the solvent, and in presence of triethylamine as a catalyst, for 4 h resulted in complete consumption of both reactants and the formation of a new product, as revealed by thin layer chromatographic examination of the reaction mixture.

Workup of the reaction mixture resulted in the isolation of a solid product , which was purified and characterized through its spectral data.

The high resolution ESI mass spectrum of the isolated compound gave a molecular ion peak with measured exact mass for $[M + H]^+$ ion of *m/z* = 215.15428, corresponding to the formula $C_{14}H_{19}N_2$ (calc., *m/z* = 215.15482). This finding coincides with the *spiro*-2,2-disubstituted-4-methyl-1,2-dihydroquinazoline structure **6a** (Scheme 2, path b), but is obviously too far to fit the formula ($C_{15}H_{21}N_3$) which corresponds to the initially presumed 2-amino-1,4-benzodiazepine structure **5a** (Scheme 2, path a).



Scheme 2. The two possible reaction pathways between α–aminonitriles and 2-aminoacetophenone.

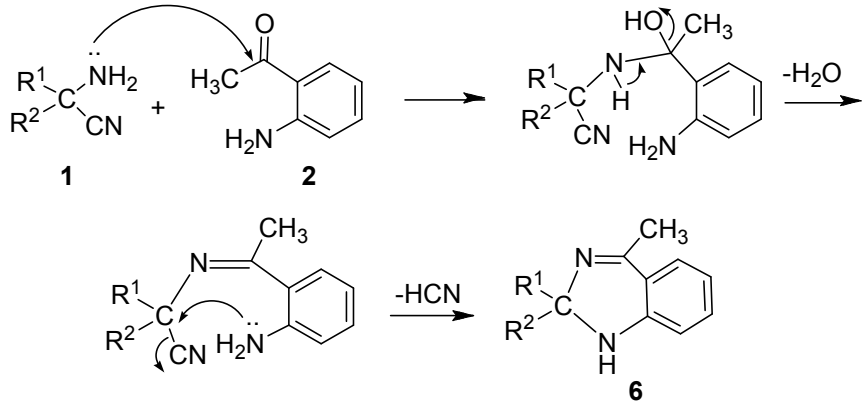
The ^{1}H NMR spectrum of compound **6a**, as an example, exhibits, besides the signals assigned to the protons of the cyclohexyl moiety (multiplets at 1.35-1.77 ppm, 10 H) and the aromatic

protons (7.26 ppm, d, 1 H; 7.14, dd, 1 H; 6.64 ppm, dd, 1 H; 6.51 ppm, d, 1 H), two additional singlets at 4.15 ppm (1H, broad) and at 2.27 ppm (3 H), assigned respectively to the N_1-H and the C-4 methyl protons.

The ^{13}C NMR spectrum displays, in addition to the cyclohexyl and phenyl carbon signals, characteristic signals at 160.6 and 69.4 ppm, assigned respectively to the C-4 and the spiro C-2 carbon of the pyrimidine nucleous. The signal at 22.6 ppm is assigned to the methyl carbon at C-4.

The IR spectra of compounds **6** reveal N-H absorption band in the range 3330-3360 cm^{-1}, and a C=N stretching at about 1640 cm^{-1}.

The formation of compounds **6** under the present reaction conditions is assumed to proceed according to the sequence depicted in Scheme 3, whereby initial nucleophilic attack through the NH_2 group of the aminonitrile (**1)** at the carbonyl of the aminoketone (**2),** followed by elimination of water, leads initially to the formation of the corresponding imine condensation product as an intermediate. The latter intermediate finally undergoes cyclization, through intramolecular nucleophilic displacement of the cyanide ion by the amino group, and subsequent deprotonation, eventually furnishing the final heterocyclic product **6**.



Scheme 3. The mechanism of reaction between compounds **1** and **2** leading to 1,2-dihydroquinazolines (**6)**.

Likewise, other selected examples of α-aminonitriles reacted in a similar manner with 2-aminoacetophenone (**2)**, and furnished the corresponding 1,2-dihydroquinazolines. The structures of the reaction products were confirmed through their MS, and ^1H- and ^{13}C NMR spectral data.

