Conversion of Some 2(3*H*)-Furanones into Pyrrolinotriazine and Oxazolopyrimidine Derivatives

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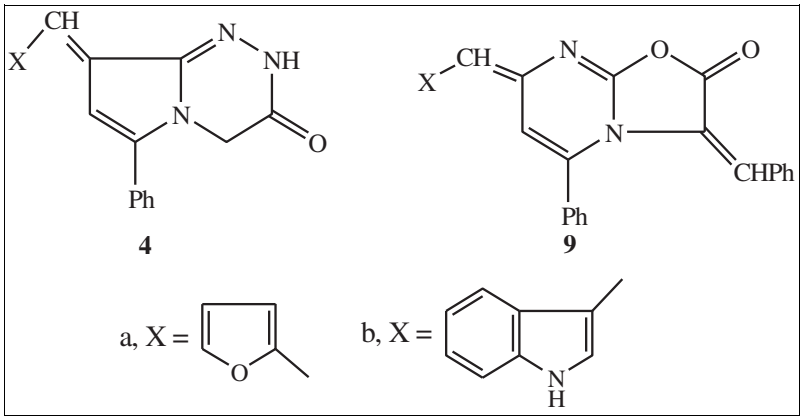

2(3*H*)-Furanones **1** were utilized for the construction of pyrrolinotriazine and oxazolopyrimidine derivatives **4** and **9**. Thus, **1** reacted with glycine in ethanol at 70°C to give the acids **2**, which were cyclized into the pyrrolin-5-one derivatives **3** by the action of HCl/AcOH. The later compounds **3** were also obtained by refluxing the furanones **1** with glycine in glacial AcOH for 10 h. The carboxy functionality in **3** was used for the construction of a triazinone ring by treatment with thionyl chloride followed by refluxing the acid chloride with hydrazine in ethanol. The conversion of the furanones **1** into the oxazolopyrimidine derivatives **9** involved the following steps: (i) ring opening of the lactone ring with hydrazine hydrate to give the acid hydrazides **5**, (ii) conversion of the hydrazides **5** into the corresponding acyl azides **6** by action of NaNO2/AcOH, (iv) base-catalyzed decomposition of the azides in the presence of glycine, (v) ring closure of the urea derivatives **7** into the pyrimidine derivatives **8**, and finally (vi) condensing **8** with benzaldehyde in the presence of NaOAc/AcOH mixture.

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INTRODUCTION

The reactions of 2(3*H*)-furanones **1** with nitrogen nucleophiles have been the subject of many investigations by our research group. It was found that under mild conditions [1–4] at room temperature, the opening of the lactone ring occurred to give the corresponding acyclic products, which on cyclization produced heterocyclic ring systems of synthetic and biological importance, e.g., pyrrolines, pyridazinones, triazoles, but when the reaction is conducted under more drastic conditions, e.g., in boiling polar solvent [5] or by fusion [6], the cyclic products are formed directly.

