Reactions of Substituted Carbohydrazides with Electron-poor Olefins

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Z. Naturforsch. **2008**, *63b,* 998 – 1004; received March 19, 2008

Substituted carbohydrazides **1a** – **e** reacted with ethenetetracarbonitrile (**2**) in dimethylformamide with formation of diacylhydrazines **4a** – **e** and 5-amino-1-substiuted pyrazole-3,3,4-tricarbonitriles **5a** – **e**. On the other hand, **1a**–**c** reacted with diethyl (*E*)-2,3-dicyanobutenedioate (**3**) to give oxadiazinone and pyrazolone derivatives **12a** – **e** and **13a** – **e**, respectively.

Key words: Substituted Carbohydrazides, Electron-poor Olefins, Heterocyclization

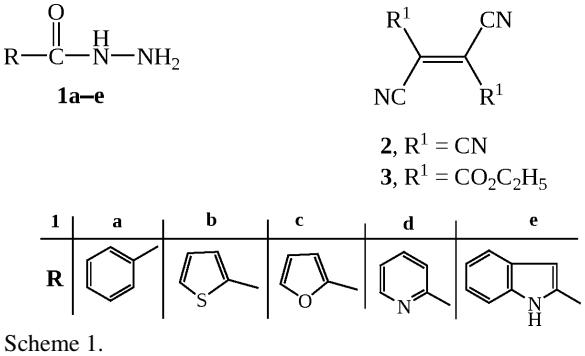
Introduction

Hydrazide compounds, such as furoic hydrazide, thiophenecarboxylic hydrazide and isonicotinic acid hydrazide react with a series of 4-alkoxy-4-alkyl(aryl)-1,1,1-trifluoro-3-alken-2-ones to give 3-alkyl(aryl)-5-trifluoromethyl substituted pyrazoles [1]. One-pot reactions between carboxylic hydrazides and 2-isothiocyanatobenzonitrile afford pharmacologically relevant 1,2,4-triazolo[1,5-*c*]quinazoline-5-thiones [2]. Hydrazide compounds can also be converted to triazole-3-thiols [3], 1,3,4-oxadiazole [4], 1,3,4-oxadiazine [4], pyrazolotriazolopyrimidine [5, 6] and pyrazolotriazoloquinoline derivatives [7]. 1,2,4-Triazines are formed *via* the condensation of 1,2-diketones with acylhydrazides and ammonium acetate under traditional thermal and dry media microwave-assisted reaction conditions [8, 9].

Ethenetetracarbonitrile (tetracyanoethylene) as well as its derivatives containing the dicyano-vinylidene moiety are electron-deficient substances, and it is well known that their monoelectronic reduction usually results in the formation of fairly long-lived radical anions [10, 11]. This also applies to other species containing cyano groups bound to a double bond [12 – 15].

Tetracyanoethylene shows a great affinity for electrons, and is thus a fairly good dehydrogenating agent towards dihydroaromatic and dihydroheteroaromatic systems [16, 17]. It behaves as a strong electron acceptor towards suitable electron donors [16 – 20].

The reaction of methylhydrazine with tetracyanoethylene (**2**) has been studied in several laboratories [21 – 23]. A mixture of 1-*N*- and 2-*N*-methyl



Scheme 1.

derivatives of 5-amino-3,4-dicyanopyrazole was isolated [23].

As a part of our program aimed at the development of new simple and efficient procedures for the synthesis of some important heterocyclic systems from hydrazinecarbothioamides, we have recently reported different successful approaches for the synthesis of thiazole, thiazine, thiadiazole, thiadiazine, thiadiazepine, indazole, and pyridazine derivatives [24 – 28]. As will be outlined in detail below, in this paper we report several heterocyclizations of substituted carbohydrazides **1a**–**e** using ethenetetracarbonitrile (tetracyanoethylene, **2**) and diethyl (*E*)-2,3-dicyanobutenedioate (dicyanofumarate, **3**) either as a reaction mediator or as a building block (Scheme 1).

Results and Discussion

When carbohydrazides **1a** – **e** were treated with two molar equivalents of tetracyanoethylene (**2**) in DMF as a solvent at r. t. with admission of air, the green color of a transient charge-transfer complex is ob-

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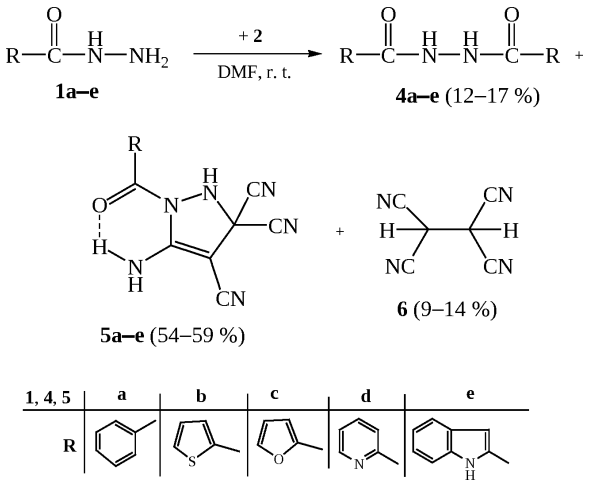


