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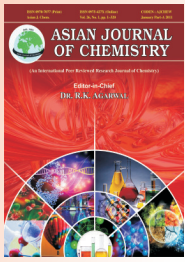

Functionalization Reactions of Various Pyrazole-3-carboxylic Acid Chlorides with Some Ureas

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The 1*H*-pyrazole-3-carboxylic acids **2** or their remarkably stable acid chlorides **3** can easily be converted into the corresponding 1*H*-pyrazole-3-carbonyl-N'-urea derivatives (**5a-k**) from reaction with urea nucleophiles. It has been demonstrated that with the variation in reaction conditions, the reaction changes thus leading to different products. All newly synthesized compounds were characterized by elemental analysis, FT-IR, ^{1}H and ^{13}C NMR spectral data. All compounds were compared with their previous analogues.

Keywords: Furan-2,3-dione, Pyrazole-3-carboxylic acid, Cyclic oxalyl compounds, Pyrazole-3-carboxylic acid chlorides.

INTRODUCTION

2,3-Furandiones in general are considered convenient and versatile synthons in heterocyclic synthesis[1]. A convenient method for their synthesis, the mechanism of reactions and semi-empirical (AM1 and PM3) and *ab initio* (DFT) calculations on the interaction of 4-benzoyl-5-phenyl-2,3-dihydro-2,3-furandione (**1**) with several semicarbazones, ureas, thioureas and anilides have been reported recently[2-7]. The reactions of 2,3-furandione (**1**) and various hydrazines or hydrazones result in new pyrazole-3-carboxylic acids, pyrazolo-pyridazinones and some of their derivatives. The pyrazole carboxylic acids can be easily transformed into the corresponding acid chloride, ester, or amide derivatives by general chemical procedures[8-12]. Pyrazole derivatives in general are well-known nitrogen-containing heterocyclic compounds and various procedures have been developed for their syntheses[13-15].

The chemistry of pyrazole derivatives has been the subject of much research due to their importance in various applications and their widespread potential biological and pharmacological activities, such as antiinflammatory, antipyretic, analgesic, antimicrobial, antiviral, antitumor, antifungal, pesticidal, anticonvulsant, CNS regulant, antihistaminic, antibiotic and antidepressant activities[16-25]. The possible biological properties of the pyrazol, pyridazinone, pyrazolopyridazinone[26] and oxazin derivatives make it attractive to study these compounds.

In view of these important properties, we decided both to provide the reproducibility of the reactions of 1*H*-pyrazole-3-carboxylic acid chlorides (**3a-b**) with urea-nucleophiles and to extend our investigations related to preparing new hetrocycles which include the pyrazole ring in their structure.

EXPERIMENTAL

Solvents were dried by refluxing over the appropriate drying agent and distilled before use. Melting points were determined on an Electrothermal 9200 apparatus and are not corrected. Microanalyses were performed on a Carlo Erba Elemental Analyzer Model 1108. The IR spectra were recorded on a Shimadzu Model 8400 FT IR spectrophotometer. The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker-400 MHz Ultra Shield instrument. The chemical shifts are reported in ppm from tetramethylsilane as an internal standard and are given in d (ppm). All experiments were followed by TLC using DC Alufolien Kieselgel 60 F 254 (Merck) and a Camag model TLC lamp (254/366 nm).

N-[4-Benzoyl-1-(4-nitrophenyl)-5-phenyl-1*H*-pyrazole-3-carbonyl]-N'-methylurea (5a): 4-Benzoyl-1-[4-nitrophenyl]-5-phenyl-1*H*-pyrazole-3-carboxylic acid chloride (**3a**) (0.50 g, 1.16 mmol) and N-methylurea (0.09 g, 1.16 mmol) were refluxed in xylene (50 mL) for 5 h. The solvent was evaporated and the remaining oily residue was treated with dry ether to give a crude product which was recrystallized from ethanol and dried on P_2O_5. m.p.: 221-222 °C, the product was obtained in 52 % (0.56 g) yield. FT-IR: 3450, 3350 (NH), 1705 (C=O, urea), 1680, 1670 (C=O). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.20, 9.10 (2H, -NH), 8.1-7.0 (m, 14H, Ar-H), 2,6 (CH_3). ^{13}C NMR (400 MHz, DMSO-d_6): δ = 190.07 (t, PhCO), 153.32 (C=O), 145.36 (C=O, urea), 144.25, (-C-NO_2), 12.39 (CH_3). Anal. calcd. for $C_{25}H_{19}N_5O_5$: C, 63.96; H, 4.05; N, 14.92. Found: C, 63.82; H, 4.11; N, 14.74.

