Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

Synthesis of New 2-Chloro-4-(3-Aryl-2,4-Diphenyl-3H-Triazolidine-5-on-1-yl)Quinoline-3-Carbonitriles by a Cyclo-Addition Route Using Carbodiimides and Nitrones. A Novel Thermal Decomposition to 4-Aminoquinolines

Ramadan AhmedMekheimer [a]

[a] Chemistry Department, Faculty of Science, El-Minia University, 61519, El-Minia, A. R. Egypt

Version of record first published: 22 Aug 2006.

SYNTHETIC COMMUNICATIONS, 28(19), 3665-3674 (1998)

SYNTHESIS OF NEW 2-CHLORO-4-(3-ARYL-2,4-DIPHENYL-3H-TRIAZOLIDINE-5-ON-1-YL)QUINOLINE-3-CARBONITRILES BY A CYCLOADDITION ROUTE USING CARBODIIMIDES AND NITRONES. A NOVEL THERMAL DECOMPOSITION TO 4-AMINOQUINOLINES.

Ramadan Ahmed Mekheimer

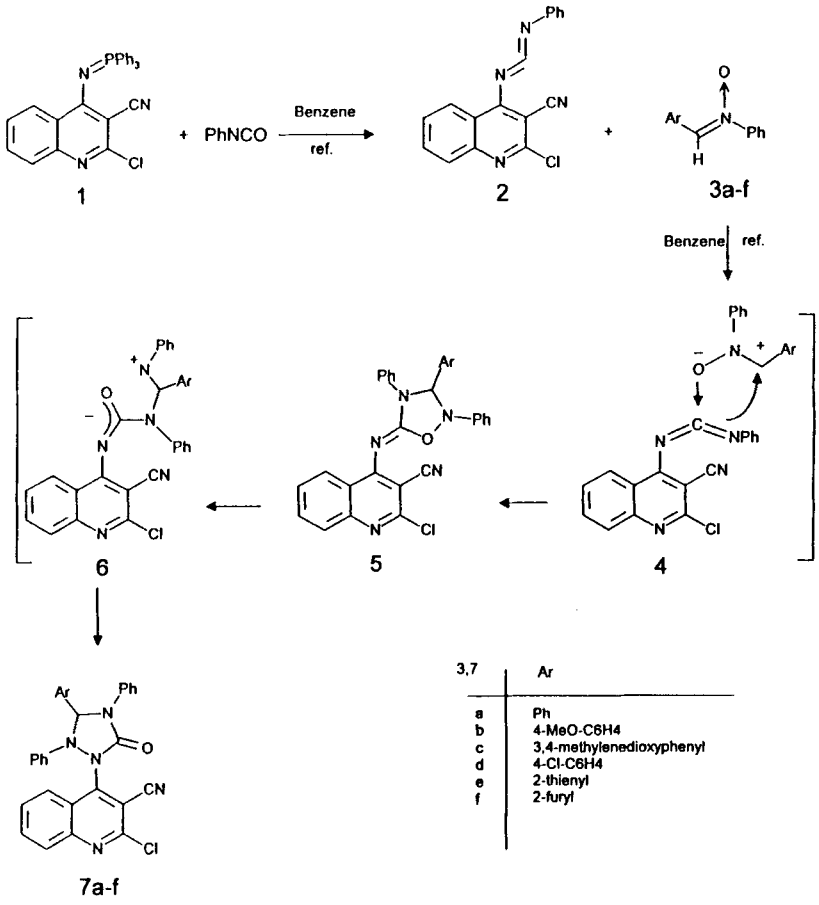
Chemistry Department, Faculty of Science,
El-Minia University 61519, El-Minia, A.R.Egypt

Abstract- A convenient synthesis of the triazolidinones-1-yl derivatives **7** via cycloaddition reactions and their thermolysis to afford 4-amino-2-chloroquinline-3-carbonitrile **10** is reported.

Reactions of carbodiimides with 1,3-dipolar compounds have been much less investigated than those of other heterocumulenes such as isocyanates and ketenes. Only two examples of reactions of carbodiimides with nitrones have been reported by Komatsu and coworkers.[1] They have isolated the stable cycloadducts of oxadiazolidine imine type from the reactions of simple N-alkyl nitrones with diphenylcarbodiimide. However, oxadiazolidine imines derived from diphenyl nitrone are unstable under the reaction conditions and rearrange to a triazolidinones. These results prompted us to examine the dipolarophilic behavior of new

the carbodiimide **2** towards some C-aryl-N-phenyl nitrones in order to synthesize a novel substituted quinolines.