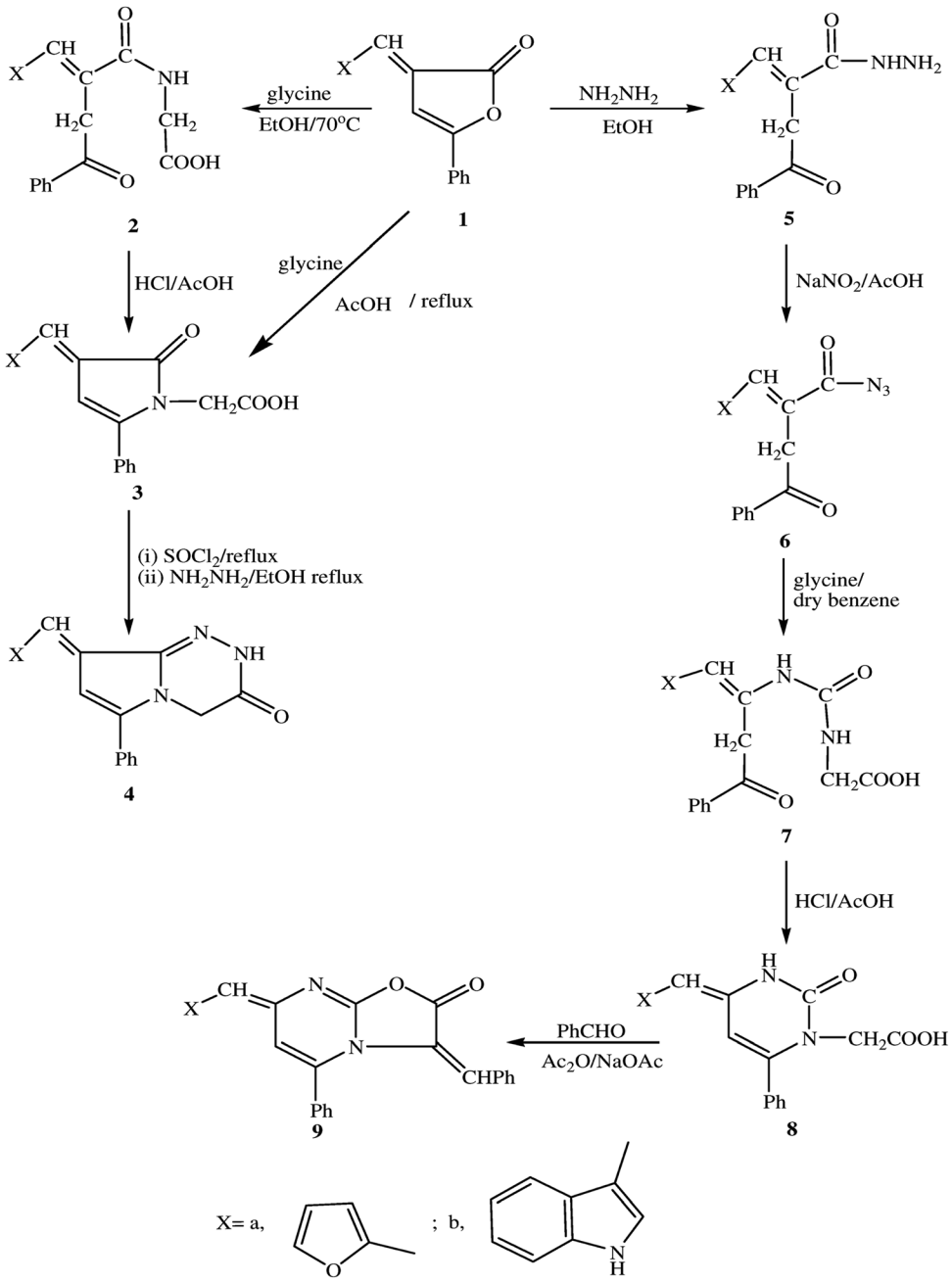
The utilization of 2(3*H*)-furanones for the construction of a wide variety of nitrogenous heterocyclic ring systems had been a subject of research concern [7]. But, to our knowledge, the conversion of 2(3*H*)-furanones into pyrimidine and triazine derivatives have not yet been reported.

In this investigation, we wish to report the conversion of the furanones **1** into pyrrolinotriazine and oxazolopyrimidine derivatives. These compounds have been reported to act as modulators of metabotropic glutamate receptors (mGluR); therefore, they are useful as pharmaceutical agents and have wide spectrum of biological activities [8,9].

RESULTS AND DISCUSSION

The amino-acid, glycine, failed to affect ring opening of the furanones **1** at room temperature, a behavior that may be attributed to the poor nucleophilicity of the glycine nitrogen atom. But, when the reaction was carried out in ethanol at 70°C, ring opening occurred with the formation of the acids **2**. Refluxing the later acids with HCl/AcOH mixture, led to the formation of the pyrrolin-5-one derivatives **3**. The same products **3** were obtained by carrying the reaction in refluxing acetic acid. The carboxy functionality in the later compounds was utilized for the construction of a triazinone ring. Thus, on treating **3** with thionyl chlorides followed by refluxing the acid chloride obtained

Scheme 1



with hydrazine hydrate in ethanol, the pyrrolinotriazinone derivatives **4** were obtained. The furanones **1** reacted with hydrazine hydrate at room temperature in ethanol to give the acid hydrazides **5**. These hydrazides were converted into the corresponding acyl azides **6** by the action of sodium nitrite and AcOH. Base-catalyzed decomposition of the later azides **6** in the presence of glycine led to the formation of the urea derivatives **7**. When the later derivatives were refluxed in HCl/AcOH mixture, ring closure occurred with the formation of the pyrimidine derivatives **8**.