N-[4-Benzoyl-1-(4-nitrophenyl)-5-phenyl-1*H*-pyrazole-3-carbonyl]-N'-ethylurea (5b): 4-Benzoyl-1-[4-nitrophenyl]-

5-phenyl-1*H*-pyrazole-3-carboxylic acid chloride (**3a**) (0.50 g, 1.16 mmol) and N-ethylurea (0.10 g, 1.16 mmol) were refluxed in xylene (50 mL) for 4 h. The solvent was evaporated and the remaining oily residue was treated with dry ether to give a crude product which was recrystallized from *n*-propanol and dried on P_2O_5. m.p.: 223-224 °C, the product was obtained in 86 % (0.48 g) yield. FT-IR: 3321, 3247 (NH), 1718 (C=O, urea), 1693, 1661 (C=O). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.95, 8.27 (2H, -NH), 8.22-7.06 (m, 14H, Ar-H), 3.30 (CH_2), 1.20 (CH_3). ^{13}C NMR (400 MHz, DMSO-d_6): δ =190.48 (t, PhCO), 161.49 (C=O), 152.51 (C=O, urea), 147.14 (-C-NO_2), 34.51 (CH_2), 19.80 (CH_3). Anal. Calcd. for $C_{26}H_{21}N_5O_5$: C, 64.59; H, 4.34; N, 14.49. Found: C, 64.87; H, 4.20; N, 14.30.

N-[4-Benzoyl-1-(4-nitrophenyl)-5-phenyl-1*H*-pyrazole-3-carbonyl]-N'-phenylurea(5c): 4-Benzoyl-1-[4-nitrophenyl]-5-phenyl-1*H*-pyrazole-3-carboxylic acid chloride (**3a**) (0.50 g, 1.16 mmol) and N-phenylurea (0.16 g, 1.16 mmol) were refluxed in xylene (50 mL) for 4 h. The solvent was evaporated and the remaining oily residue was treated with dry ether to give a yellow crude product which was recrystallized from *n*-propanol and dried on P_2O_5. m.p.: 212-213 °C, the product was obtained in 66 % (0.40 g) yield. FT-IR: 3337, 3263 (NH), 1693 (C=O, urea), 1680, 1670 (C=O). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.68, 8.45 (2H, -NH), 8.25-6.95 (m, 19H, Ar-H). ^{13}C NMR (400 MHz, DMSO-d_6): δ = 189.45 (t, PhCO), 155.81 (C=O), 146.25 (C=O, urea), 143.43 (-C-NO_2). Anal. calcd. for $C_{30}H_{21}N_5O_5$: C, 67.79; H, 3.95; N, 13.18. Found: C, 68.10; H, 3.69; N, 13.04.

N-[4-Benzoyl-1-(4-nitrophenyl)-5-phenyl-1*H*-pyrazole-3-carbonyl]-N'-ethylthiourea (5d): 4-Benzoyl-1-[4-nitrophenyl]-5-phenyl-1*H*-pyrazole-3-carboxylic acid chloride (**3a**) (0.50 g, 1.16 mmol) and N-ethylthiourea (0.12 g, 1.16 mmol) were refluxed in xylene (50 mL) for 4 h. The solvent was evaporated and the remaining oily residue was treated with dry ether to give a orange crude product which was recrystallized from *n*-propanol and dried on P_2O_5. m.p.: 195-196 °C, the product was obtained in 81 % (0.47 g) yield. FT-IR: 3300, 3263 (NH), 1672, 1660 (C=O), 1517, (C=S). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.70, 8.45 (2H, -NH), 8.30-7.02 (m, 14H, Ar-H), 3.70 (CH_2), 1.30 (CH_3). ^{13}C NMR (400 MHz, DMSO-d_6): δ = 190.11 (t, PhCO), 162.50 (C=O), 149.00 (C=S), 146.91, (-C-NO_2), 35.06 (CH_2), 26.08 (CH_3). Anal. calcd. for $C_{26}H_{21}N_5O_4S$: C, 62.52; H, 4.20; N, 14.03, S, 6.41. Found: C, 62.66; H, 4.17; N, 13.85; S,.6.17.

