Iranian Journal of Organic Chemistry Vol. 6, No. 3 (2014) 1299-1303

Synthesis of 4*H*-pyrano[2,3-*d*]pyrimidine derivatives under solvent-free conditions

Ghasem Marandi[a]*, Malek Taher Maghsoodlou[b], Nourallah Hazeri[b], Sayed Mostafa Habibi-Khorassani[c], Zahra Shakarami[b] and Hasan Hosseini-Mahdiabad[b]

[a]*Shahid Bakeri High Education Center of Miandoab, Urmia University, Urmia, Iran*
[b]*Department of Organic Chemistry, Faculty of Science, the University of Sistan and Baluchestan, P. O. Box 98135-674, Zahedan, Iran*
[c]*Department of Physical Organic Chemistry, Faculty of Science, the University of Sistan and Baluchestan, P. O. Box 98135-674, Zahedan, Iran.*

Received: May 2014; Revised: June 2014; Accepted: July 2014

Abstract: A convenient one-pot synthesis of 4*H*-pyrano[3,2-*d*]pyrimidine derivatives is presented from reaction between dialkyl acetylenedicarboxylates and alkyl isocyanides in the presence of *N*,*N*′–dimethylbarbituric acid under solvent-free conditions.

Keywords: Alkyl or aryl isocyanides, Acetylenic diester, *N*,*N*′-dimethylbarbituric acid, Pyrimidine derivatives, Solvent-free conditions.

Introduction

The preparation of organic compounds using eco-friendly synthetic methodologies is a major task for organic chemists [1-3]. One strategy to address this goal involves the development of reactions in which reactants are combined, without any solvent, to gather [4,5]. Such protocols have a specific position in synthetic organic chemistry. The reactions were undertaken in the absent of using any toxic organic solvents, thus advantage of present method is minimizing of cost, operational hazards and environmental pollution. To deploy the green chemistry approaches in organic reactions, we were encouraged to use no solvent in our works for the synthesis of 4*H*-pyrano[3,2-*d*]pyrimidine derivatives.

Results and discussion

Recently, we reported the reaction between isocyanides and dialkyl acetylenedicarboxylates in the presence of *N*,*N*′-dimethylbarbituric acid. The reaction undergoes a smooth reaction in dichloromethane at room temperature to produce the isomeric products (**1**) and (**2**) (Figure 1) [6-8].

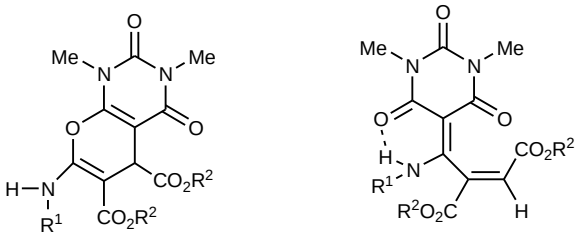


Figure 1: Pyrimidine containing structures.

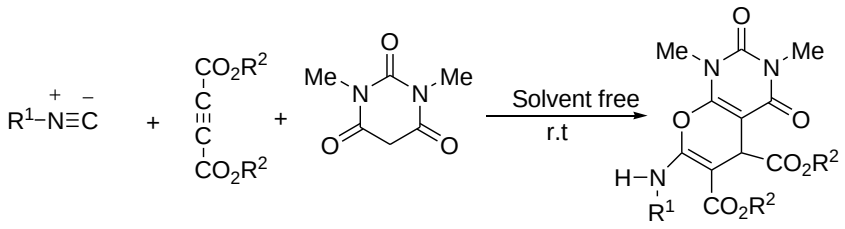
This endeavor succeeded in numerous cases if the reactions could be ran as solid-state reactions. The use of less solvent in organic reaction in place of

*Corresponding author. Tel: (+98) 4445266070, Fax: (+98) 4445265756, E-mail: marandi_gh@yahoo.com

commonly used organic solvents as reported in the application of green chemistry, also has been promoted us to use it in our current work to develop an alternate route for the recent synthesis, in improved yield, short reaction time and safe condition, while many previous works suffer since prolonged reaction time, use of excess of reagent/catalyst, low yield and also use of toxic organic solvent.

In continuation to our synthetic investigations on the base of isocyanide chemistry and also electron deficient acetylenic diesters [9-12], we now describe an efficient synthesis of 4*H*-pyrano[2,3-*d*]pyrimidine derivatives with mixture of identical stoichiometric proportion of pure reactants under solvent-free conditions.