It was of interest to the authors to obtain the oxazolopyrimidine derivatives **9** by refluxing **8** with benzaldehyde in the presence of NaOAc/Ac_2O mixture. All these reactions involved in this study are illustrated by Scheme 1. The structures of the products obtained were

inferred from their analytical, as well as, spectral data (cf. Experimental section).

EXPERIMENTAL

Melting points were measured on an electrothermal melting point apparatus. Elemental analyses were performed using a Heraeus CHN rapid analyzer at the Microanalytical unit, Cairo University. IR spectra were measured on a Unicam SP-1200 spectrophotometer using KBr wafer technique. ^{1}H NMR spectra were measured in DMSO-d_6 on a Varian plus instrument (300 MHz).

General procedure for the preparation of 5-phenyl-3-heterylmethylene-2(3*H*)-furanones (1). These compounds were prepared according to the procedure described by previous investigators [10–12].

General procedure for the preparation of 3-benzoyl-2-heterylmethylene propionic acid hydrazides (5). These compounds were prepared according to the procedure described by previous investigators [1,5].

General procedure for the reaction of the 5-phenyl-3-heterylmethylene-2(3H)-furanones 1 with glycine. A suspension of the furanones **1** (1 mmol) and glycine (2 mmol) in (20 mL) ethanol were refluxed at 70°C for 6 h and left to cool. The solid obtained was filtered off, washed, and recrystallized from ethanol and was found to be 2-(2-heterylmethylene-4-oxo-4-phenylbutanamido) acetic acid **2**.

2-(2-(Furan-2-ylmethylene)-4-oxo-4-phenylbutanamido) acetic acid (2a). Colorless crystals (60% yield), m.p 170–172°C. IR: ν_{max} 3,150–3,500 (OH), 3,320 (NH), 1,700, 1,680, 1,630 (C═O) cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 3.19 (s, 2H, CH_2—CO), 3.95 (s, 2H, $\underline{CH_2}$—COOH), 6.50 (s, 1H, HC═), 7.01–7.98 (m, 8H, ArH), 8.12 (br.s, 1H, NH, exchangeable), 12.01 (br.s, 1H, OH, exchangeable). *Anal.* Calcd. for $C_{17}H_{15}NO_5$: C, 65.17; H, 4.83; N, 4.47. Found: C, 65.41; H, 4.65; N, 4.61.

2-(2-((1H-indol-3-yl)methylene)-4-oxo-4-phenylbutanamido) acetic acid (2b). Colorless crystals (50% yield), m.p 140–141°C. IR: ν_{max} 3,220–3,500 (OH), 3,300 (NH), 1,705, 1,677, 1,640 (C═O) cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 3.22 (s, 2H, CH_2CO), 3.91 (s, 2H, $\underline{CH_2}$—COOH), 6.52 (s, 1H, HC═), 6.97–8.03 (m, 11H, 10ArH + NH), 8.23 (br.s, 1H, NH—CO, exchangeable), 11.95 (br.s, 1H, OH, exchangeable). *Anal.* Calcd. for $C_{21}H_{18}N_2O_4$: C, 69.60; H, 5.01; N, 7.73.Found: C, 69.89; H, 4.77; N, 7.92.

General procedure for the ring closure of compounds (2). A solution of **2** (1 gm) in a mixture of (HCl-AcOH) (1:1) (30 mL), was heated under reflux for 1 h and then left to cool. The solid obtained was collected by filtration, washed with water and recrystallized from benzene/ethanol to give pyrrolone derivatives **3**.

The same products **3** were obtained when furanones **1** (1 mmol) and glycine (2 mmol) were refluxed in acetic acid (10 mL) for 10 hrs and then poured into ice-cold water. The crystals separated were filtered off and recrystallized from ethanol.

