CYANOACETANILIDE IN HETEROCYCLIC CHEMISTRY: AN EFFICIENT AND IMPROVED METHOD FOR THE SYNTHESIS OF PYRAZOLO[1,5-A]PYRIMIDINE, THIAZOLIDINE AND THIOPHENE DERIVATIVES

AWATEF E. FARRAG¹, ABD ALLAH G. AL-SEHEMI², MOHAMED A. SALEM³, HAMDY KH. SABET³ AND MOHAMED H. HELAL³

¹ Chemistry Department, Faculty of Science (Girl’s), Al-Azhar University, Nasr City, Cairo, Egypt, ² Chemistry Department, Faculty of Teachers, Abha, Saudi Arabia, ³ Chemistry Department, Faculty of Science, Al-Azhar University, Nasr City, Cairo, Egypt.

Abstract

Many pyrazolo[1,5-a]pyrimidine, thiazolidine and thiophene derivatives have been synthesized via the reaction of potassium 3-(4-chloro-phenylamino)-2-cyano-3-oxo-1-(phenylamino)prop-1-ene-1-thiolate 2 with many different reagents.

Key words: Pyrazolo[1,5-a]pyrimidine, thiazolidine and thiophene derivatives

Introduction

The interesting pharmacological properties of thiophene, thiazole, pyrazolo[1,5-a]pyrimidine derivatives (1,2) in relation to the various changes in the structures of these compounds are important in the synthesis of some less toxic and more potent drugs. In continuation of our previous interest in the chemistry of azole derivatives from the readily obtainable inexpensive starting materials (3-8), we report here on the utility of cyanoacetanilide derivatives as building blocks for the synthesis of polysubstituted derivatives of pyrazole, pyrazolo[1,5-a]pyrimidine, thiophene and thiazole derivatives.

Results and Discussion

The cyanoacetanilide derivative 1 reacted with phenyl isothiocyanate in DMF in the presence of potassium hydroxide to give the corresponding potassium salt 2. The ketene N,S-acetal derivative 3 was obtained on treatment the potassium salt 2 with dimethyl sulfate. Treatment of compound 3 with hydrazine hydrate in refluxing ethanol yielded the corresponding 5-aminopyrazole derivative 4 (9), (cf. Scheme 1 and experimental section).
Scheme 1.

Pyrazolo[1,5-a]pyrimidines are considerable chemical and pharmacological importance as purine analogues and as such have useful properties as antimetabolites in purine biochemical reaction (10-12). The reactivity of aminopyrazole 4 towards some electrophilic reagents was investigated. Thus, compound 4 reacted with an equimolar amount of \( p \)-methoxybenzylidenemalononitrile 5 in refluxing ethanol catalyzed with piperidine yielded a single product for which structure 7 or 8 seemed possible. Structure 7 appears more likely than 8 on the basis that the ring nitrogen of pyrazole nucleus is the most nucleophilic one in the molecule. Formation of 7 was assumed to proceed via initial Michael type addition of the endocyclic NH in 4 to the electron deficient carbon in the \( \alpha,\beta \) unsaturated-cinnamonitrile system in 5 to form the intermediate 1:1 Michael adduct 6a (13), which cyclized and auto-oxidized under the reaction conditions to yield the final product 7. Both elemental and spectroscopic data of 7 are consistent with the assigned structure. Thus, its IR spectrum showed absorption peaks at \( \nu \) 3438, 3306 and 2212 cm\(^{-1}\) corresponding to the presence of NH\(_2\) and CN functional groups respectively. Its mass spectrum revealed a molecular ion peak at m/z (intensity %) 509 (32.4) corresponding to the molecular formula C\(_{27}\)H\(_{20}\)ClN\(_7\)O\(_2\) with a base peak at m/z 383 [M-(ClC\(_6\)H\(_4\)NH)]. The \(^1\)HNMR spectrum of compound 7 (DMSO-\( d_6 \)) exhibited a singlet at \( \delta \) 3.91 for the methoxy group with a singlet at \( \delta \) 9.04 ppm observed for the NH\(_2\) group.
Similar to its behavior towards α-substituted-cinnamonitrile, compound 4 reacted with tetracyanoethylene 9 in ethanol containing piperidine as a catalyst to produce pyrazolopyrimidine derivative 11 on the basis of analytical and spectral measurements. Thus, the IR spectrum of 11 revealed characteristic bands for NH$_2$ and CN functional groups. The formation of 11 proceeds via initial addition of the endocyclic NH followed by HCN elimination to give the intermediate 10 which then cyclized to afford the final product 11, (cf. Scheme 2 and experimental section).