N-[4-Benzoyl-1-(2,4-dinitrophenyl)-5-phenyl-1*H*-pyrazole-3-carbonyl]-N'-methylurea (5e): 4-Benzoyl-1-[2,4-dinitrophenyl]-5-phenyl-1*H*-pyrazole-3-carboxylic acid chloride (**3b**) (0.50 g, 1.05 mmol) and N-methylurea (0.08 g, 1.05 mmol) were refluxed in xylene (50 mL) for 5 h. The solvent was evaporated and the remaining oily residue was treated with dry ether to give a crude product which was recrystallized from ethanol and dried on P_2O_5. m.p.: 211-212 °C, the product was obtained in 56 % (0.6 g) yield. FT-IR: 3450-3350 (NH); 1705 (C=O, urea), 1680, 1670 (C=O). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.10, 9.20 (2H, -NH), 8.1-7.0 (m, 13H, Ar-H), 2,8 (CH_3). ^{13}C NMR (400 MHz, DMSO-d_6): δ =189.19 (t, PhCO), 154.81(C=O), 146.55 (C=O, urea), 145.36, 143.38 (-C-NO_2), 12.96 (CH_3). Anal. calcd. for $C_{25}H_{18}N_6O_7$: C, 58.36; H, 3.50; N, 16.34. Found: C, 58.25; H, 3.61; N, 16.53.

N-[4-Benzoyl-1-(2,4-dinitrophenyl)-5-phenyl-1*H*-pyrazole-3-carbonyl]-N'-ethylurea (5f): 4-Benzoyl-1-[2,4-dinitrophenyl]-5-phenyl-1*H*-pyrazole-3-carboxylic acid chloride (**3b**) (0.50 g, 1.05 mmol) and N-ethylurea (0.09 g, 1.05 mmol) were refluxed in xylene (50 mL) for 4 h. The solvent was evaporated and the remaining oily residue was treated with dry ether to give a yellow crude product which was recrystallized from ethanol and dried on P_2O_5. m.p.: 195-196 °C, the product was obtained in 83 % (0.46 g) yield. FT-IR: 3450-3350 (NH); 1700 (C=O, urea), 1643, 1610 (C=O). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.10, 8.90 (2H, -NH), 8.80-7.20 (m, ^{13}H, Ar-H), 2.80 (CH_2), 1.10 (CH_3). ^{13}C NMR (400 MHz, DMSO-d_6): δ = 189.19 (t, PhCO), 154.81 (C=O), 146.55 (C=O, urea), 145.36, 143.38 (-C-NO_2), 34.57 (CH_2), 12.96 (CH_3). Anal. calcd. for $C_{26}H_{20}N_6O_7$: C, 59.09; H, 3.78; N, 15.91. Found: C, 58.90; H, 3.66; N, 16.10.

N-[4-Benzoyl-1-(2,4-dinitrophenyl)-5-phenyl-1*H*-pyrazole-3-carbonyl]-N'-phenylurea (5g): 4-Benzoyl-1-[2,4-dinitrophenyl]-5-phenyl-1*H*-pyrazole-3-carboxylic acid chloride (**3b**) (0.50 g, 1.05 mmol) and N-phenylurea (0.14 g, 1.05 mmol) were refluxed in xylene (50 mL) for 4 h. The solvent was evaporated and the remaining oily residue was treated with dry ether to give a white crude product which was recrystallized from ethanol and dried on P_2O_5. m.p.: 175-176 °C, the product was obtained in 68 % (0.41 g) yield. FT-IR: 3328-3198 (NH); 1680 (C=O, urea), 1670, 1639 (C=O). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.80, 8.60 (2H, -NH), 8.20-7.10 (m, 18H, Ar-H). ^{13}C NMR (400 MHz, DMSO-d_6):δ =189.43 (t, PhCO), 155.82 (C=O), 146.24 (C=O, urea), 137.95, 136.73 (-C-NO_2). Anal. calcd. for $C_{30}H_{20}N_6O_7$: C, 62.50; H, 3.47; N, 14.58. Found: C, 62.65; H, 3.60; N, 14.45.