2-(3-(Furan-2-ylmethylene)-2-oxo-5-phenyl-2,3-dihydropyrrol-1-yl)acetic acid (3a). Bright yellow crystals (70% yield), m.p 130–131°C. IR: ν_{max} 3,200–3,450 (OH), 1,700, 1,641 (C═O) cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 3.92 (s, 2H, $\underline{CH_2}$COOH), 6.50 (s, 1H, HC═), 6.65–7.89 (m, 9H, ArH), 12.01 (br.s, 1H, OH, exchangeable). *Anal.* Calcd. for $C_{17}H_{13}NO_4$: C, 69.15; H, 4.44; N, 4.74. Found: C, 68.93; H, 4.60; N, 4.89.

2-(3-((1H-indol-3-yl)methylene)-2-oxo-5-phenyl-2,3-dihydropyrrol-1-yl)acetic acid (3b). Bright yellow crystals (75% yield), m.p 115–117°C. IR: ν_{max} 3,250–3,420 (OH), 3,300 (NH), 1,700, 1,640 (C═O) cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 3.90 (s, 2H, $\underline{CH_2}$COOH), 6.54 (s, 1H, HC═), 6.90–7.99 (m, 12H, 11ArH + NH), 12.01 (br.s, 1H, OH, exchangeable). *Anal.* Calcd. for $C_{21}H_{16}N_2O_3$: C, 73.24; H, 4.68; N, 8.13. Found: C, 73.40; H, 4.81; N, 8.24.

General procedure for the preparation of pyrrolotriazinone derivatives (4). A mixture of pyrrolin-5-one derivatives **3** (1 mmol) and thionyl chloride (20 mL, 0.17 mol) was refluxed for 3 h. The excess thionyl chloride was then evaporated under vacuum. The oily product obtained was dissolved in ethanol (20 mL), and 4 mL of hydrazine was added. The reaction mixture was heated under reflux for 2 h and left to cool. The solid obtained was filtered off, washed and recrystallized from ethanol and was found to be 8-heterylmethylene-6-phenylpyrrolo[2,1-c][1,2,4]triazin-3(2*H*, 4*H*, 8*H*)-one **4**.

8-(Furan-2-ylmethylene)-6-phenylpyrrolo[2,1-c][1,2,4]triazin-3(2H, 4H, 8H)-one (4a). Yellow crystals (60% yield), m.p 250–252°C. IR: ν_{max} 3,210 (NH), 1,631 (C═O) cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 3.62 (s, 2H, CH_2CO), 6.62 (s, 1H, CH═), 6.80–7.56 (m, 9H, ArH), 8.32 (s, 1H, NH—CO, exchangeable). *Anal.* Calcd. for $C_{17}H_{13}N_3O_2$: C, 70.09; H, 4.50; N, 14.42. Found: C, 70.21; H, 4.68; N, 14.67.

8-((1H-indol-3-yl)methylene)-6-phenylpyrrolo[2,1-c][1,2,4]triazin-3(2H, 4H, 8H)-one (4b). Yellow crystals (65% yield), m.p 300–302°C. IR: ν_{max} 3,200, 3,210 (NH), 1,640 (C═O) cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 3.60 (s, 2H, CH_2CO), 6.66 (s, 1H, HC═), 6.80–7.86 (m, 12H, 11ArH + NH), 8.21 (br.s, 1H, NH, exchangeable). *Anal.* Calcd. for $C_{21}H_{16}N_4O$: C, 74.10; H, 4.74; N, 16.46. Found: C, 73.95; H, 4.91; N, 16.63.

General procedure for the reaction of hydrazides 5 with $NaNO_2$/AcOH. To a solution of hydrazide **5** (2 gm) in AcOH (20 mL) cooled in an ice-bath at 5°C, a cold $NaNO_2$ solution was added dropwise while stirring. After complete addition, the reaction mixture was left at room temperature for 30 min and then poured into ice-cold water. The crystals separated were filtered-off, washed with cold water, and found to be 1-azido-2-heterylmethyl-4-phenylbutane-1,4-dione **6**.

1-Azido-2-(furan-2-ylmethylene)-4-phenylbutane-1,4-dione (6a). Yellow crystals (52% yield), m.p 94–96°C. IR: ν_{max} 2,150 (N_3), 1,760, 1,710 (C═O) cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 3.22 (s, 2H, CH_2CO), 6.60 (s, 1H, HC═), 7.21–7.88 (m, 8H, ArH). *Anal.* Calcd. for $C_{15}H_{11}N_3O_3$: C, 64.05; H, 3.94; N, 14.94. Found: C, 64.23; H, 3.71; N, 15.02.