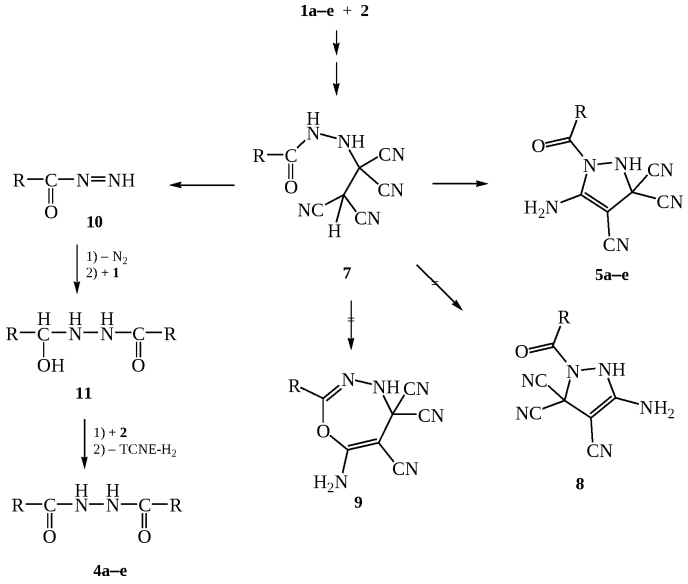
Scheme 2.

served which quickly gives way to brown. After concentration of the mixture to dryness and subjecting the residue to vacuum sublimation to remove any unreacted **2**, chromatographic separation of the residue in each case gave three zones, containing diacylhydrazines **4a** – **e** (12 – 17 %), 5-amino-1-substituted-1*H*-pyrazole-3,3,4(2*H*)-tricarbonitriles **5a** – **e** (54 – 59 %) and 1,1,2,2-tetracyanoethane (TCNE-H_2) (**6**, 9 – 14 %). On the other hand, an equimolar solution of **2** and **1a** – **e** in DMF, under the previous conditions, formed the previous products only in low yield in addition to unreacted **1a** – **e** (Scheme 2).

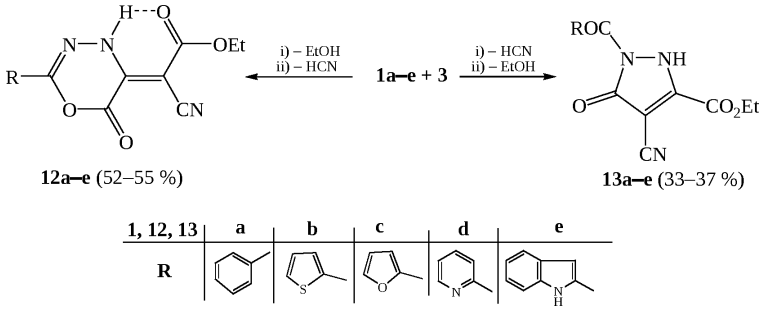
Diacylhydrazine products **4a** – **e** are not observed when no **2** is added to the solution of **1a** – **e** in DMF; thus the presence of **2** is definitely required for the transformations observed. Charge-transfer complexes may (but not necessarily have to) play an intermediate role. The formation of **4a** – **e** involves intermolecular nucleophilic attack by a hydrazide-NH_2 group on the carbonyl group of the aldehyde formed from **7**, followed by dehydrogenation with another molecule of **2** (Scheme 3).

The structures of **4a** – **e** are confirmed by characteristic IR, NMR and mass spectral data, and comparison with authentic samples. Singh *et al*. [29] earlier reported that iodobenzene diacetate (IBD) was found to be an excellent reagent for the oxidation of similar acid hydrazides [R = methyl(phenyl)pyrazolyl, methyl(4-methylquinolinyl)pyrazolyl, phenyl, 4-Cl-C_6H_4, 4-MeO-C_6H_4 and $PhCH_2$] to *N,N*^{1}-diacylhydrazines [29].

The dihydropyrazole structure of **5a** – **e** has been assigned on the basis of elemental analyses and spectral data. The ^{1}H NMR spectrum of **5b**, for example clearly shows two broad signals with the ratio of 2 : 1 centered at δ = 6.92 and 11.52 ppm due to exocyclic -NH_2 and pyrazole -NH, in addition to thiophene protons. The ^{13}C NMR spectrum shows signals at δ = 46.23 (C-3), 117.89, 118.96 (CN) and 169.86 (CO). Pyrazole C-4 and C-5 resonate at δ = 64.51 and 158.52, respectively, in accordance with the observed trends in the δ values for C atoms in push-pull alkenes [30, 31]. Further signals supporting the assigned structure are given in the Experimental Section.



Scheme 3.



Scheme 4.

The analytical data of compound **5** would also match for the alternative structures **8** and **9**, but these could be ruled out on the basis of ^{1}H NMR, ^{13}C NMR, and IR data and the fragment ions in the mass spectrum of **5b** at *m/z* = 243, 215, 111, 83 and 66 (Scheme 3).