N-[4-Benzoyl-1-(4-nitrophenyl)-5-phenyl-1*H*-pyrazole-3-carbonyl]-N',N'-dimethylurea (5h): 4-Benzoyl-1-[4-nitrophenyl]-5-phenyl-1*H*-pyrazole-3-carboxylic acid chloride (**3a**) (0.50 g, 1.16 mmol) and N,N-dimethylurea (0.10 g, 1.16 mmol) were refluxed in xylene (50 mL) for 4 h. The solvent was evaporated and the remaining oily residue was treated with dry ether to give a brown crude product which was recrystallized from *n*-propanol and dried on P_2O_5. m.p.: 209-210 °C, the product was obtained in 77 % (0.44 g) yield. FT-IR: 3394, (NH), 1705 (C=O, urea), 1664, 1620 (C=O). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.20 (1H, -NH), 7.70-7.02 (m, 14H, Ar-H), 3.23, 2.98 ($2CH_3$). ^{13}C NMR (400 MHz, DMSO-d_6): δ = 190.32 (t, PhCO), 178.52 (C=O), 178.45 (C=O, urea), 159.94 (-C-NO_2), 13.59, 13.44 ($2CH_3$). Anal. calcd. for $C_{26}H_{21}N_5O_5$: C, 64.59; H, 4.34; N, 14.49. Found: C, 64.45; H, 4.02; N, 14.70.

N-[4-Benzoyl-1-(2,4-dinitrophenyl)-5-phenyl-1*H*-pyrazole-3-carbonyl]-N',N'-dimethylurea (5k): 4-Benzoyl-1-[2,4-dinitrophenyl]-5-phenyl-1*H*-pyrazole-3-carboxylic acid chloride (**3b**) (0.50 g, 1.05 mmol) and N,N-dimethylurea (0.09 g, 1.05 mmol) were refluxed in xylene (50 mL) for 4 h. The solvent was evaporated and the remaining oily residue was treated with dry ether to give a brown crude product which was recrystallized from *n*-propanol and dried on P_2O_5. m.p.: 164-165 °C, the product was obtained in 82 % (0.45 g) yield. FT-IR: 3394 (NH); 1703 (C=O, urea), 1643, 1606 (C=O). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.80 (1H, -NH), 8.60-7.20 (m, 13H, Ar-H), 3.00 ($2CH_3$). Anal. Calcd. for $C_{26}H_{20}N_6O_7$: C, 59.09; H, 3.78; N, 15.91. Found: C, 59.34; H, 3.87; N, 15.69.

RESULTS AND DISCUSSION

In the present study, our approach to obtaining the particular heterocyclic systems uses the synthesis of the 1*H*-pyrazole-3-carboxylic acid (**2a-b**) from 4-benzoyl-5-phenyl-2,3-dihydro-2,3-furandione (**1**) and 4-nitrophenylhydrazine and 2,4-dinitrophenylhydrazine, respectively. The compounds **2a-b** can easily be transformed into the corresponding 1*H*-pyrazole-3-carboxylic acid chlorides (**3a-b**) by the usual chemical procedures. Substituted 2,3-furandione, acid **2** and acid chlorides **3a-b**, which are used as important materials in the synthesis of the target heterocycles, were prepared using the literature procedures[1,8,26-30].