Scheme 2

![Scheme 2](image)

The basic strategy to synthesize pyrazolo[1,5-a]pyrimidines is based on the cyclocondensation of aminopyrazole 4 with β-diketone and β-keto-ester (11,14). Thus, condensation of 4 with symmetrical and unsymmetrical diketones in acetic acid under reflux conditions furnished the pyrazolopyrimidine derivatives 12a,b. The structure of 12 was elucidated from their elemental analysis and spectroscopic data. The $^1$HNMR spectrum of 12a in (DMSO-$d_6$) showed two signals at δ 2.5 and 2.6 ppm corresponding for the two methyl groups of the pyrimidine ring and a signal singlet at δ 7.08 ppm for the proton at C$_5$ in the pyrimidine moiety. Mass spectrum
of 12b showed a molecular ion peak at m/z (intensity %) 453 (21.5) corresponding to a molecular formula C_{26}H_{20}ClN_{5}O with a base peak at 327 [M-(Cl.C_{6}H_{4}.NH)].

On the other hand, reaction of aminopyrazole 4 with ethyl aceto-acetate in acetic acid afforded two possible isomeric products 13 and 14. Structure 14 was excluded on the basis of spectral data and analogy with previous work (15), compound 13 was found mainly in the keto form due to the presence of the carbonyl amide group which decreases the possibility of conjugation to form the enol form (16), (cf. Scheme 3 and experimental section).

Scheme 3.

Due to the possibility of existence in both tautomeric forms 13a,b, therefore, we undertook a quantum chemical study in order to elucidate the tautomeric interconversions. Geometry optimization by ab initio quantum mechanical calculations were carried out, using several basis set effects using the GAUSSIAN 98 program (17). For all calculations the most stable tautomer corresponds to the keto form 13a. The optimizational keto-enol tautomerization are illustrated in Fig. 1.
The result of quantum mechanical calculations was shown in the following table.

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The conjugation of the π-electrons of the carbonyl groups with the \( \pi \)-system of the molecular skeleton probably enhances the energy of the ketone, which leads to its predominance over the enol.

In this context, we report herein a convenient route to a variety of thiazolidine and thiophene derivatives. Thus, compound 2 was reacted with ethyl chloroacetate and ethyl 2-bromobutyrate to afford in each a single product identified as the thiazolidine derivatives 16a,b, rather than the thiophene derivative 17 based on the elemental and spectral data. IR spectrum of 16a showed the presence of CN stretching band at \( \nu \) 2200 cm\(^{-1}\). Also, \(^1\)HNMR spectrum in (DMSO-\( d_6 \)) exhibited two singlets at 4.03 and 9.5 corresponding for CH\(_2\) and NH function groups respectively. The mass spectrum of compound (16a) showed a molecular ion peak at m/z (intensity %) 369 (35) in addition to other peaks were observed at m/z: 243 [66.2; M-(ClC\(_6\)H\(_4\)NH-p)], 215 [100; (M- ClC\(_6\)H\(_4\)NH-p + CO)], 187 (7.5) and 120 (0.5;
PhNHCO). The formation of 16 was assumed to proceed through initial alkylation to give the thioether 15 as intermediate followed by intramolecular cyclization via C₂H₅OH elimination. Similarly, the thioether derivative 19 was obtained on treatment of the salt 2 with N-(4-ethoxy-phenyl)chloroacetamide 18 at room temperature. The structure of 19 was assigned by ¹HNMR spectrum in (DMSO-d₆) which exhibited signals at δ 1.37(t, 3H, CH₃), 3.77(s, 2H, SCH₂), 4.02(q, 2H, CH₂) and the presence of three D₂O exchangeable singlets at 9.7, 10.1 and 11.36 ppm. Cyclocondensation of compound 19 in ethanolic piperidine solution furnished a product 16a through elimination of p-ethoxyaniline, this product is identical in all aspects (TLC, spectral data, m.p. and mixed m.p) with the thiazolidine derivative 16a, (cf. Scheme 4 and experimental section).