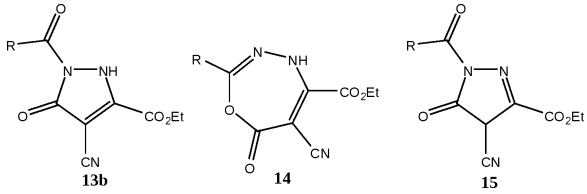
Furthermore, compound **5b** was also identified on the basis of an intramolecular hydrogen bond detected by IR (in dilute CCl_4) and ^{1}H NMR spectroscopy (see Experimental Section) as shown in Scheme 2.

Diethyl (*E*)-2,3-dicyanobutenedioate (dicyanofumarate, **3**) was chosen to compare its reactivity towards the substituted carbohydrazides **1a**–**e** with **2** (Scheme 4). One might expect that **1a**–**e** should react with **3** similarly to **2**, but the results were completely different (Scheme 4). Not only the structure of the acceptor is the reason for the instability of the CT complexes and subsequent chemical reaction, but also the electron affinity of the acceptors and the ease of undergoing the formation of an adduct or a tricyanovinylation product are important factors.

Mixing equimolar amounts of **1a**–**e** and **3** in ethyl acetate under reflux for 4–18 h led to the formation of oxadiazinone **12a**–**e** and pyrazolone **13a**–**e** derivatives. The structural assignment of **12a**–**e** and **13a**–**e** was based on their spectral data. The oxadiazinone derivative **12d** exhibited four IR absorption bands at ν = 3315 (NH), 2225 cm^{-1} (CN), and two bands at 1690 and 1730 cm^{-1} due to carbonyl ester and oxadiazinone-CO groups, respectively. These observations indicate the presence of an intramolecular hydrogen bond between oxadiazine-NH and the ester group on the side chain of **12**. The ester carbonyl band of lower frequency was attributed to an intramolecular hydrogen-bonded α,β-unsaturated ester carbonyl common to all related compounds as stated in the literature [32–34]. The ^{1}H NMR spectrum displayed one broad signal at δ = 9.91 ppm for one proton due to oxadiazine –NH; the chemical shift of this proton also supports the presence of intramolecular hydrogen bonding [34].

The salient features of the ^{13}C NMR spectra (including ^{13}C DEPT spectra) of **12d** are the signals at δ = 14.28 (CH_3), 61.17 (CH_2O), 69.89 (C-CN), 153.12 (C-5), 156.24 (C-2), 167.85 (ester-CO), and 171.36 (oxadiazinone-CO). The EI mass spectra of **12a**–**e** are characterized by molecular ions of low intensity and the loss of 27 a. m. u. (representing HCN). The resulting fragment ions undergo loss of 28 a. m. u. (N_2 or CO) followed by loss of EtO and RCO groups.

For compounds **13a**–**e**, the molecular ions in their EI mass spectra confirm the molecular masses and the gross compositions. Further, the following common fragmentation patterns lend support to the assigned structure: loss of N_2 giving intense $[M–28]^+$ ions and loss of RCO giving rise to the ion with *m/z* = 180 common in the spectra of all the five compounds. The IR spectra show characteristic absorptions for the NH group in the range of 3325 to 3345, sharp bands in the range 2215–2225 due to the cyano group, and three bands around 1660, 1675 and 1715 cm^{-1} assigned to carbonyl groups. The ^{1}H NMR spectra show the presence of an NH group by broad signals for one proton between δ = 12.43 and 12.55 ppm. For **13e**, the expected signals for indole –CH (δ = 6.72) and indole –NH (δ = 11.63) are observed. Signals around δ =



1) 3 CO	1) 2 CO	1) 3 CO
2) Pyrazole -NH	2) Oxadiazepine -NH	2) No -NH
3) One CN	3) One CN	3) One CN
4) No cyclic -CH	4) No cyclic -CH	4) Cyclic -CH

Scheme 5.

89.19 (C-4), 118.84 (CN), 155.98 (C-3), 165.34 (C-5), 168.49 (ester-CO), and 171.36 (CO) in the ^{13}C NMR spectrum of **13e** lend further support to the structures assigned to **13a – e**. The analytical data of compounds **13** would also match for the isomeric products **14** and **15** (Scheme 5). These could be ruled out on the basis of IR, ^{1}H NMR, and ^{13}C NMR spectra, and of the fragment ions in the mass spectrum of **13b** at *m/z* = 263, 246, 180, 111 and 83.

Experimental Section

Melting points have been determined using open glass capillaries on a Gallenkamp melting point apparatus and are uncorected. The IR spectra were recorded with Shimadzu 408 or Bruker Vector 22 FTIR instruments, using potassium bromide pellets or CCl_4. The ^{1}H NMR (400.134 MHz) and ^{13}C NMR (100.6 MHz) spectra were measured in [D_6]DMSO using a Bruker AM400 with TMS as an internal standard; chemical shifts are expressed as δ (ppm), (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet and b = broad).