In the course of our studies directed toward the synthesis of new heterosystems incorporating a quinoline nucleus,[2-6] we wish to describe in this paper useful one-pot route for the preparation of new substituted triazolidinones pendant to quinoline in the 4-position via 1,3-dipolar cycloaddition reactions. This study has been carried out because of the biological importance of quinoline derivatives[7-9] as well as the triazolidinone derivatives which have chemotherapeutic activity and act as bronchodilators[10] and control of hyperlipidemias.[11] In addition, they can act as herbicides reagents.[12] Thus the products of the reactions could possess interesting and useful biological activity. The preparation of the desired carbodiimide **2** was accomplished very easily through the classical Staudinger reaction[13] of 4-azido-2-chloroquinoline-3-carbonitrile[14,15] with triphenylphosphine in refluxing toluene to give the iminophosphorane **1**.[14] The Aza-Wittig reaction of iminophosphorane **1** with phenyl isocyanate in dry benzene leads to carbodiimide **2**, which was obtained as a viscous oil. The reaction of carbodiimide **2** with nitrones **3** in benzene at reflux temperature afforded exclusively the 2-chloro-4-(3-aryl-2,4-diphenyl-3H-triazolidine-5-on-1-yl)quinoline-3-carbonitriles **7a-f** (see scheme 1). The structure of the isolated cycloadducts was assigned to **7** on the basis of their elemental analysis and IR, ^{1}H NMR and mass spectral data. Thus, the IR spectra of the isolated products showed the presence of an absorption band at 1730 cm^{-1}, characteristic of the carbonyl group of the triazolidinone ring residue.[1,16] Structure **7** was further confirmed by ^{1}H NMR spectra which revealed a sharp



Scheme 1

singlet signal for each compound in the region δ = 6.51-6.99 ppm assignable to the methine proton at C-3 of the triazolidinone ring, in addition to signals due to phenyl and aryl protons.

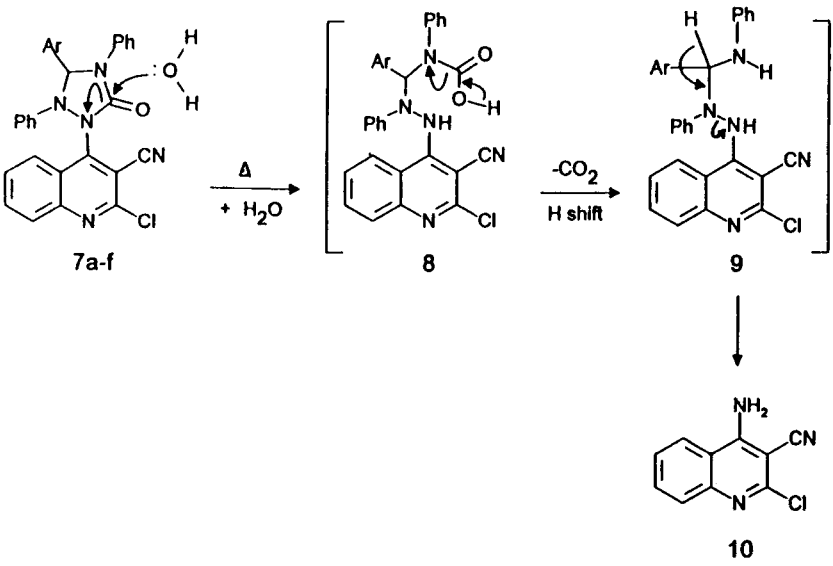
The formation of **7a-f** may take place through an initial 1,3-dipolar cycloaddition of **3** to the C=N bond of **2** to give 1:1 adduct product **5**.

The unstable oxadiazolidines **5** undergo ring opening, through N-O bond fission, to yield further intermediates **6** which undergo thermal rearrangement to afford the final products **7** (cf. Scheme 1).