Scheme 4.
Moreover, when potassium salt 2 was treated with chloroacetone, the thiazole derivative 20 was obtained. The results of elemental analysis and spectral data are of good agreement with the proposed structure. The infrared spectrum of compound 20 showed the characteristic absorption band at $\nu$ 2222 cm$^{-1}$ for the C≡N functional group. $^1$HNMR spectrum of the reaction product revealed a signal at $\delta$ 1.87 ppm for CH$_3$ proton in addition to the presence of CH-thiazole at $\delta$ 6.96 ppm. The mass spectrum showed a molecular ion peak at m/z (intensity %) 367 (17.7), the base peak in the spectrum was found at m/z 241 [M-(ClC$_6$H$_4$NH)]. The formation of 20 was assumed to obtain through the initial alkylation followed by intramolecular cyclization and dehydration. The addition reaction of the intermediate 2 with chloroacetonitrile at room temperature furnished the iminothiazolidine derivative 21 in high yield. Its infrared spectrum showed a strong absorption band at $\nu$ 2174 cm$^{-1}$ due to C≡N group in addition to the absorption bands characteristic for NH and C=O (amide) functional groups. Furthermore, $^1$HNMR spectrum of the reaction product revealed a signal at $\delta$ 4.04 ppm for methylene protons in addition to the presence of two NH and aromatic protons signals. The formation of 21 was believed to proceed via the initial alkylation followed by heterocyclization (18) through nucleophilic addition of the NH to the cyano group.

Finally, treatment of compound 2 with phenacyl bromide gave the thioether derivative as intermediate 22, followed by intramolecular cyclization to give the aminothiophene derivative 23, via Thorpe-Ziegler reaction (19). The structure of compound 23 was confirmed by its infrared spectrum which indicated the absence of C≡N absorption band and the presence of characteristic absorption bands for NH$_3$ and C=O functional groups. In addition, $^1$HNMR spectrum showed the absence of the methylene protons, (cf. Scheme 5 and experimental section).
Experimental Section

All melting points are uncorrected. IR spectra (KBr) were measured on Shimadzu 440 spectrometer, $^1$H NMR spectra were obtained in DMSO on a Varian Gemini 200 (200 MHz) spectrometer using TMS as internal standard; Chemical shifts are reported as $\delta$ units. Mass spectra were obtained on GC MSQP 1000 Ex mass spectrometer at 70 eV. Elemental analyses were carried out at the Microanalytical Center of Cairo University.

5-Amino-6-cyano-N-(4-chlorophenyl)-7-(4-methoxyphenyl)-2-(phenylamino)pyrazolo[1,5-a]pyrimidine-3-carboxamide (7)

To a solution of 4 (0.01 mole) in ethanol (30 mL), 4-methoxy-cinnamonicitrile 5 (0.01 mole) and piperidine (0.5 ml) were added and the mixture was heated under reflux for 3h. The solid product thus formed was filtered off and recrystallized from acetic acid to give 7 as yellow crystals (60%), m.p. >300 °C. IR ν (cm$^{-1}$): 3438, 3306, 3200, 3150 (NH$_2$ + 2NH), 2212 (C≡N), 1650 (C=O; amide).$^1$HNMR (DMSO-d$_6$): $\delta$ 3.90 (s, 3H, OCH$_3$), 6.97–8.01 (m, 13H, Ar-H) 9.04, 9.32, 10.15 (3s, 4H, NH$_2$ + 2NH; lost after D$_2$O exchange). Anal. Calcd. for C$_{27}$H$_{20}$ClN$_7$O$_2$ (509.5): C, 63.59, H, 3.92, N, 19.23,. Found: C, 63.50, H, 3.80, N, 19.10.
5-Amino-6,7-dicyano-N-(4-chlorophenyl)-2-(phenylamino)pyrazolo-[1,5-a]pyrimidine-3-carboxamide (11)

A mixture of compound 4 (0.01 mole), tetracyanoethylene 9 (0.01 mole), triethylamine (0.01 mole) in dioxane (10 mL) was heated under reflux for 30 min, then allowed to cool. The solid product thus formed after cooling was collected by filtration and recrystallized from acetic acid to yield compound 11 as brown crystals (55%), m.p. 290°C. IR ν (cm⁻¹): 3408, 3312, 3252, 3170 (NH₂ + 2NH), 2217 (C≡N), 1644 (C=O; amide). ¹HNMR (DMSO-d₆): δ 7.03–7.89 (m, 11H, Ar-H + NH₂), 9.43, 9.71 (2s, 2H, 2NH; exchangeable by D₂O). Anal. Calcd. for C₂₁H₁₃ClN₈O (428.5): C, 58.80, H, 3.06, N, 26.13. Found: C, 58.70, H, 3.00, N, 26.00.