Assignments of carbon resonances have been supported by DEPT experiments. Moreover, the signals caused by quaternary carbons were identified by the comparison between ^{13}C NMR and DEPT spectra. Mass spectra have been obtained with a Varian MAT 312 instrument using electron impact ionization (70 eV). Elemental analyses have been determined by the Microanalytical Center, Cairo University, Egypt. Preparation layer chromatography (plc): Glass plates (48 cm × 20 cm) were coated with silica gel Merck Pf_{254} (applied as aqueous slurry and air-dried affording a 1 mm layer). Zones were detected by indicator fluorescence quenching upon 254 nm illuminations, removed from plates and extracted with acetone.

Starting materials

Substituted carboxylic hydrazides **1a – e** were prepared according to published procedures [4, 35 – 40], as were thiophene-2-carboxylic hydrazide (**1b**, m. p. 135 – 137 °C, lit. [35]: 134 – 136 °C), furan-2-carboxylic hydrazide (**1c**, m. p. 77 – 79 °C, lit. [36]: 78 °C), pyridine-2-carboxylic hydrazide (**1d**, m. p. 136 – 138 °C, lit. [37, 38]: 137 °C), indole-2-carboxylic hydrazide (**1e**, m. p. 243 – 245 °C, lit. [4, 39, 40]: 246 °C). Benzene carboxylic hydrazide (**1a**) and diethyl (*E*)-2,3-dicyanobutenedioate (**3**) (Aldrich) were used as received. Ethenetetracarbonitrile (**2**, Merck) was purified by crystallization from chlorobenzene and sublimation.

*Reaction of substituted carboxylic hydrazides **1a – e** with ethenetetracarbonitrile (**2**)*

To a stirred solution of 256 mg (2.0 mmol) of **2** in 10 mL of dimethylformamide, a solution of 1.0 mmol of **1a – e** was added dropwise, which caused a spontaneous change of color from yellow to dark green and finally to brown. The mixture was stirred for 4 h and left standing for 48 h at r. t. After concentration to dryness, the residues were sublimed at 80 °C and then subjected to plc using toluene/ethyl acetate (3 : 1) as eluent for the reaction of **1a – e** with **2**. On the other hand, toluene/ethyl acetate (2 : 1) was used as eluent for the reaction of **1d**,**e** with **2**. Chromatographic separation of the residue (after sublimation) gave numerous zones, three of which (with high intensity) were removed and extracted. The fastest moving zone contained the pyrazole derivatives **5a – e** (characterized with pale yellow color), the second moving zone contained the diacylhydrazines **4a – c**, and finally the slowest migrating zone contained TCNE-H_2 as colorless crystals after sublimation which decomposed at 165 – 170 °C (lit. [41]: 165 – 170 °C). Extraction of the other zones with acetone and concentration gave residues, which were rechromatographed and recrystallized to give pure samples.

*N′-Benzoylbenzohydrazide (**4a**):* lit. [29, 42]; *N′-(thiophene-2-carbonyl)thiophene-2-carbohydrazide (**4b**):* lit. [42, 43]; *N′-(furan-2-carbonyl)furan-2-carbohydrazide (**4c**):* lit. [44]; *N′-picolinoylpicolinohydrazide (**4d**):* lit. [44]; *N′(1H-indole-2-carbonyl)-1H-indole-2-carbohydrazide (**4e**):* lit. [43].

*5-Amino-1-benzoyl-1H-pyrazole-3,3,4(2H)-tricarbonitrile (**5a**)*

M. p. 210 – 212 °C. – IR (KBr): ν = 3380, 3300 – 3220 (NH_2, NH), 2225, 2220 (CN), 1660 (CO), 1585 cm^{-1} (Ar-C=C). – ^{1}H NMR ([D_6]DMSO): δ = 6.98 (br, 2H, NH_2), 7.57 – 7.93 (m, 5H, Ar-H), 11.47 (pyrazole-NH). – ^{13}C NMR ([D_6]DMSO): δ = 48.48 (C-3), 64.14 (C-4), 117.94, 118.18, 119.26 (CN), 127.76, 128.93, 130.17 (Ar-CH), 134.36 (Ar-C), 158.64 (pyrazole-C-5), 170.19 (CO). – MS (EI, 70 eV): *m/z* (%) = 264 (33) $[M]^+$, 237 (18), 171 (26), 105 (100), 66 (71). – $C_{13}H_8N_6O$ (264.08): calcd. C 59.09, H 3.05, N 31.80; found C 58.87, H 2.92, N 32.04.