The thermal rearrangement of **5** to **7** implies that a triazolidinone **7** is more stable than an oxadiazolidine **5** under these reaction conditions. This observation prompted us to investigate the stability of the cycloadduct **7** towards thermal conditions. On heating of **7** in solvents such as toluene, xylene, bromobenzene and 1,2-dichlorobenzene, the starting materials were recovered unchanged even after extend periods. Then, we tried the thermolysis in a basic and high-boiling solvent such as DMF. However, when cycloadducts **7** were heated in boiling DMF for 2h, 4-aminoquinoline-3-carbonitriles **10** were unexpectedly obtained as the only identifiable product (see Scheme 2).

A mechanistic proposal for the formation of 4-aminoquinolines **10** involves nucleophilic attack of H_2O (probably present in solvent) on the carbonyl group in the triazolidinone ring to form the ring-opened intermediate **8,** which loses molecular CO_2. A proton shift to intermediate **9** is followed by intramolecular rearrangement to yield the final product **10** and the corresponding amidines Ar-C(NHPh)=NPh (see Scheme 2). Presumbly, the thermal decomposition of these amidines under these reaction conditions prevents their isolation. On the basis of these results, it may be concluded that the use of DMF, as a basic solvent, facilitates the opening of the triazolidinone ring in **7**.

We conclude that the 1,3-dipolar cycloaddition reactions described in this paper are a simple synthetic route to new quinoline derivatives of biological interest.



Scheme 2

To the best of our knowledge, this is the first reported cleavage of the triazolidinone ring system to the corresponding amine.

Experimental

M.P.'s were measured on a GallenKamp melting apparatus and are uncorrected. IR spectra were recorded on a Shimadzu 470 spectrophtometer (KBr pellets). The ^{1}H NMR spectra were obtained using Varian EM390 (400 MHz) spectrometer in (DMSO-d_6) using TMS as internal standard, and chemical shifts are expressed as δ values (ppm). Microanalyses were performed by the Microanalytical Data Unit at Cairo University. Mass spectra were obtained using a Varian MAT 311 or Finnigan MAT 8430 spectrometer (ionization energy 70 eV). Nitrones **3a-f** [17] were prepared as reported.

Synthesis of carbodiimide 2

A solution of iminophosphorane **1** (0.5g, 1.08 mmol) in dry benzene (10 ml) was treated with phenyl isocyanate (0.128g, 1.08 mmol). The mixture was refluxed for 1h. The solvent was removed under reduced pressure to give **2** as a clear oil which was used without further purification in the next step. Infrared (neat): 3060 (ArCH), 2230 (CN), 2170 (N=C=N) and 1630 (C=N) cm^{-1}.

General Procedure For Synthesis of 2-Chloro-4-(3-Aryl-2,4-Diphenyl-3H-Triazolidine-5-on-1-yl)Quinoline-3-Carbonitriles 7a-f

A solution of nitrones **3a-f** (1.08 mmol) in dry benzene (10 ml) was treated with carbodiimide **2** (1.08 mmol). The reaction mixture was refluxed for 1.5 h, until the TLC showed the disappearance of the starting compounds. After evaporation to dryness under reduced pressure, the resulting oil was triturated with methanol. The precipitated solid product was collected by filtration, washed with a small amount of methanol, dried and recrystallized from ethanol to give **7a-f.**

2-Chloro-4-(2,3,4-triphenyl-3H-triazolidine-5-on-1-yl)quinoline-3-carbonitrile, 7a

Colorless crystals, Yield 70 %, mp 214-215 °C; ^{1}H NMR (DMSO-d_6): δ 6.81 (s, 1H), 7.18-7.57 (m, 15H), 7.76 (d, 1H), 7.92 (m, 1H), 8.03 (m, 1H), and 8.13 (d, 1H) ppm; Infrared (KBr): 3050 (ArCH), 2220 (CN), and 1730 (CO) cm^{-1}; Mass Spectrum (m/z): 502 (15) (M^+); Anal. Calcd. for $C_{30}H_{20}Cl\,N_5O$: C, 71.77; H, 4.02; Cl, 7.07; N, 13.95. Found: C, 71.64; H, 4.13; Cl, 7.22; N, 13.90.

