Reactions of 1,4-Dianion of Methyl 2-Thienyl Ketone N-Ethoxycarbonylhydrazone with Carboxylic Acid Derivatives and the Synthesis of Pyrazolotriazin-7-ones

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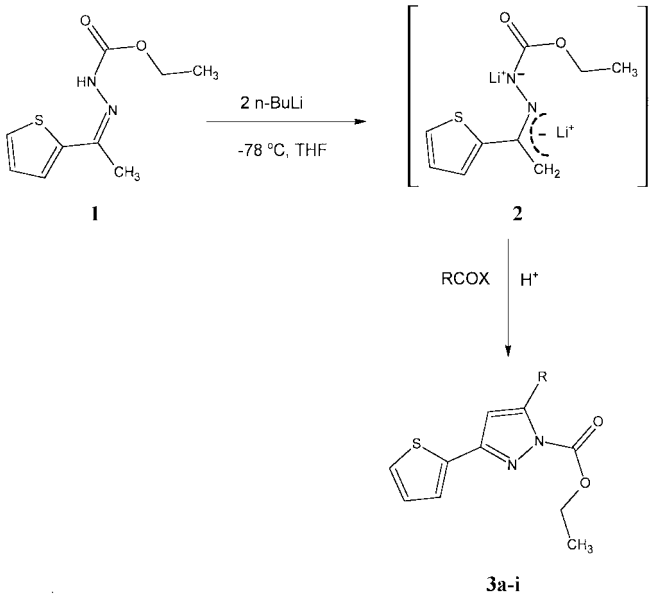
Received January 11, 2002

Keywords : Dianion reactions, 1,3,5-Trisubstituted pyrazoles, Pyrazolotriazin-7-ones.

Pyrazoles and pyrazolotriazines are important materials for medicinal, agricultural and other studies.[1-4] Diverse biological activities such as bactericidal, pesticidal, anticonvulsant, tuberculostatic, anti-inflammatory, etc., have been found to be associated with pyrazole derivatives. In recent years, several new methods for the preparation of pyrazole derivatives have been reported in the literatures.[5-7] However, little attention has been directed to obtain 3-hetero substituted pyrazoles. Thus, we reported here the synthesis of some 3-thiophen-2-yl-5-substituted pyrazoles by the reaction of butyl formate, methyl benzoate, ethyl benzoylacetate, methyl 3-chlorobenzoate, ethyl hexanoate, ethyl pyruvate, ethyl phenylglyoxylate, acetyl chloride and phenoxyacetyl chloride with dianion of methyl 2-thienyl ketone N-ethoxycarbonyl-hydrazone. Moreover, 1,4-dianion of N-monosubstituted hydrazones[8] have received much attention as synthetic intermediates owing to their interesting reactivities and preparative significance.

In a typical reaction, a freshly prepared methyl 2-thienyl ketone N-ethoxycarbonylhydrazone **1** (mp. 114 °C) which was obtained from condensation of methyl 2-thienyl ketone and N-ethoxycarbonylhydrazide[9] in ethanol was dissolved in tetrahydrofuran and treated with 2 molar equiv. of *n*-buthyl-lithium in hexane under argon. To the resulting reddish brown colored solution **2** was added methyl 2-thienyl ketone N-ethoxycarbonylhydrazone (**1**) one molar equivalent of esters or acid chlorides at -78 °C, and this was followed by acid cyclization with 3N hydrochloric acid, and chromatography of the product. Optimum yields of products were obtained when the ratio of hydrazone : base : ester (or acid chloride) was 1 : 2 : 1; this is consistent with the proposed mechanism. The sequence in Scheme 1 would account for the results obtained. We also treated **3f** and **3g** with phenylhydrazine in methanol under reflux. The hydrazone indermediate was converted into the corresponding 4-methyl (or phenyl)-6-phenyl-2-(thiophen-2-yl)-6H-pyrazolo[1,5-d]-[1,2,4]triazin-7-ones **4a**, **b** by treatment with potassium hydroxide in methanol under reflux.[10]