*5-Amino-1-(thiophene-2-carbonyl)-1H-pyrazole-3,3,4(2H)-tricarbonitrile (**5b**)*

M. p. 224 – 226 °C. – IR (KBr): ν = 3385, 3310, 3210 (NH_2, NH), 2225, 2220 (CN), 1655 (CO), 1590 cm^{-1} (Ar-C=C); ν (CCl_4, 10^{-3} M, *d* = 3 cm) = 3370, 3195 (broad NH_2 and OH assoc.), 1660 cm^{-1} (CO). – ^{1}H NMR ([D_6]DMSO): δ = 6.92 (br, 2H, NH_2), 7.21 – 7.87 (thiophene-CH), 11.52 (br, H, pyrazole-NH). – ^{13}C NMR ([D_6]DMSO): δ = 46.23 (C-3), 64.51 (C-4), 117.89, 118.08, 118.96 (CN), 129.23, 130.34, 131.67 (thiophene-CH), 137.69 (thiophene-C-2), 158.52 (C-5), 169.86 (CO). – MS (EI, 70 eV): *m/z* (%) = 270 (27) $[M]^+$, 243 (31), 215 (23), 111 (100), 83 (69), 66 (49). – $C_{11}H_6N_6OS$ (270.27): calcd. C 48.88, H 2.24, N 31.09, S 11.86; found C 49.08, H 2.31, N 30.88, S 12.05.

*5-Amino-1-(furan-2-carbonyl)-1H-pyrazole-3,3,4(2H)-tricarbonitrile (**5c**)*

M. p. 183 – 185 °C. – IR (KBr): ν = 3375, 3315, 3320 (NH_2, NH), 2220, 2215 (CN), 1655 (CO), 1590 (Ar-C=C), 1080 cm^{-1} (C–O–C). – ^1H NMR ([D_6]DMSO): δ = 6.89 (br, 2H, NH_2), 6.87 – 8.10 (furan-CH), 11.62 (br, 1H, pyrazole-NH). – ^{13}C NMR ([D_6]DMSO): δ = 46.41 (C-3), 64.48 (C-4), 117.95, 118.23, 119.12 (CN), 128.12, 142.81 (furan-CH), 147.63 (furan-C-2), 158.38 (C-5), 169.94 (CO). – MS (EI, 70 eV): *m/z* (%) = 254 (56) $[M]^+$, 227 (16), 199 (9), 95 (100), 67 (55), 66 (63). – $C_{11}H_6N_6O_2$ (254.20): calcd. C 51.97, H 2.38, N 33.06; found C 52.14, H 2.29, N 32.84.

*5-Amino-1-picolinoyl-1H-pyrazole-3,3,4(2H)-tricarbonitrile (**5d**)*

M. p. 215 – 217 °C. – IR (KBr): ν = 3375, 3300, 3230 (NH_2, NH), 2225, 2220 (CN), 1660 (CO), 1585 cm^{-1} (Ar-C=C). – ^1H NMR ([D_6]DMSO): δ = 6.95 (br, 2H, NH_2), 7.81 – 8.39 (pyridine-CH), 11.64 (pyrazole-NH). – ^{13}C NMR ([D_6]DMSO): δ = 45.96 (C-3), 64.22 (C-4), 118.02, 118.28, 119.14 (CN), 126.56, 128.77, 131.12, 142.66 (pyridine-CH), 150.34 (pyridine-C), 158.56 (C-5), 170.12 (CO). – MS (EI, 70 eV): *m/z* (%) = 265 (37) $[M]^+$, 238 (22), 210 (11), 106 (100), 78 (57), 66 (42). – $C_{12}H_7N_7O$ (265.23): calcd. C 54.34, H 2.66, N 36.97; found C 54.16, H 2.59, N 37.15.

*5-Amino-1-(1H-indole-2-carbonyl)-1H-pyrazole-3,3,4(2H)-tricarbonitrile (**5e**)*

M. p. 276 – 278 °C. – IR (KBr): ν = 3410, 3350 – 3230 (NH_2, NH), 2225, 2220 (CN), 1650 (CO), 1595 cm^{-1} (Ar-C=C). – ^1H NMR ([D_6]DMSO): δ = 6.87 (br, 2H, NH_2), 7.11 – 7.67 (m, 5H, Ar-H), 11.41 (br, 1H, pyrazole-NH), 11.76 (br, 1H, indole-NH). – ^{13}C NMR ([D_6]DMSO): δ = 46.18 (C-3), 64.42 (C-4), 115.18 (indole-CH), 117.93, 118.17, 119.12 (CN), 126.71, 127.16, 128.57, 129.63 (Ar-CH), 131.84, 138.66, 139.94 (Ar-C and indole-C-2), 158.45 (C-5), 170.72 (CO). – MS (EI, 70 eV): *m/z* (%) = 303 (41) $[M]^+$, 276 (17), 248 (21), 144 (100), 116 (64), 66 (54). – $C_{15}H_9N_7O$ (303.28): calcd. C 59.40, H 2.99, N 32.33; found C 59.23, H 3.11, N 32.19.