2-Chloro-4-[2,4-diphenyl-3-(4-methoxyphenyl)-3H-triazolidine-5-on-1-yl]-quinoline-3-carbonitrile, 7b

Colorless crystals, Yield 76 %, mp 224-225 °C; ^{1}H NMR (DMSO-d_6): δ 3.72 (s, 3H), 6.60 (s, 1H), 7.15-7.54 (m, 14H), 7.76 (d, 1H), 7.92 (m, 1H), 8.02 (m, 1H), and 8.13 (d, 1H) ppm; Infrared (KBr): 3050 (ArCH), 2920 (aliph. CH), 2220 (CN), 1730 (CO), and 1620 (C=N) cm^{-1}; Mass Spectrum (m/z): 532 (13) (M^+); Anal. Calcd. for $C_{31}H_{22}Cl\ N_5O_2$:C, 69.98; H, 4.17; Cl, 6.67; N, 13.16. Found: C, 69.82; H, 4.39; Cl, 6.59; N, 13.45.

2-Chloro-4-[2,4-diphenyl-3-(3,4-methylenedioxyphenyl)-3H-triazolidine-5-on-1-yl]quinoline-3-carbonitrile, 7c

Colorless crystals, Yield 71 %, mp 230-231°C; ^{1}H NMR (DMSO-d_6): δ 5.95 (s, 2H), 6.51 (s, 1H), 6.67 (m, 1H), 6.76 (d, 1H), 6.82-6.90 (m, 3H), 6.97 (s, 1H), 7.14-7.57 (m, 7H), 7.76 (d, 1H), 7.92 (m, 1H), 8.02 (m, 1H), and 8.13 (d, 1H) ppm; Infrared (KBr): 3050 (ArCH), 2900 (aliph. CH), 2220 (CN), and 1720 (CO) cm^{-1}; Mass Spectrum (m/z): 545 (49) (M^+-1), 546 (19)(M^+); Anal. Calcd. for $C_{31}H_{20}ClN_5O_3$: C, 68.19; H, 3.69; Cl, 6.50; N, 12.83. Found: C, 68.12; H, 3.78; Cl, 6.35; N, 13.05.

2-Chloro-4-[2,4-diphenyl-3-(4-chlorophenyl)-3H-triazolidine-5-on-1-yl]quinoline-3-carbonitrile, 7d

Colorless crystals, Yield 61 %, mp 227-228 °C; ^{1}H NMR (DMSO-d_6): δ 6.88 (s, 1H), 7.16-7.53 (m, 14H), 7.78 (d, 1H), 7.93 (m, 1H), 8.03 (m, 1H), and 8.14 (d, 1H) ppm; Infrared (KBr): 3050 (ArCH), 2220 (CN), and 1720 (CO) cm^{-1};

Mass Spectrum (m/z): 536 (3) (M^+). Anal. Calcd. for $C_{30}H_{19}Cl_2N_5O$: C, 67.16; H, 3.57; Cl, 13.23; N, 13.05 %. Found: C, 67.12; H, 3.51; Cl, 13.27; N, 13.19.

2-Chloro-4-[2,4-diphenyl-3-(2-thienyl)-3H-triazolidine-5-on-1-yl]quinoline-3-carbonitrile, 7e

Colorless crystals, Yield 66 %, mp 173-175 °C; ^{1}H NMR (DMSO-d_6): δ 6.99 (s, 1H), 7.16 (m, 1H), 7.21 (d, 1H), 7.28 (d, 1H), 7.34-7.60 (m, 10H), 7.77 (d, 1H), 7.92 (m, 1H), 8.02 (m, 1H), and 8.13 (d, 1H) ppm; Infrared (KBr): 3050 (ArCH), 2220 (CN), and 1730 (CO) cm^{-1} ; Mass Spectrum (m/z): 507 (38) (M^+-1), 508 (13)(M^+); Anal. Calcd. for $C_{28}H_{18}ClN_5OS$: C, 66.20; H, 3.57; Cl, 6.99; N, 13.79; S, 6.31. Found: C, 66.36; H, 3.60; Cl, 7.10; N, 13.60; S, 6.19.