Reaction of compound 4 with 1,3-dicarbonyl compounds

General procedure:

A mixture of compound 4 (0.01 mole) and 1,3-dicarbonyl compounds (0.01 mole) in glacial acetic acid (20 mL) was heated under reflux for 3h. The solid products obtained after cooling were filtered off and crystallized from the proper solvent to afford compounds 12a,b, respectively.

N-(4-Chlorophenyl)-5,7-dimethyl-2-(phenylamino)pyrazolo[1,5-a]pyrimidine-3-carboxamide (12a)

This compound was formed as yellow crystals from dimethylformamide (70%), m.p. >300°C. IR ν (cm⁻¹): 3274, 3180 (2NH), 1660 (C=O; amide). ¹HNMR (DMSO-d₆): δ 2.67, 2.77 (2s, 6H, 2CH₃), 7.08 (s, 1H, pyrimidine-H), 7.42–7.79 (m, 9H, Ar-H), 9.35, 10.16 (2s, 2H, 2NH; exchangeable by D₂O). Anal. Calcd. for C₂₁H₁₅ClN₅O (391.5): C, 64.36, H 4.59, N, 17.87. Found: C, 64.30, H, 4.50, N, 17.80.

N-(4-chlorophenyl)-5-methyl-7-phenyl-2-(phenylamino)pyrazolo[1,5-a]pyrimidine-3-carboxamide (12b)

This compound was formed as yellow crystals from dioxane (65%), m.p. >300°C. IR ν (cm⁻¹): 3310 (broad; 2NH), 1650 (C=O; amide). ¹HNMR (DMSO-d₆): δ 2.52 (s, 3H, CH₃), 6.98 (s, 1H, pyrimidine-H), 7.35–7.93 (m, 14H, Ar-H), 9.85, 10.07 (2s, 2H, 2NH; exchangeable by D₂O). Anal. Calcd. for C₂₆H₂₀ClN₅O (453.5): C, 68.79, H, 4.41, N, 15.43. Found: C, 68.70, H, 4.30, N, 15.40.
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N-(4-Chlorophenyl)-5-hydroxy-7-methyl-2-(phenylamino)pyrazolo[1,5-a]pyrimidine-3-carboxamide (13)

A mixture of compound 4 (0.01 mole) and ethyl acetoacetate (0.01 mole) in glacial acetic acid (20 mL) was heated under reflux for 3 hr. The solid product obtained on hot was filtered off and crystallized from dioxane to give compound 13 as yellow crystals (60%), m.p. 290°C. IR ν (cm⁻¹): 3366, 3240, 3180 (3NH), 1670, 1666 (2C=O; amide). ¹H NMR (DMSO-d₆): δ 2.52 (s, 3H, CH₃), 5.98 (s, 1H, pyrimidine-H), 6.99-7.74 (m, 9H, Ar-H), 8.79, 9.85, 11.92 (3s, 3H, 3NH; exchangeable by D₂O). Anal. Calcd. for C₂₀H₁₆ClN₅O₂ (393.5): C, 60.99, H, 4.06, N, 17.78. Found: C, 60.90, H, 4.00, N, 17.70.

Reaction of compound 2 with halo-reagents

General procedure:

To a suspension of finely powdered potassium hydroxide (0.01 mole) in dry N,N-dimethylformamide (10 mL), the anilide derivative 1 (0.01 mole) and then the phenyl isothiocyanate (0.01 mole) were added in portions for 1 h. The reaction mixture was stirred at room temperature with α-halogenated compound (0.01 mole) and left at room temperature for 3 h, then it was produced into ice/water and acidified with 0.1 N HCl at pH 3-4. The resulting precipitate was filtered off, dried and recrystallized from the proper solvent to afford compounds 16a,b, 19, 20, 21, 23.

N-(4-Chlorophenyl)-2-cyano-2-(5-ethyl-4-oxo-3-phenylthiazolidine-2-ylidene)acetamide (16a)

This compound was formed as yellow crystals from ethanol (70%), m.p. 270°C. IR ν (cm⁻¹): 3332 (NH), 2200 (C≡N), 1736 (C=O; thiazole), 1652 (C≡O; amide). ¹H NMR (DMSO-d₆): δ 4.03 (s, 2H, SCH₂), 7.14-7.96 (m, 9H, Ar-H), 9.59 (1s, 1H, NH; exchangeable by D₂O). Anal. Calcd. for C₁₈H₁₇ClN₅O₂S (369.55): C, 58.45, H 3.24, N, 11.36. Found: C, 58.40, H, 3.20, N, 11.30.