Since several quinazoline- and dihydroquinazoline derivatives exhibit biological activities[xvii-xix], and many of them are being marketed as drugs[xx] for treatment of various biological disorders, such as high blood pressure, high blood sugar, cancer, etc., the development of facile synthetic routes towards these heterocyclic systems is therefore desirable.

The most commonly used general method for synthesis of this class of heterocycles is based on the use of aniline derivatives carrying an electrophilic center at the *ortho*-position, such as derivatives of anthranilic acid, and *o*-aminobenzonitrile[xxi-xxiv]. Other less commonly used starting materials include *o*-haloaniline[xxv], and *o*-halobenzonitrile[xxvi].

In one case, dihydroquinazolines were synthesized through the condensation of *O*-phenyl-2-aminoacetophenone oxime with aldehydes and ketones, followed by free-radical cyclization under microwave irradiation[xxvii]. This method, however, is sensitive to the nature of substituents

on the carbonyl component, and was found inapplicable if aromatic, or sterically-hindered ketones, such as acetophenone, were employed in the condensation. Consequently, 2,2-disubstituted derivatives, such as compound **6e** were not accessible by this method[xxvii].

Conclusions:

It has been shown, in the present work, that the one-pot reaction of α-aminocarbonitriles with 2-aminoacetophenone constitutes a convenient synthetic route towards 1,2-dihydroquinazolines (*d*-fused benzopyrimidine derivatives), which supplements existing synthetic pathways for these heterocycles[xx].

Experimental section:

2-Aminoacetophenone, and all aldehydes and ketones employed in the reactions were products of Aldrich Chemical Company. Solvents were of commercial grade, and silica-coated TLC plates were from Merck.

High resolution mass spectra (HRMS) were measured in positive ion mode by Electrospray Ionization (ESI) on a Bruker Apex IV high resolution instrument, using arginine cluster for external mass calibration. ^{1}H NMR, and ^{13}C NMR spectra were measured on a Bruker DPX-500 instrument using $CDCl_3$ as solvent, and TMS as internal reference. IR spectra were recorded on a Nicolet Impact-400 FT-IR spectrophotometer using KBr pellets.

Preparation of α-aminonitriles (1). These compounds were prepared from the corresponding aldehyde or ketone by the Strecker synthesis [i, vii, viii]. Thus, to a well stirred mixture of the carbonyl compound (0.1 mol) and water (40 mL) in a round bottomed flask, was added concentrated ammonium hydroxide solution (60 mL), followed by potassium cyanide (0.15 mol). The flask was securely stoppered, and left under continuous stirring for 24 h at room temperature inside the fume hood. The product was the extracted from the aqueous mixture with diethyl ether (2 x 20 mL). Evaporation of the organic solvent under reduced pressure gave almost quantitative yield of the aminonitrile as an oil, which was used for the next reaction without further purification.

Following this procedure, the following aminonitriles were prepared:

α -aminocyclohexanecarbonitrile (**1a)** from cyclohexanone;
α aminocycloheptanecarbonitrile (**1b)** from cycloheptanone;
α -aminocyclopentanecarbonitrile (**1c)** from cyclopentanone;
α aminodiethylacetonitrile (**1d)** from diethyl ketone;
α -amino- α-phenylpropionitrile (**1e)** from acetophenone.

Preparation of compounds 6a-e: A mixture of the appropriate aminonitrile (5 mmol), 2-aminoacetophenone (5 mmol) and triethylamine (1 mL) in ethanol (30 mL) was refluxed for 4-6 h, with continuous stirring, until TLC examination indicated complete consumption of the starting materials. The mixture was cooled and the solvent was evaporated under reduced pressure to yield the crude product. In case of **6a,** the product was a solid, and it was purified by recrystallization from chloroform / petroleum ether (b.p. 40-60 ^{o}C). Otherwise the product was obtained as oil, and it was purified by separation on preparative TLC plates, using silica gel-coated glass plates, using chloroform / hexane (1:3 v/v) as the mobile phase.