We carried out the reaction of the compounds **3a-b** with various urea derivatives in boiling xylene which gave the corresponding new structures 1*H*-pyrazole-3-carbonyl-N'-urea derivatives (**5a-k**) as main product (**Scheme-I**). The progress of the reactions was monitored by thin-layer chromatography until complete consumption of the starting materials. The compounds **5a-k** were obtained in excellent yields (52-86 %), after evaporation of the organic solvents and recrystallization from proper solvents (like ethanol, *n*-propanol). The reactions of the compound **3a** with N-ethylurea led to the formation of **5b**, under reflux in xylene for 4 h, in 86 % yield without opening the pyrazole ring. In order to make the reaction selective, we had to determine the parameters, in other words, the reaction pathway, leading to such results. The good yield of the reaction can be explained by the chemical behaviour of compounds **3a-b** towards H-active nucleophiles, such as ureas. It should start with a nucleophilic attack of the nitrogen atoms' lone pair electrons of the urea to the antibonding (π^*) orbital at the carbonyl carbon at C3 position of the pyrazol ring. The by-products formed in this way are removed when the raw products are treated with diethyl ether.

The obtained new products **5a-k** followed by the elimination of hydrogen chloride. In the FT-IR spectrum of compound **5b**, the -NH absorption bands were found to be at about 3321-3247 cm^{-1} and the C=O absorption was seen at 1718 cm^{-1}. The ^1H NMR signals were found to be at 8.95 and 8.27 (2H, -NH); 8.22-7.06 (m, 14H, Ar-H), 3.30 (CH_2), 1.20 (CH_3). The ^{13}C NMR signals were observed at 190.48 (t, PhCO), 161.49 (C=O), 152.51 (C=O, urea), 147.14, (-C-NO_2), 34.51 (CH_2) and 19.80 (CH_3). Finally, the elemental analysis data along with spectroscopic data confirm the structure of **5b**.

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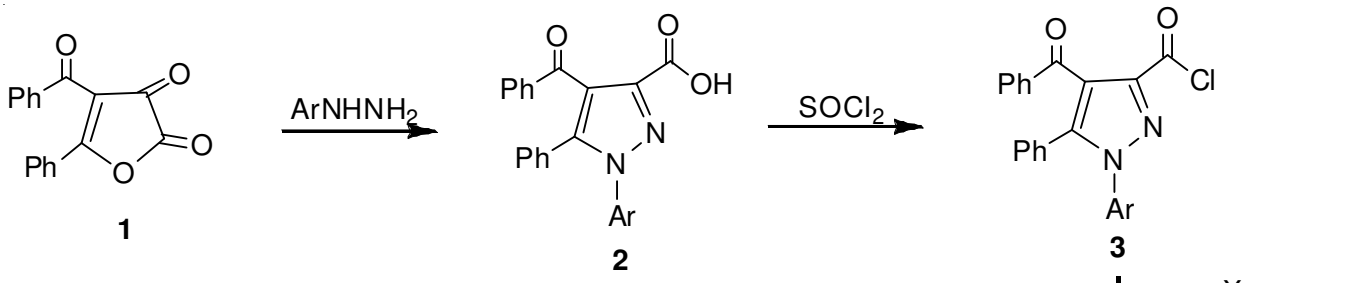
REFERENCES

1. E. Ziegler, M. Eder, C. Belegratis and E. Prewedourakis, *Monatsh. Chem.*, **98**, 2249 (1967).
2. B. Altural, Y. Akçamur, E. Saripinar, I. Yildirim and G. Kollenz, *Monatsh. Chem.*, **120**, 1015 (1989).



4,5	X	R_1	R_2
a	O	-H	$-CH_3$
b	O	-H	$-C_2H_5$
c	O	-H	-Ph
d	S	-H	$-C_2H_5$
e	O	-H	$-CH_3$
f	O	-H	$-C_2H_5$
g	O	-H	-Ph
h	O	$-CH_3$	$-CH_3$
k	O	$-CH_3$	$-CH_3$

2, 3	Ar
a	O_2N, NO_2
b	NO_2

Scheme-I: Synthesis of the 1*H*-pyrazole-3-carbonyl-N'-urea derivatives (**5a- k**)