The work reported here was undertaken in order to study the reaction between alkyl or aryl isocyanides **3** and acetylenic diesters **4** in the presence of *N*,*N*′-dimethylbarbituric acid **5** (Scheme 1).



3 **4** **5** **6**

Scheme 1: Synthesis of 4*H*-pyrano[2,3-*d*]pyrimidine.

The spectral data and physical properties of the 4*H*-pyrano[2,3-*d*]pyrimidines **6a-k** are in a good agreement with those of literature reported [6-8]. Our work shows that the 4*H*-pyrano[2,3-*d*]pyrimidine derivatives can be synthesized in solvent-free conditions in excellent yields (Table I).

Table 1: Hydroarylation reaction of phenylacetylene **1** with mesitylene **2d** in the presence of BF_3 catalyst under different reaction conditions.

Entry	R^1	R^2	Yield(%)	m.p	m.p[ref]
6a	Cyclohexyl	Me	97	208-209	210-211 [6]
6b	Cyclohexyl	Et	95	126-128	128-130 [7]
6c	Cyclohexyl	*t*-Bu	90	161-162	161-163 [7]
6d	*t*-Bu	Me	90	149-150	150-151 [6]
6e	*t*-Bu	Et	95	114-116	116-118 [7]
6f	*t*-Bu	*t*-Bu	90	144-146	146-148 [7]
6g	2,6-dimethylphenyl	Et	90	136-137	135-137 [7]
6h	2,6-dimethyl phenyl	*t*-Bu	94	142-143	142-144 [7]
6i	CH_2CO_2Et	Me	96	209-211	210-211 [6]
6j	CH_2CO_2Et	Et	90	126-128	……
6k	CH_2CO_2Et	*t*-Bu	87	120-122	……

On the basis of the well-established chemistry of isocyanides [13-17], the reaction undergoes a smooth 1:1:1 addition reaction under solvent free at room temperature to produce the 4*H*-pyrano[2,3-*d*]pyrimidines **6a-k** (Scheme 1).

Although the compounds **6a-i** are known compounds, but compounds **6j** and **6k** are new

compounds whose structure are deduced from elemental analysis, IR, ^{1}H and ^{13}C NMR as well as mass spectroscopy.

Conclusion

In conclusion, solventless system was chosen because it has been proved to have many advantages: reduced pollution, low cost and simplicity in process and handling.

Experimental

Dialkyl acetylenedicarboxylates, alkyl or aryl isocyanides and *N*,*N'*- dimethylbarbituric acid were obtained from Fluka and Merck and used without further purification. Melting points were measured on an Electrothermal 9100 apparatus. IR spectra were recorded on a Shimadzu IR-460 spectrometer (pellets with KBr). Elemental analyses for C, H and N were performed using a Heraeus CHN-O-Rapid analyzer. The ^{1}H and ^{13}C NMR spectra were measured on a BRUKER DRX-300 AVANCE spectrometer instrument with $CDCl_3$ as a solvent.

*General Procedures (Exemplified by **6a**):*

In a mortar, a mixture of *N*,*N'*- dimethylbarbituric acid (1 mmol) and dimethyl acetylenedicarboxylate (DMAD) (1 mmol) was crushed vigorously to give a homogeneous mass, and then cyclohexyl isocyanide (1 mmol) was added dropwise and the mixture was thoroughly ground with a pestle at ambient temperature for 30 min. The reaction mixture was allowed to stand for 24 h at room temperature until the reaction was completed by TLC monitoring. The precipitate was thoroughly washed with (2×3) mL diethyl ether to obtained compound (**6a**).

Dimethyl-7-cyclohexylamino-2,4-dioxo-1,3-dimethyl-4H-pyrano[2,3-d]pyrimidine-5,6-dicarboxylate (**6a**):

Yellow powder, yield: (97%), mp. 208-209 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.10-2.10 (m, 10 H, 5 CH_2), 3.27 (m, 1 H, N-CH), 3.35, 3.48 (2s, 6 H, 2 N-CH_3), 3.70 and 3.80 (2s, 6 H, 2 OMe), 4.60 (s, 1 H, CH), 8.72 (br s, 1 H, NH…O=C) ppm; IR (KBr) (ν_{max}, cm^{-1}): 3255 (N-H), 1698, 1730 (C=O).