6a: Yield 80%; m.p. 148-150 ^{o}C (from chloroform / petroleum ether, Lit.[xxviii]: brown oil.); $[M+H]^+$ calc. for $C_{14}H_{19}N_2$, 215.15482; found, 215.15428. ^{1}H NMR, δ (ppm): 7.26 (1H, d, *J*= 6.5Hz), 7.14 (1H, dd, *J*= 6.5, 7.5 Hz), 6.64 (1H, dd, *J*= 7.5, 8.0 Hz), 6.51 (1H, d, *J*= 8.0 Hz), 4.15

(NH), 2.27 (Me), 1.77-1.35 (10H, m). ^{13}C NMR, δ (ppm): 160.6, 144.1, 132.3, 126.2, 118.0, 117.4, 114.1, 69.4, 37.1, 25.3, 22.6, 21.9.

6b: Yield 72%; oil; $[M+H]^+$ calc. for $C_{15}H_{21}N_2$, 229.17047; found, 229.16993. ^{1}H NMR, δ (ppm): 7.29 (1H, d, *J*= 6.5Hz), 7.19 (1H, dd, *J*= 6.5, 7.5 Hz), 6.68 (1H, dd, *J*= 7.5, 8.0 Hz), 6.55 (1H, d, *J*= 8.0 Hz), 4.32 (NH), 2.35 (Me), 1.87-1.98 (4H, m), 1.51-1.67 (8H, m). ^{13}C NMR, δ (ppm): 159.9, 144.3, 132.8, 126.3, 117.5, 117.1, 114.4, 73.8, 40.6, 30.1, 22.1, 22.0.

6c: Yield 74%; oil; $[M+H]^+$ calc. for $C_{13}H_{17}N_2$, 201.13917; found, 201.13862. ^{1}H NMR, δ (ppm): 7.26 (1H, d, *J*= 6.5Hz), 7.16 (1H, dd, *J*= 6.5, 7.5 Hz), 6.66 (1H, dd, *J*= 7.5, 8.0 Hz), 6.50 (1H, d, *J*= 8.0 Hz), 5.27 (NH), 2.31 (Me), 1.67-2.01 (4H, m), 1.16-1.23 (4H, m). ^{13}C NMR, δ (ppm): 161.7, 145.0, 132.8, 126.5, 117.7, 117.5, 114.3, 79.5, 40.5, 29.7, 23.1, 21.8.

6d: Yield 56%; oil; $[M+H]^+$ calc. for $C_{13}H_{19}N_2$, 203.15482; found, 203.15428. ^{1}H NMR, δ (ppm): 7.27 (1H, d, *J*= 6.5Hz), 7.15 (1H, dd, *J*= 6.5, 7.5 Hz), 6.60 (1H, dd, *J*= 7.5, 8.0 Hz), 6.46 (1H, d, *J*= 8.0 Hz), 1.79 (4H, q, *J*= 7Hz), 0.96 (6H, t, *J*= 7Hz), 3.85 (NH), 2.35 (Me). ^{13}C NMR, δ (ppm): 161.3, 145.2, 132.9, 126.3, 116.5, 115.8, 113.2, 74.0, 33.8, 29.7, 22.0.

6e: Yield 68%; oil; $[M+H]^+$ calc. for $C_{16}H_{17}N_2$, 237.13891; found, 237.13862. ^{1}H NMR, δ (ppm): 7.58 (2H, d, *J*= 6.5Hz), 7.34-7.21 (5H, m), 6.68 (2H, m), 4.72 (NH), 2.42 (Me), 1.87 (Me). ^{13}C NMR, δ (ppm): 161.9, 147.0, 144.3, 133.2, 128.1, 127.2, 126.6, 125.4, 117.7, 116.8, 114.2, 71.9, 30.7, 27.7.

Acknoledgements:
This work was done during a sabbatical leave granted by The University of Jordan to A. Q. Hussein and spent at An-Najah National University, Palestine. We thank both universities for financial support.