2-Chloro-4-[2,4-diphenyl-3-(2-furyl)-3H-triazolidine-5-on-1-yl]quinoline-3-carbonitrile, 7f

Colorless crystals, Yield 57%, mp 198-200 °C; ^{1}H NMR (DMSO-d_6): δ 6.40 (d, 1H), 6.84 (s, 1H), 7.19-7.64 (m, 12H), 7.76 (d, 1H), 7.99 (m, 1H), 8.06 (m, 1H), and 8.13 (d, 1H); Infrared (KBr): 3050 (ArCH), 2220 (CN), and 1720 (CO) cm^{-1}; Mass Spectrum (m/z): 492 (36) (M^+); Anal. Calcd for $C_{28}H_{18}ClN_5O_2$: C, 68.36; H, 3.69; Cl,7.22; N, 14.23. Found: C, 68.32; H, 3.76; Cl, 7.39; N, 14.02.

Thermolysis of 2-chloro-4-(3-aryl-2,4-diphenyl-3H-triazolidine-5-on-1-yl)quinoline-3-carbonitriles 7a-f. General procedure for the synthesis of 4-amino-2-chloroquinoline-3-carbonitrile (10)

A solution of **7a-f** (0.56 mmol) in DMF (5 ml) was refluxed for 2h, until the TLC showed the disappearance of the starting compound. After concentration to dryness, the residual oil crystallized on trituration with methanol. The resulting

solid product was collected by filtration, washed with a small amount of methanol and dried to give the aminoquinolines **10**. Colorless crystals from DMF, Yield 90-92 %, mp 305-307°C (decp.); ^{1}H NMR (DMSO-d_6): δ 7.51-7.59 (m, 1H); 7.69-7.84 (m, 2H); 8.27 (br s, 2H), and 8.37 (d, 1H) ppm; Infrared (KBr): 3380, 3350, 3210 (NH), and 2220 (CN) cm^{-1}; Mass Spectrum (m/z): 203 (100) (M^+); Anal. Calcd. for $C_{10}H_6ClN_3$: C, 58.97; H, 2.97; Cl, 17.43; N, 20.63. Found: C, 59.07; H, 3.09; Cl,17.68; N, 20.82.

References

1. Komatsu, M.; Ohshiro, Y.; Agawa, T.; J. Org. Chem., **1972**, 37, 3192.
2. Mekheimer, R.; Ahmed, E. Kh.; Khattab, A. F.; Bull. Chem. Soc. Jpn., **1993,** 66, 2936
3. Mekheimer, R. ; Die Pharmazie; **1994,** 49, 486.
4. Mekheimer, R.; Bull. Soc. Chim. Fr.; **1994,** 131, 279.
5. Mekheimer, R.; J. Chem. Res.; **1994,** 304.
6. Hassan, A. A.; Mekheimer, R.; Mohamed, N. K.; Die Pharmazie, **1997,** 52, 589.
7. Skotnicki, S. J.; Gilman, C. S.; Steinbaugh, A. B.; Musser, H. J.; U. S. patent 1988, 4748246 C. A., **1988,** 109, 110425u.
8. Juergen, S.; Jochen, W.; Karl, R.; Hubert, S.; DE , 1988, 3716512; C. A.**1989,** 111, 57554y.
9. Bell, R. M.; Ackerman, H. J.; U. S. Patent 1990, 4920128; C. A.**1990,** 113, 172015b.
10. Frederick, C.; Crossan, G. A.; Eur. Pat. 1980, 7180; C. A. **1980,** 93, 149884u.

11. Robert, I. A.; Iris, H. H.; PCT Int. 1990, 9000897; C. A. **1991,** 114, 36008v.

12. Stephen, Z. D.; U. S.1981, 4276420 ; C. A. **1981,** 95, 132904u.

13. Staudinger, H.; Meyer, J.; Helv. Chim. Acta, **1919,** 2, 635.

14. R. Mekheimer, Ph. D. Thesis, El-Minia University, AR Egypt, **1990.**

15. Steinschifter, W.; Stadlbauer, W.; J. Prakt. Chem., **1994,** 336, 311.

16. Pretsch, E.; Seibl, J.; Simon, W.; Clerc, Th.; in Spectral Data For Structure Determination of Organic Compounds, ed. by W. Fresenius, Springer-Verlag, Berlin, **1989,** I 162.

17. Rundel, W.; in Methode der Organischen Chemie (Houben-Weyl-Muller), Thieme, Stuttgart, **1968,** vol. X14, p. 309.

(RECEIVED IN THE U.S.A. 19 APRIL 1998)