C=O band of ester group which is attached on nitrogen appeared at 1690-1670 cm^{-1}. The methylene and methyl signals of ethyl group of ester appeared at δ 1.49-1.44 ppm as a quartet and δ 4.57-4.50 ppm as a triplet in their ^1H NMR

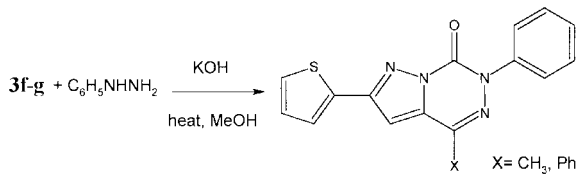


1 **2** **3a-i**

Scheme 1. Synthesis of **3a-i**.

spectra, respectively in $CDCl_3$. Compound **3f** and **3h** had methyl signals as a singlet at 2.25 ppm and 2.43 ppm, respectively. Besides, methylene groups of the substituents (benzoylmethyl- and phenoxymethyl-) at 5-position of the pyrazole ring displayed a singlet at δ 4.52 ppm for **3c** and a singlet at δ 5.35 ppm for **3i**. Compound **3e** gave multiplet peaks at δ 1.36-1.07 ppm due to hexyl substituent. **4a,b** are also in agreement with the structures reported.[11]

The ^{13}C NMR spectra of the compounds **3a,b,d,e,h,i** in $CDCl_3$ gave C=O signals at 150.00-139.53 ppm. On the other hand, phenyl substituted C=O signal appeared for **3c** at δ 201.60 ppm for **3f** at 191.12 ppm, for **3g** at 183.49 ppm respectively. The structures of the all compounds have also been confirmed by their mass spectral data.



4a,b

Scheme 2. Synthesis of **4a-b**.

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Table 1. Yields of **3a-i**

Compound	R	X	Yield (%)
3a	H	$OCH_2(CH_2)_2CH_3$	78
3b	C_6H_5	OCH_3	92
3c	$C_6H_5COCH_2$	OC_2H_5	53
3d	*m*-Cl C_6H_5	OCH_3	58
3e	$CH_3(CH_2)_4CH_2$	OC_2H_5	72
3f	CH_3CO	C_6H_5	44
3g	C_6H_5CO	C_6H_5	56
3h	CH_3	Cl	23
3i	$C_6H_5OCH_2$	Cl	43

Experimental Section

Melting points are uncorrected and were measured in open capillaries with an Electrothermal IA 9100 melting point apparatus. Infrared spectra were recorded on a Philips PU 9714 spectrometer as KBr pellets unless otherwise indicated. NMR spectra were determined on a Nicolet 300 MHz (compounds **3a**, **e-h**, **4a**, **b**) and on a Varian 200 MHz spectrometers in $CDCl_3$ with TMS as internal standard. Mass spectra of new compounds were obtained with a Shimadzu GS/MS QP 2000A spectrometer with 70 ev electron impact ionization. Column chromatography was performed with silica gel 60 (70-230 mesh) purchased from E. Merck AG. Thin layer choromatography (TLC) were carried out using Merck 5554 and Watmann 4410222 silica gel sheets with fluorescent indicators.

Synthesis of 5-substituted 1-ethoxycarbonyl-3-(2-thienyl) pyrazoles (3a-i); General Procedure. To a THF solution of **1** (2.42 mmol) was added a hexane solution of *n*-buthyllithium (5.32 mmol) with stirring at -78 ºC under argon. To the resulting reddish brown colored solution was added dropwise a THF solution of an ester or acid chloride (2.18 mmol). After complete fading of the color, the reaction mixture **2** was stirred for additional 2 hours at -78 ºC, and the solvent was removed in vacuo. The residual mixture was treated with conc.HCl, acetic acid, water and methanol (10 ml each), and stirred for 2 hours at room temperature. After methanol was evaporated, the residue was extracted with ether, and the extract chromatographed on silica gel column with toluene. Evaporation of the solvent gave pure compound **3**.