*Reaction of substituted carboxylic hydrazides **1a – e** with diethyl (E)-2,3-dicyanobutenedioate (**3**)*

A solution of 222 mg (1.0 mmol) of **3** in 30 mL of dry ethyl acetate was heated with a) 136 mg (1.0 mmol) of **1a**, b) 142 mg (1.0 mmol) of **1b**, c) 126 mg (1.0 mmol) of **1c**, d) 137 mg (1.0 mmol of **1d**, e) 175 mg (1.0 mmol) of **1e** and stirred under reflux for 4 h (a), 8 h (b, c) and 18 h (d, e), respectively. The color of the solution changed from colorless to reddish orange. After concentration of the reaction mixture to dryness, the residue was subjected to plc using toluene/ethyl acetate (2 : 1) as eluent. Chromatographic separation of the residue gave numerous zones, two of which (with high intensity) were collected and extracted. The fastest moving zone contained the oxadiazinone derivatives **12a – e** with orange color, while the slowest moving zone contained the pyrazolone derivatives **13a – e** (which were characterized by a brown color). Extraction of the zones with acetone and recrystallization gave the pure compounds.

*Ethyl 2-cyano-2-(6-oxo-2-phenyl-4H-1,3,4-oxadiazin-5(6H)-ylidene)acetate (**12a**)*

M. p. 192 – 194 °C. – IR (KBr): ν = 3335 (NH), 2225 (CN), 1695, 1730 (CO), 1620 cm^{-1} (C=N). – ^1H NMR ([D_6]DMSO): δ = 1.20 (t, J = 7.12 Hz, 3H, CH_3), 4.21 (q, J = 7.12 Hz, 2H, CH_2O), 7.07 – 7.64 (m, 5H, Ar-H), 9.89 (br, 1H, oxadiazine-NH). – ^{13}C NMR ([D_6]DMSO): δ = 14.43 (CH_3), 61.12 (CH_2O), 70.14 (C-CN), 118.36 (CN), 126.76, 128.93, 131.12 (Ar-CH), 132.77 (Ar-C), 152.84 (C-5), 156.18 (C-2), 167.83 (ester-CO), 171.18 (oxadiazine-CO). – MS (EI, 70 eV): *m/z* (%) = 285 (39) $[M]^+$, 258 (22), 230 (16), 185 (38), 105 (100), 77 (86), 45 (56). – $C_{14}H_{11}N_3O_4$ (285.25): calcd. C 58.95, H 3.89, N 14.73; found C 58.77, H 3.98, N 14.91.

*Ethyl 2-cyano-2-(6-oxo-2-(thiophen-2-yl)-4H-1,3,4-oxadiazin-5(6H)-ylidene)acetate (**12b**)*

M. p. 207 – 209 °C. – IR (KBr): ν = 3320 (NH), 2220 (CN), 1690, 1735 (CO), 1625 cm^{-1} (C=N). – ^1H NMR ([D_6]DMSO): δ = 1.22 (t, J = 7.10 Hz, 3H, CH_3), 4.18 (q, J = 7.10 Hz, 2H, CH_2O), 7.19 – 7.18 (m, thiophene-H), 9.92 (br, 1H, oxadiazine-NH). – ^{13}C NMR ([D_6]DMSO): δ = 14.39 (CH_3), 61.26 (CH_2O), 70.26 (C-CN), 118.67 (CN), 126.84, 127.56, 127.83 (thiophene-CH), 129.35 (thiophene-C), 153.12 (C-5), 156.26 (C-2), 167.64 (ester-CO), 171.36 (oxadiazine-CO). – MS (EI, 70 eV): *m/z* (%) = 291 (53) $[M]^+$, 264 (37), 236 (63), 191 (52), 111 (100), 45 (86). – $C_{12}H_9N_3O_4S$ (291.28): calcd. C 49.48, H 3.11, N 14.43, S 11.01; found C 49.32, H 2.94, N 14.67, S 10.83.

*Ethyl 2-cyano-2-(2-(furan-2-yl)-6-oxo-4H-1,3,4-oxadiazin-5(6H)-ylidene)acetate (**12c**)*

M. p. 169 – 171 °C. – IR (KBr): ν = 3330 (NH), 2225 (CN), 1695, 1725 (CO), 1630 cm^{-1} (C=N). – ^1H NMR ([D_6]DMSO): δ = 1.25 (t, J = 6.97 Hz, 3H, CH_3), 4.21 (q, J = 6.97 Hz, 2H, CH_2O), 7.16 – 7.74 (m, 3H, furan-H), 9.86 (br, 1H, oxadiazine-NH). – ^{13}C NMR ([D_6]DMSO): δ = 14.35 (CH_3), 61.19 (CH_2O), 69.82 (C-CN), 118.44 (CN), 126.18, 141.83 (furan-CH), 144.12 (furan-C), 152.88 (C-5), 156.27 (C-2), 167.90 (ester-CO), 171.28 (oxadiazine-CO). – MS (EI, 70 eV): *m/z* (%) = 275 (24) $[M]^+$, 248 (33), 220 (6), 175 (34), 140 (27), 95 (100), 45 (31). – $C_{12}H_9N_3O_5$ (275.22): calcd. C 52.37, H 3.30, N 15.27; found C 52.16, H 3.42, N 15.48.