1-Azido-2-((1H-indol-3-yl)methylene)-4-phenylbutane-1,4-dione (6b). Yellow crystals (50% yield), m.p 114–116°C. IR: ν_{max} 2,120 (N_3), 1,757, 1,712 (C═O) cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 3.20 (s, 2H, CH_2CO), 6.62 (s, 1H, HC═), 7.30–8.11 (m,11H, 10ArH + NH). *Anal.* Calcd. for $C_{19}H_{14}N_4O_2$: C, 69.08; H, 4.27; N, 16.96. Found: C, 69.27; H, 4.35; N, 17.10.

General procedure for the reaction of azido compounds 6 with glycine. The azido compound **6** (1 mmol) and glycine (1mmol) in 10 mL of dry benzene was heated under reflux for 1 h. The reaction mixture was concentrated, and the solid product obtained was filtered off and recrystallized from benzene/ethanol and was found to be ureido acetic acid derivatives **7**.

2-(3-(1-(Furan-2-yl)-4-oxo-4-phenylbut-1-en-2-yl)ureido) acetic acid (7a). Brown crystals (45% yield), m.p 224–226°C. IR: ν_{max} 3,300–3,450 (OH), 3,320 (NH), 1,705, 1,680, 1,632

(C═O) cm^{-1}. ^1H NMR (DMSO-d_6): δ 3.19 (s, 2H, CH_2CO), 4.21 (s, 2H, CH_2COOH), 6.12 (s, 1H, HC═), 7.06–8.17 (m, 8H, ArH), 9.30 (br.s, 1H, NH, exchangeable), 9.51 (br.s, 1H, NH, exchangeable), 11.92 (br.s, 1H, COOH, exchangeable). *Anal*. Calcd. for $C_{17}H_{16}N_2O_5$: C, 62.19; H, 4.91; N, 8.53. Found: C, 62.35; H, 5.02; N, 8.77.

2-(3-(1-H-indol-3-yl)-4-oxo-4-phenylbut-1-en-2-yl)ureido) acetic acid(7b). Orange crystals (40% yield), m.p 260–261°C. IR: ν_{max} 3,310–3,500 (OH), 3,325, 3,320 (NH), 1,700, 1,671, 1,630 (C═O) cm^{-1}. ^1H NMR (DMSO-d_6): δ 3.22 (s, 2H, CH_2CO), 4.23 (s, 2H, CH_2COOH), 6.21 (s, 1H, HC═), 6.83–8.12 (m, 11H, 10ArH + NH), 9.32 (br.s, 1H, NH, exchangeable), 9.54 (br.s, 1H, NH, exchangeable), 12.02 (br.s, 1H, COOH, exchangeable). *Anal*. Calcd. for $C_{21}H_{19}N_3O_4$: C, 66.83; H, 5.07; N, 11.13. Found: C, 66.97; H, 5.31; N, 10.95.

General procedure for the ring closure of compounds (7). A solution of **7** (1 gm) in a mixture of (HCl-AcOH) (1:1) (30 mL), was heated under reflux for 1 hr. Then left to cool, the solid obtained was collected by filtration, washed with water and recrystallized from benzene/ethanol to give pyrimidinone derivatives **8**.

2-(4-Furan-2-ylmethylene)-2-oxo-6-phenyl-3,4-dihydropyrimidin-1(2H)-yl)acetic acid (8a). Yellow crystals (50% yield), m.p 195–196°C. IR: ν_{max} 3,200–3,500 (OH), 3,320 (NH), 1,701, 1,645 (C═O) cm^{-1}. ^1H NMR (DMSO-d_6): δ 4.17 (s, 2H, CH_2), 5.93 (br.s, 1H, NH, exchangeable), 6.31 (s, 1H, HC═), 6.52–7.54 (m, 9H, ArH), 12.09 (br.s, 1H, OH, exchangeable). *Anal*. Calcd. for $C_{17}H_{14}N_2O_4$: C, 65.80; H, 4.55; N, 9.03. Found: C, 66.07; H, 4.80; N, 9.15.