3a: mp. 129 ºC; IR (KBr): ν 1670 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 8.14-6.62 (m, 5H, aromatic), 4.56-4.50 (q, 2H, $OC\mathbf{H_2}CH_3$), 1.49-1.45 (t, 3H, $OCH_2C\mathbf{H_3}$) ppm; ^{13}C NMR ($CDCl_3$, 300 MHz): δ 151.88-107.54 (aromatic), 149.97 (N-C=O), 65.31(OCH_2), 14.88 (CH_3) ppm; MS: m/z 222.26 (M^+), ($C_{10}H_{10}N_2O_2S$).

3b: mp. 114 ºC; IR (KBr): ν 1680 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 7.65-6.52 (m, 9H, aromatic), 4.55-4.51 (q, 2H, $OC\mathbf{H_2}CH_3$), 1.48-1.44 (t, 3H, $OCH_2C\mathbf{H_3}$) ppm; ^{13}C NMR ($CDCl_3$, 200 MHz): δ 158.97-105.37 (aromatic), 141.31 (N-C=O), 62.80 (OCH_2), 13.90 (CH_3) ppm; MS: m/z 298.35 (M^+), ($C_{16}H_{14}N_2O_2S$).

3c: mp. 136 ºC; IR (KBr): ν 1750, 1690 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 7.72-7.05 (m, 9H, aromatic), 4.54-4.50 (q, 2H, $OC\mathbf{H_2}CH_3$), 4.52 (s, 2H, CH_2), 1.46-1.45 (t, 3H, $OCH_2C\mathbf{H_3}$) ppm; ^{13}C NMR ($CDCl_3$, 200 MHz): δ 201.60 (C=O), 155.38-118.17 (aromatic), 139.53 (N-C=O), 62.80 (OCH_2), 38.41 (CH_2), 13.90 (CH_3) ppm; MS: m/z 340.39 (M^+), ($C_{18}H_{16}N_2O_3S$).

3d: mp. 108 ºC; IR (KBr): ν 1680 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 7.88-6.86 (m, 8H, aromatic), 4.57-4.53 (q, 2H, $OC\mathbf{H_2}CH_3$), 1.48-1.46 (t, 3H, $OCH_2C\mathbf{H_3}$) ppm; ^{13}C NMR ($CDCl_3$, 200 MHz): δ 158.97-105.37 (aromatic), 141.31 (N-C=O), 62.81 (OCH_2), 13.90 (CH_3) ppm; MS: m/z 332.80 (M^+), ($C_{16}H_{13}N_2O_2SCl$).

3e: mp. 138 ºC; IR (KBr): ν 1670 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.72-6.38 (m, 4H, aromatic), 4.57-4.51 (q, 2H, $OC\mathbf{H_2}CH_3$), 2.97-2.95 (t, 2H, CH_2), 1.73-1.67 (p, 2H, CH_2), 1.48-1.44 (t, 3H, $OCH_2C\mathbf{H_3}$), 1.36-1.07 (m, 9H, CH_2) ppm; ^{13}C NMR ($CDCl_3$, 300 MHz): δ 160.40-109.33 (aromatic), 141.51 (N-C=O), 62.80 (OCH_2), 31.46-27.37 (CH_2), 14.01 (CH_3), 13.89 (CH_3) ppm; MS: m/z 306.42 (M^+), ($C_{16}H_{22}N_2O_2S$).

3f: mp. 98 ºC; IR (KBr): ν 1720, 1670 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.52-7.22 (m, 4H, aromatic), 4.59-4.53 (q, 2H, $OC\mathbf{H_2}CH_3$), 2.25 (s, 3H, CH_3), 1.45-1.43 (t, 3H, $OCH_2C\mathbf{H_3}$); ^{13}C NMR ($CDCl_3$, 300 MHz): δ 191.12 (C=O), 156.31-112.55 (aromatic), 143.16 (N-C=O), 63.43 (OCH_2), 12.75 (CH_3), ppm; MS: 264.30 m/z (M^+), ($C_{12}H_{12}N_2O_3S$).