*Ethyl 2-cyano-2-(6-oxo-2-(pyridin-2-yl)-4H-1,3,4-oxadiazin-5(6H)-ylidene)acetate (**12d**)*

M. p. 202 – 204 °C. – IR (KBr): ν = 3315 (NH), 2225 (CN), 1690, 1725 (CO), 1630 cm^{-1} (C=N). – ^1H NMR ([D$_6$]DMSO): δ = 1.18 (t, J = 7.05 Hz, 3H, CH_3), 4.21 (q, J = 7.05 Hz, 2H, CH_2O), 7.58 – 8.42 (m, 4H, pyridyl-H), 9.91 (br, 1H, oxadiazine-NH). – ^{13}C NMR ([D$_6$]DMSO): δ = 14.28 (CH_3), 61.17 (CH_2O), 69.89 (C-CN), 118.72 (CN), 126.18, 127.83, 130.12, 144.11 (pyridyl-CH), 147.82 (pyridyl-C), 153.12 (C-5), 156.24 (C-2), 167.85 (ester-CO), 171.36 (oxadiazine-CO). – MS (EI, 70 eV): *m/z* (%) = 286 (51) $[M]^+$, 259 (28), 231 (11), 186 (44), 106 (93), 78 (100), 45 (32). – $C_{13}H_{10}N_4O_4$ (286.24): calcd. C 54.55, H 3.52, N 19.57; found C 54.37, H 3.66, N 19.41.

*Ethyl 2-cyano-2-(2-1H-indole-2-yl)-6-oxo-4H-1,3,4-oxadiazin-5(6H)-ylidene)acetate (**12e**)*

M. p. 259 – 261 °C. – IR (KBr): ν = 3340 – 3305 (NH), 2220 (CN), 1695, 1730 (CO), 1620 cm^{-1} (C=N). – ^1H NMR ([D$_6$]DMSO): δ = 1.21 (t, J = 6.90 Hz, 3H, CH_3), 4.16 (q, J = 6.90 Hz, 2H, CH_2O), 6.98 – 7.55 (m, 5H, Ar-H), 9.85 (br, 1H, oxadiazine-NH), 11.71 (br, 1H, indole-NH). – ^{13}C NMR ([D$_6$]DMSO): δ = 14.31 (CH_3), 61.33 (CH_2O), 70.12 (C-CN), 111.23 (indole-CH), 118.65 (CN), 126.26, 126.76, 128.75, 129.24 (Ar-CH), 130.61, 131.55, 1232.25 (Ar-C and indole-C-2), 152.81 (C-5), 155.93 (C-2), 167.91 (ester-CO), 171.42 (oxadiazine-CO). – MS (EI, 70 eV): *m/z* (%) = 324 (26) $[M]^+$, 297 (16), 269 (28), 224 (51), 140 (33), 144 (100), 116 (76), 92 (67), 77 (54). – $C_{16}H_{12}N_4O_4$ (324.29): calcd. C 59.26, H 3.73, N 17.28; found C 59.41, H 3.64, N 17.46.

*Ethyl 1-benzoyl-4-cyano-5-oxo-2,5-dihydro-1H-pyrazole-3-carboxylate (**13a**)*

M. p. 227 – 229 °C. – IR (KBr): ν = 3345 (NH), 2220 (CN), 1710, 1680 and 1655 (CO), 1620 (C=N), 1590 cm^{-1} (Ar-C=C). – ^1H NMR ([D$_6$]DMSO): δ = 1.27 (t, J = 7.10 Hz, 3H, CH_3), 4.28 (q, J = 7.10 Hz, 2H, CH_2O), 7.36 – 7.87 (m, 5H, Ar-H), 12.51 (br, 1H, pyrazole-NH). – ^{13}C NMR ([D$_6$]DMSO): δ = 14.28 (CH_3), 61.49 (CH_2O), 88.12 (C-4), 118.62 (CN), 128.22, 128.93 and 129.84 (Ar-CH), 131.55 (Ar-C), 156.11 (C-3), 166.53 (C-5), 169.23 (CO-ester), 171.12 (CO). – MS (EI, 70 eV): *m/z* (%) = 285 (51) $[M]^+$, 257 (27), 240 (29), 180 (64), 105 (82), 77 (100), 65 (66). – $C_{14}H_{11}N_3O_4$ (285.25): calcd. C 58.95, H 3.89, N 14.73; found C 59.19, H 4.12, N 14.51.

*Ethyl 1-(thiophene-2-carbonyl)-4-cyano-5-oxo-2,5-dihydro-1H-pyrazole-3-carboxylate (**13b**)*

M. p. 237 – 239 °C. – IR (KBr): ν = 3330 (NH), 2225 (CN), 1725, 1675 and 1660 (CO), 1625 (C=N), 1585 cm^{-1} (Ar-C=C). – ^1H NMR ([D$_6$]DMSO): δ = 1.24 (t, J = 7.06 Hz, 3H, CH_3), 4.25 (q, J = 7.06 Hz, 2H, CH_2O), 7.19 – 7.82 (m, 3H, thiophene-H), 12.46 (br, 1H, pyrazole-NH). – ^{13}C NMR ([D$_6$]DMSO): δ = 14.28 (CH_3), 61.36 (CH_2O), 88.38 (C-4), 118.76 (CN), 127.83, 128.24 and 128.55 (thiophene-CH), 130.12 (thiophene-C-2), 155.89 (C-3), 165.94 (C-5), 168.97 (ester-CO), 170.92 (CO). – MS (EI, 70 eV): *m/z* (%) = 291 (39) $[M]^+$, 263 (11), 246 (54), 180 (36), 111 (100), 83 (56). – $C_{12}H_9N_3O_4S$ (291.28): calcd. C 49.48, H 3.11, N 14.43, S 11.01; found C 49.61, H 3.39, N 14.51, S 10.87.