N-(4-Chlorophenyl)-2-cyano-2-(4-oxo-3-phenylthiazolidine-2-ylidene)acetamide (16b)

Yellow crystals from ethanol (60%), m.p. 250°C. IR ν (cm⁻¹): 3342(NH), 2928 (CH-aliph.), 2198 (C≡N), 1736 (C≡O; thiazole), 1654 (C≡O; amide). ¹H NMR (DMSO-d₆): δ 1.56 (t, 3H, CH₃), 2.1 (q, 2H, CH₂), 4.30 (q, 1H, CH), 7.19-7.96 (m, 9H, Ar-H), 9.5 (1s, 1H, NH; lost exchangeable by D₂O). Anal. calcd. for C₂₀H₁₆ClN₅O₂S (397.5): C, 60.37, H, 4.02, N, 10.56. Found: C, 60.30, H, 3.90, N, 10.50.
N-(4-Chlorophenyl)-2-cyano-3-(2-(4-ethoxyphenylamino)-2-oxoethyl-thio)-3-(phenylamino)acrylamide (19)

Yellow crystals (60%, benzene), m.p. 170°C. IR ν (cm⁻¹): 3200 (NH), 2900 (CH aliph.), 2170 (C≡N), and 1660 (C=O; amide). ¹HNMR (DMSO-d₆): δ 1.33 (t, 3H, CH₃), 3.77 (2, 2H, SCH₂), 4.02 (q, 2H, CH₂), 6.85-7.42 (m, 13H, Ar-H), 9.77, 10.14, 11.38 (3s, 3H, 3NH; exchangeable by D₂O). Anal. calcd. for C₂₆H₂₃ClN₄O₃S (506.5): C, 61.59; H, 4.54; N, 11.05. Found: C, 61.50; H, 4.40; N, 10.90.

N-(4-Chlorophenyl)-2-cyano-2-(4-methyl-3-phenylthiazol-2(3H)-ylidene)acetamide (20)

Yellow crystals (50%, acetic acid), m.p. 270°C. IR ν (cm⁻¹): 3252 (NH), 2222 (C≡N), 1644 (C=O; amide). ¹HNMR (DMSO-d₆): δ 1.87 (s, 3H, CH₃), 6.96 (s, CH-thiazole), 7.28-7.71 (m, 9H, Ar-H), 8.86 (s, 1H, NH; exchangeable by D₂O). Anal. calcd. for C₁₉H₁₄ClN₃OS (367.5): C, 62.04; H, 3.80; N, 11.42. Found: C, 62.00; H, 3.75; N, 11.30.

N-(4-Chlorophenyl)-2-cyano-2-(4-imino-3-phenylthiazolidin-2(3H)-ylidene)acetamide (21)

Yellowish crystals (75%, ethanol), m.p. 250°C. IR ν (cm⁻¹): 3394, 3282, 3150 (NH₂ + NH), 1672 (C=O), 1644 (C=O; amide). ¹HNMR (DMSO-d₆): δ 4.04 (s, 2H, CH₂-thiazole), 7.03-7.79 (m, 9H, Ar-H), 9.59, 13.00 (2s, 2H, 2NH; exchangeable by D₂O). Anal. calcd. for C₁₈H₁₃ClN₄OS (368.5): C, 58.61; H, 3.52; N, 15.19. Found: C, 58.50; H, 3.50; N, 15.10.

4-amino-5-benzoyl-N-(4-chlorophenyl)-2-(phenyl-amino)thiophene-3-carboxamide (23)

Yellowish crystals (60%, acetic acid), m.p. 240°C. IR ν (cm⁻¹): 3394, 3282, 3150 (NH₂ + NH), 1672, (C=O), 1644 (C=O; amide). ¹HNMR (DMSO-d₆): δ 6.98-7.61 (m, 14H, Ar-H), 8.24, 9.39, 10.21 (3s, 4H, NH₂ + 2NH; exchangeable by D₂O). Anal. Calcd. for C₂₅H₁₈ClN₅O₂S (447.5): C, 64.35; H, 4.02; N, 9.38; found: C, 64.30; H, 4.00; N, 9.30.

Formation of 16a from compound 19:

To a solution of 19 (0.01 mole) in ethanol (30 mL), the piperidine (0.01 mole) was added and the mixture was refluxed for 1 h. The solid product thus formed was collected by filtration and recrystallized to give 16a.
References