3g: mp. 107 ºC; IR (KBr): ν 1710, 1690 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 8.27-7.04 (m, 9H, aromatic), 4.54-4.51 (q, 2H, $OC\mathbf{H_2}CH_3$), 1.48-1.42 (t, 3H, $OCH_2C\mathbf{H_3}$); ^{13}C NMR ($CDCl_3$, 300 MHz): δ 183.49 (C=O), 157.41-110.30 (aromatic), 140.71 (N-C=O), 62.81 (OCH_2), 13.93 (CH_3), ppm; MS: 325.36 m/z (M^+), ($C_{17}H_{13}N_2O_3S$).

3h: mp. 126 ºC; IR (KBr): ν 1690 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.72-6.49 (m, 4H, aromatic), 4.57-4.51 (q, 2H, $OC\mathbf{H_2}CH_3$), 2.43 (CH_3), 1.46-1.43 (t, 3H, $OCH_2C\mathbf{H_3}$) ppm; ^{13}C NMR ($CDCl_3$, 300 MHz): δ 159.58-105.69 (aromatic), 141.67 (N-C=O), 62.80 (OCH_2), 13.90 (CH_3), 13.04 (CH_3) ppm; MS: m/z 236.29 (M^+), ($C_{11}H_{12}N_2O_2S$).

3i: mp. 139 ºC; IR (KBr): ν 1685 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 7.72-6.72 (m, 9H, aromatic), 5.35 (s, 2H, CH_2), 4.57-4.51 (q, 2H, $OC\mathbf{H_2}CH_3$), 1.48-1.44 (t, 3H, $OCH_2C\mathbf{H_3}$) ppm; ^{13}C NMR ($CDCl_3$, 200 MHz): δ 160.50-104.07 (aromatic), 139.30 (N-C=O), 64.80 (OCH_2), 62.95 (OCH_2), 14.25 (CH_3) ppm; MS: m/z 328.39 (M^+), ($C_{17}H_{16}N_2O_3S$).

General procedure for the synthesis of 4-substituted 6-phenyl-2-thiophen-2-yl-6H-pyrazolo[1,5-d][1,2,4]triazin-7-ones (**4a**, **b**). To a stirred solution of **3f** or **3g** (1 mmol) in methanol (10 mL) was added the phenylhydrazine (1 mmol) in methanol (10 mL) and the reaction was allowed to react at room temperature for 4h under magnetic stirring. The solvent was evaporated under reduced pressure and the crude reaction product was purified by column chromatography (cyclohexane-ethyl acetate 2 : 1) affording the pure compounds **4a**, **b**.

4a: mp.162 ºC; IR (KBr): ν 1685 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 8.92-6.36 (m, 9H, aromatics), 2.48 (s, 3H, CH_3) ppm; ^{13}C NMR ($CDCl_3$, 300 MHz): δ 158.25-105.42 (aromatics and carbonyl), 12.77 (CH_3) ppm; MS : m/z

308.36 (M^+), ($C_{16}H_{12}N_4OS$).

4b: mp.132 °C; IR (KBr): ν 1678 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 8.87-6.43 (m, 14H, aromatic) ppm; ^{13}C NMR ($CDCl_3$, 300 MHz): δ 156.13-109.42 (aromatics and carbonyl) ppm; MS: m/z 370.42 (M^+), ($C_{21}H_{14}N_4OS$).

Acknowledgment. This work was completed Dr. Ihsan Erdens laboratory in San Francisco State University. We thank to him for kindly helping for our work and NMR and mass measurements. We are grateful for a NATO post-doctoral fellowship, administered by Tubitak of Turkey to Dr. Öcal.

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