Diethyl-7-cyclohexylamino-2,4-dioxo-1,3-dimethyl-4H-pyrano[2,3-d]pyrimidine-5,6 dicarboxylate (**6b**):

Yellow powder, yield: (95%), mp. 126-128 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.32-2.10 (m, 10 H, 5 CH_2), 1.25 and 1.36 (t, 6 H, 2 Me of 2 CH_2CH_3), 3.34, 3.46 (2s, 6 H, 2 N-CH_3), 3.62 (s, 1 H, N-CH), 4.12 and 4.21 (m, 4 H, 2 OCH_2), 4.58 (s, 1 H, CH), 8.72 (br s, 1 H, NH…O=C) ppm; IR (KBr) (ν_{max}, cm^{-1}): 3350 (N-H), 1651, 1709 (C=O).

Di-tert-butyl-7-cyclohexylamino-2,4-dioxo-1,3-dimethyl-4H-pyrano[2,3-d]pyrimidine-5,6-dicarboxylate (**6c**):

Yellow powder, yield: (90%), mp. 161-162 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.34-2.10 (m, 10 H, 5 CH_2), 1.44 and 1.49 (s, 18 H, 2 CMe_3), 3.32 and 3.43 (2s, 6 H, 2 N-CH_3), 3.45 (s, 1 H, N-CH), 4.42 (s, 1 H, CH), 8.65 (br s, 1 H, NH…O=C) ppm; IR (KBr) (ν_{max}, cm^{-1}): 3380 (N-H), 1690, 1717 (C=O).

Dimethyl-7-tert-butylamino-2,4-dioxo-1,3-dimethyl-4H-pyrano[2,3-d]pyrimidine-5,6-dicarboxylate (**6d**):

Pale Yellow powder, yield: (90%), mp. 149-150 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ= 1.52 (s, 9 H, CMe_3), 3.40 and 3.58 (2s, 6 H, 2 N-CH_3), 3.78 and 3.82 (2s, 6 H, 2 OMe), 4.62 (s, 1 H, CH), 9.0 (br s, 1 H, NH…O=C) ppm; IR (KBr) (ν_{max}, cm^{-1}): 3216(N-H); 1693, 1720 (C=O).

Diethyl-7-tert-butylamino-2,4-dioxo-1,3-dimethyl-4H-pyrano[2,3-d]pyrimidine-5,6-dicarboxylate (**6e**):

Pale Yellow powder, yield: (95%), mp. 114-116 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.22 and 1.25 (t, 6 H, 2 Me of 2 CH_2CH_3), 1.41 (s, 9 H, CMe_3), 3.28 and 3.51 (2s, 6 H, 2 N-CH_3), 4.07 and 4.21 (m, 4 H, 2 OCH_2), 4.53 (s, 1 H, CH), 8.95 (br s, 1 H, NH…O=C) ppm; IR (KBr) (ν_{max}, cm^{-1}): 3270 (N-H); 1606, 1652, 1716 (C=O).

Di-tert-butyl-7-tert-buthylamino-2,4-dioxo-1,3-dimethyl-4H-pyrano[2,3-d]pyrimidine-5,6-dicarboxylate (**6f**):

Yellow powder, yield: (90%), mp. 144-146 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ= 1.42 (s, 9 H, $NCMe_3$), 1.43 and 1.49 (s, 18 H, 2 CMe_3), 3.34 and 3.51 (2s, 6 H, 2 N-CH_3), 4.42 (s, 1 H, CH), 8.91 (br s, 1 H, NH…O=C) ppm; IR (KBr) (ν_{max}, cm^{-1}): 3400 (N-H); 1652, 1683, 1712 (C=O).

Diethyl-7(2,6-dimethylphenylamino)-2,4-dioxo-1,3-dimethyl-4H-pyrano[2,3-d]pyrimidine-5,6-dicarboxylate (**6g**):

Yellow powder, yield: (90%), mp. 136-137 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ= 1.29 and 1.33 (t, 6 H, 2 Me of 2 CH_2CH_3), 2.20 and 2.33 (s, 6 H, 2 Me of $ArMe_2$), 2.79 and 3.29 (2s, 6 H, 2 N-CH_3), 4.18 and 4.27 (m, 4 H, 2 OCH_2), 4.65 (s, 1 H, CH), 7.09 (t, 1 H,

J_{meta}= 3.2 Hz, ArH), 7.13 (dd, 2H, J_{orto}= 8.2 Hz, ArH), 9.74 (br s, 1 H, NH…O=C) ppm; IR (KBr) (ν_{max}, cm^{-1}): 3270 (N-H); 1695, 1715, 1725 (C=O).