References:

i) J. Taillades, A. Commeyrans, *Tetrahedron*, *30*, 2493-2496, **1974.**
ii) R.C.F. Jones, L.E. Seager, M.R.J. Elsegood, *Synlett*., 211-214, **2011**
iii) A.I. Markosyan, S.V. Dilanyan, S.A. Gabrielyan, F.G. Arsenyan, R.S. Sukasyan, B.T. Garibdzhanyan, *Pharm. Chem. J.*, *44*, 352-355, **2010.**
iv) T. Kurz, K. Widyan, *Tetrahed. Lett*., *45*, 7049-7051, **2004**.
v) B.W. Parcher, D.M. Erion, Q. Dang, *Tetrahed. Lett*., *45*, 2677-2679, **2004**.
vi) M. McLaughlin, R.M. Mohareb, H. Rapoport, *J. Org. Chem*., *68*, 50-54, **2003**.
vii) Y.M. Shafran, V.A. Bakulev, V.S. Mokrushin, *Russian Chemical Reviews(Eng. Transl.)*, *58* (2), 148-162, **1989**.
viii) E.A. Younes, A.Q. Hussein, M.A. May, F.R. Fronczek, *ARKIVOC*, 322-330, **2011**.
ix) J. Cobo, M. Nogueras, J.N. Low, R. Rodriguez, *Tetrahed. Lett*., *49*, 7271-7273, **2008**.
x) A. Kamal, N. Shankaraiah, N. Markandeya, K.L. Reddy, C.S. Reddy, *Tetrahed. Lett*., *49*, 1465-1468, **2008**.
xi) S. Fotso, T.M. Zabriskie, P.J. Proteau, P.M. Flatt, D.A. Santosa, S. Sulastri, T. Mahmud, *J. Natural Prod*., *72*, 690-695, **2009**.
xii) L.P. Tardibono, M.J. Miller, *Org. Lett*., *11*, 1575-1578, **2009**.
xiii) L. Cipolla, A.C. Araujo, C. Airoldi, D. Bini, *Anticancer Agents Med. Chem*., *9*, 1-31, **2009**.
xiv) D. Berezhnoy, T.T. Gibbs, D.H. Farb, *Mol. Pharmacol.*, *76*, 440-450, **2009**.
xv) R.I. Shader, D.J. Greenblatt, *Brit. J. Clin. Pharmac*., *11*, 5S-9S, **1981.**

xvi) N.A. Meanwell, M.A. Walker, *Comprehensive Heterocyclic Chemistry III*; A.R. Katritzky, C.A. Ramsden, E.F.V. Scriven, R.J.K. Taylor, Eds., Elsevier: Oxford*, Vol. 13* , p 183, **2008**.
xvii) W. Pao, V. Miller, M. Zakowski, J. Doherty, K. Politi, I. Sarkaria, B. Singh, R. Heelan, V. Rusch, L. Fulton, E. Mardis, D. Kupfer, R. Wilson, M. Kris, H. Varmus, *Proc Natl. Acad. Sci. (USA)*, *101*, 13306-13311, **2004**.
xviii) R.S. Giri, H.M. Thaker, T. Giordano, J Williams, D. Rogers, V. Sodersanam, K.K. Vasu, *Eur. J. Med. Chem*., *44*, 2184-2189, **2009**.
xix) D. Wang, F. Gao, *Chem. Cent. J*., *7*, 95-110, **2013**.
xx) T.P. Selvam, P.V. Kumar, *Res. Pharmacy*, *1*, 1-21, **2011**.
xxi) S. Balalaie, A. Sharifi, B. Ahangarian, E. Kowsari, *Heterocycl. Comm*., *7*,337, **2001**.
xxii) F.R. Alexandre, A. Berecibar, T. Besson, *Tetrahed. Lett*., *43*, 3911-3913, **2002**.
xxiii) A. Kamal, K.S. Reddy, B.R. Prasad, A.H. Babu, A.V. Ramana, *Tetrahed. Lett*., *45*, 6517-6521, **2004**.
xxiv) A.J.A. Watson, A.C. Maxwell, J.M.J. Williams, *Org. Biomol. Chem.*, *10*, 240-243, **2012.**
xxv) J. Bergman, A. Brynolf, B. Elman, E. Vuorinen, *Tetrahedron*, *42*, 3697-3706, **1986**.
xxvi) J.B. Hynes, A. Tomazic, C.A. Parrish, o.S. Fetzer, *J. Heterocycl. Chem*., *28*, 1357-1363, **1991**.
xxvii) F. Portela-Cubillo, J.S. Scott, J.C. Walton, *J. Org. Chem.*, *74*, 4934-4942, **2009**.

Received on September10, 2014.