*Ethyl 1-(furan-2-carbonyl)-4-cyano-5-oxo-2,5-dihydro-1H-pyrazole-3-carboxylate (**13c**)*

M. p. 199 – 201 °C. – IR (KBr): ν = 3340 (NH), 2220 (CN), 1720, 1685 and 1660 (CO), 1625 (C=N), 1590 (Ar-C=C), 1083 cm^{-1} (C–O–C). – ^1H NMR ([D$_6$]DMSO): δ = 1.22 (t, J = 7.11 Hz, 3H, CH_3), 4.27 (q, J = 7.11 Hz, 2H, CH_2O), 7.24 – 7.77 (m, 3H, furan-H), 12.62 (br, 1H, pyrazole-NH). – ^{13}C NMR ([D$_6$]DMSO): δ = 14.26 (CH_3), 61.34 (CH_2O), 89.11 (C-4), 118.81 (CN), 125.66, 140.18 (furan-CH), 143.36 (furan-C-2), 155.66 (C-3), 165.48 (C-5), 169.24 (ester-CO), 171.35 (CO). – MS (EI, 70 eV): *m/z* (%) = 275 (26) $[M]^+$, 247 (16), 180 (25), 95 (100), 67 (74). – $C_{12}H_9N_3O_5$ (275.05): calcd. C 52.37, H 3.30, N 15.27; found C 52.49, H 3.14, N 15.46.

*Ethyl 1-picolinoyl-4-cyano-5-oxo-2,5-dihydro-1H-pyrazole-3-carboxylate (**13d**)*

M. p. 231 – 233 °C. – IR (KBr): ν = 3325 (NH), 2215 (CN), 1710, 1680 and 1665 (CO), 1625 (C=N), 1600 cm^{-1} (Ar-C=C). – ^1H NMR ([D$_6$]DMSO): δ = 1.29 (t, J = 7.05 Hz, 3H, CH_3), 4.28 (q, J = 7.05 Hz, 2H, CH_2O), 7.61 – 8.44 (pyridyl-H), 12.45 (br, 1H, pyrazole-NH). – ^{13}C NMR ([D$_6$]DMSO): δ = 14.29 (CH_3), 61.41 (CH_2O), 89.35 (C-4), 119.16 (CN), 126.83, 127.22, 130.14, 143.22 (pyridyl-CH), 147.12 (pyridyl-C-2), 156.24 (C-3), 165.54 (C-5), 168.84 (ester-CO), 171.38 (CO). – MS (EI, 70 eV): *m/z* (%) = 286 (46) $[M]^+$, 258 (6), 180 (19), 106 (100), 78 (87). – $C_{13}H_{10}N_4O_4$ (286.24): calcd. C 54.55, H 3.52, N 19.57; found C 54.76, H 3.36, N 19.69.

*Ethyl 1-(1H-indole-2-carbonyl)-4-cyano-5-oxo-2,5-dihydro-1H-pyrazole-3-carboxylate (**13e**)*

M. p. 287 – 289 °C. – IR (KBr): ν = 3335, 3270 (NH), 2220 (CN), 1715, 1675 and 1660 (CO), 1625 (C=N), 1595 cm^{-1} (Ar-C=C). – ^1H NMR ([D$_6$]DMSO): δ = 1.23 (t, J = 7.12 Hz, 3H, CH_3), 4.25 (q, J = 7.12 Hz, 2H, CH_2O), 6.72 (indole-CH), 7.22 – 7.65 (m, 4H, Ar-H), 11.63 (br, 1H, indole-NH), 12.55 (br, 1H, pyrazole-NH). – ^{13}C NMR ([D$_6$]DMSO): δ = 14.22 (CH_3), 61.72 (CH_2O), 89.19 (C-4), 111.22 (indole-CH), 118.89 (CN), 126.74, 128.12, 128.81, 129.17 (Ar-CH), 130.55, 131.67 (Ar-C), 155.98

(C-3), 165.34 (C-5), 168.49 (ester-CO), 171.36 (CO). – MS (EI, 70 eV): *m/z* (%) = 324 (35) $[M]^+$, 296 (24), 180 (52), 144 (86), 116 (43), 92 (91), 77 (100), 65 (86). – $C_{16}H_{12}N_4O_4$ (324.29): calcd. C 59.26, H 3.73, N 17.28; found C 59.02, H 3.92, N 17.45.

Acknowledgement

A. A. Hassan is indebted to the Alexander von Humboldt-Foundation, Bonn, for the donation of the Shimadzu 408 IR spectrophotometer.

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