3. I. Yildirim, E. Saripinar, Y. Güzel, S. Patat and Y. Akçamur, *J. Mol. Struct*., **334**, 165 (1995).
4. I. Yildirim, M. Tezcan, Y. Güzel, E. Saripinar and Y. Akçamur, *Turk J. Chem*, **20**, 27 (1996).
5. I. Yildirim and I.Ö. Ilhan, *J. Heterocycl. Chem*., **34**, 1047 (1997).
6. E. Saripinar, I. Ozer Ilhan and Y. Akçamur, *Heterocycles*, **57**, 1445 (2002).
7. I.Ö. Ilhan, E. Saripinar and Y. Akçamur, *J. Heterocycl. Chem*., **42**, 117 (2005).
8. Y. Akcamur, G. Penn, E. Ziegler, H. Sterk, G. Kollenz, K. Peters, E.-M. Peters and H.G. Schnering, *Monatsh. Chem*., **117**, 231 (1986).
9. Y. Akçamur, A. Sener, A.M. Ipekoglu and G. Kollenz, *J. Heterocycl. Chem.*, **34**, 221 (1997).
10. A. Sener, M. Kasim Sener, I. Bildmci, R. Kasimogullari and Y. Akçamur, *J. Heterocycl. Chem.*, **39**, 869 (2002).
11. I. Yildirim, F. Kandemirli and Y. Akçamur, *J. Mol. Struct*., **738**, 275 (2005).
12. I. Yildirim, F. Kandemirli and E. Demir, *Molecules*, **10**, 559 (2005).
13. J.A. Joule, K. Mills and G.F. Smith, Heterocyclic Chemistry, Chapman & Hall: London, UK, edn, 3, Chap. 22, pp. 402-405 (1995).
14. G. Daidone, D. Rafa, F. Plescia, B. Maggio and A. Roccaro, ARKIVOC, XI, 227 (2002).
15. J. Elguero, in eds.: A.R. Katritzky and C.W. Rees, In: Comprehensive Heterocyclic Chemistry, Pergamon, Oxford, Vol. 5, p. 167 (1984).
16. R.N. Mahajan, F.H. Havaldar and P.S. Fernandes, *J. Indian Chem. Soc*., **68**, 245 (1991).
17. P.G. Baraldi, S. Manfredini, R. Romagnoli, L. Stevanato, A.N. Zaid and R. Manservigi, *Nucleosides Nucleotides*, **17**, 2165 (1998).
18. G.J. Hatheway, C. Hansch, K.H. Kim, S.R. Milstein, C.L. Schmidt, R.N. Smith and F.R. Quinn, *J. Med. Chem*., **21**, 563 (1978).
19. R. Riedel, *Drug Res*., **31**, 655 (1981).
20. P.D. Mishra, S. Wahidullah and S.Y. Kamat, *Indian. J. Chem.*, **37B**, 199 (1998).
21. M. Londershausen, *Pestic. Sci*., **48**, 269 (1996).
22. M.R. Harnden, S. Bailey, M.R. Boyd, D.R. Taylor and N.D. Wright, *J. Med. Chem*., **21**, 82 (1978).
23. A.G.A. Elagamey, F.A. El-Taweel, F.A. Amer and H.H. Zoorob, *Arch. Pharm*., **320**, 246 (1987).
24. A.K. Tewari and A. Mishra, *Bioorg. Med. Chem*., **9**, 715 (2001).
25. P. Máatyus, *J. Heterocycl. Chem*., **35**, 1075 (1998).
26. I. Bildirici, A. Sener and I. Tozlu, *Med. Chem. Res*., **16**, 418 (2007).
27. I.Ö. Ilhan, Y. Akçamur, E. Saripinar and E. Aslan, *Asian J. Chem*, **15**, 1373 (2003).
28. I.Ö. Ilhan, S. Zühal, Z. Önal and E. Saripinar, *Heterocycl. Commun*., **15**, 279 (2009).
29. I.Ö. Ilhan, Ö. Bahadir, Z. Önal and E. Saripinar, *Asian J. Chem*., **24**, 141 (2012).
30. I.Ö. Ilhan and M. Çadir, *Asian J. Chem*., **25**, 1647 (2013).