2-(4-((1H-indol-3-yl)methylene)-2-oxo-6-phenyl-3,4-dihydropyrimidin-1(2H)-yl)acetic acid (8b). Yellow crystals (62% yield), m.p 200–202°C. IR: ν_{max} 3,250–3,490 (OH), 3,300, 3,250 (NH), 1,690, 1,642 (C═O) cm^{-1}. ^1H NMR (DMSO-d_6): δ 4.10 (s, 2H, CH_2), 6.01 (s, 1H, HC═), 6.21 (br.s, 1H, NH, exchangeable), 7.10–8.21 (m, 12H, 11ArH + NH), 11.98 (br.s, 1H, OH, exchangeable). *Anal*. Calcd. for $C_{21}H_{17}N_3O_3$: C, 70.18; H, 4.77; N, 11.69. Found: C, 70.35; H, 4.98; N, 11.92.

General procedure for the preparation of oxazolopyrimidinone derivatives(9). A mixture of **8** (10 mmol), benzaldehyde (10 mmol), sodium acetate (30 mmol), and acetic anhydride (10 mL) was heated under reflux for 1 h, whereby a clear solution was obtained. On cooling, a brown yellow material was obtained, which was triturated with ethanol. The solid obtained was filtered off and recrystallized from methanol to give oxazolopyrimidinone derivatives **9**.

3-Benzylidene-7-(furan-2-ylmethylene)-5-phenyl-3H-oxazolo [3,2-a] pyrimidin-2(7H)-one (9a). Bright yellow crystals (72% yield), m.p 215–216°C. IR: ν_{max} 1,750 (C═O), 1,620 (C═N), 1,600 (C═C) cm^{-1}. ^1H NMR (DMSO-d_6) : δ 6.55 (s, 1H, ═CH),6.69 (s, 1H, ═CH),6.92–7.51 (m, 14H, ArH). *Anal*. Calcd. for $C_{24}H_{16}N_2O_3$: C, 75.78; H, 4.24; N, 7.36. Found: C, 75.93; H, 4.51; N, 7.19.

7-((1H-indol-3-yl)methylene)-3-benzylidene-5-phenyl-3H-oxazolo[3,2-a] pyrimidin-2(7H)-one (9b). Orange crystals (75% yield), m.p 219–220°C. IR: ν_{max} 3,312 (NH), 1,753 (C═O), 1,620 (C═N), 1,598 (C═C) cm^{-1}. ^1H NMR (DMSO-d_6): δ 6.10 (s, 1H, ═CH), 6.80 (s, 1H, ═CH),7.14–8.30 (m, 17H, 16ArH + NH). *Anal*. Calcd. for $C_{28}H_{19}N_3O_2$: C, 78.31; H, 4.46; N, 9.78. Found: C, 78.54; H, 4.70; N, 9.93.

REFERENCES AND NOTES

[1] Hashem, A. I.; Shaban, M. E. J Prakt Chem 1981, 323, 164.

[2] Hamad, A. S.; Hashem, A. I. J Heterocycl Chem 2002, 39, 1325.

[3] Kandeel, K. A.; Youssef, A. S. A.; Abou Elmagd, W. S. I.; Hashem, A. I. J Heterocycl Chem 2006, 43, 957.

[4] Hamad, A. S.; Zaki, M. Y.; Eid, N. N.; Hashem, A. I. Heteroatom Chem 2003, 14, 570.

[5] Hashem, A. I.; Youssef, A. S. A.; Kandeel, K. A.; Abou Elmagd, W. S. I. Eur J Med Chem 2007, 42, 934.

[6] Hamad, A. S.; Derbala, H. A.; Elsayed, W. A.; Hashem, A. I. Acta Chim Solv 2001, 48, 417.

[7] Hashem, A. I.; Senning, A. Adv Heterocycl Chem 1999, 73, 275.

[8] Möhrle, H.; Hemmerling, H. Arch Pharm 1977, 310, 588.

[9] Lancelot, J. C.; Maume, D.; Robba, M. J Heterocycl Chem 1980, 17, 631.

[10] Khan, R. H.; Rastogi, R. C. J Chem Res 1991, 260.

[11] Hashem, A. I.; Kandeel, K. A.; Youssef, A. S. A.; Abou-Elmagd, W. S. I. J Chem Res 2006, 315.

[12] Hashem, A. I. J Prakt Chem 1977, 319, 689.