Di-tert-butyl-7(2,6-dimethylphenylamino)-2,4-dioxo-1,3-dimethyl-4H-pyrano[2,3-d]pyrimidine-5,6-dicarboxylate (**6h**):

Yellow powder, yield: (94%), mp. 142-143 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.47 and 1.56 (s, 18 H, 2 CMe_3), 2.18 and 2.33 (s, 6 H, 2Me of $ArMe_2$), 2.77 and 3.32 (2s, 6 H, 2 N-CH_3), 4.51 (s, 1 H, CH), 7.07 (t, 1 H, J_{meta}= 3 Hz, ArH), 7.12 (dd, 2H, J_{orto}=8.6, ArH), 9.71 (br s, 1 H, NH…O=C) ppm; IR (KBr) (ν_{max}, cm^{-1}): 3250 (N-H); 1650, 1660, 1690 (C=O).

Dimethyl-7-ethoxycarbonylmethylamino-2,4-dioxo-1,3-dimethyl-4H-pyrano[2,3-d]pyrimidine-5,6-dicarboxylate (**6i**):

Yellow powder, yield: (96%), mp. 209-211 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.30 (t, 3 H, $^3J_{HH}$= 7.0 Hz, CH_3), 3.31 and 3.43 (2s, 6 H, 2 N- CH_3), 3.70 and 3.76 (2s, 6 H, 2 O-CH_3), 4.13 (complex ABX system, 2 H, N-CH_2), 4.24 (m, 2 H, O-CH_2), 4.60 (s, 1 H, CH), 8.86 (br s, 1 H, NH…O=C) ppm; IR (KBr) (ν_{max}, cm^{-1}): 3255 (N-H); 1653, 1701, 1736 (C=O).

Diethyl-7-ethoxycarbonylmethylamino-2,4-dioxo-1,3-dimethyl-4H-pyrano[2,3-d]pyrimidine-5,6-dicarboxylate (**6j**):

Yellow powder, yield: (90%), mp. 126-128 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.26-1.32 (m, 9 H, 3 CH_3), 3.34 and 3.41 (2s, 6 H, 2 N- CH_3), 4.02-4.34 (m, 8 H, 4 CH2), 4.60 (s, 1 H, CH), 8.90 (br t, 1 H, NH…O=C) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$): δ= 14.09, 14.11 and 14.27 (3Me of CH_2-*CH_3*), 28.26 and 28.91 (2 NMe), 35.78 (CH), 43.17 (NCH_2), 60.23, 61.27 and 62.29 (3 OCH_2), 75.50 and 88.52 (2 *C*=C-O), 150.22 and 151.26 (2 C=*C*-O), 157.57, 161.09, 168.40, 168.89 and 173.3 (5 C=O); IR (KBr) (ν_{max}, cm^{-1}): 3265 (N-H); 1654, 1721, 1729 (C=O); MS (70 eV): *m*/*z* = 440 (M^+, 2), 394 (3), 366 (100), 338 (3), 322 (1), 263 (8), 292 (15), 235 (33), 66 (8); Anal. Calcd for $C_{19}H_{25}N_3O_9$ (439.42): C, 51.94; H, 5.69; N, 9.57. Found: C, 52.15; H, 5.65; N, 9.48.

Di-tert-butyl-7-Ethoxycarbonylmethyl-amino-2,4-dioxo-1,3-dimethyl-4H-pyrano[2,3-d]pyrimidine-5,6-dicarboxylate (**6k**):

Yellow powder, yield: (87%), mp. 120-122 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ= 1.30 (t, 3 H, $^3J_{HH}$= 7.1 Hz, CH_3), 1.46 and 1.53 (2s, 19 H, 2 C-*Me_3*), 3.36 and 3.42 (2s, 6 H, 2 N-CH_3), 4.12 (complex ABX system, 2 H, N-CH_2), 4.24 (m, 2 H, O-CH_2), 4.47 (s, 1 H, CH), 8.89 (br t, 1 H, NH…O=C) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 14.15 (Me), 28.01 and 28.41 (3Me of CMe_3), 28.28 and 28.93 (2 NMe), 36.91 (CH), 43.19 (NCH_2), 61.57 and 61.79 (2 OCH_2), 77.13 and 88.28 (2 *C*=C-O), 150.37 and 151.44 (2 C=*C*-O), 157.47, 161.05, 168.12, 169.53 and 173.00 (5 C=O) ppm; IR (KBr) (ν_{max}, cm^{-1}): 3255 (N-H); 1699, 1725, 1745 (C=O); MS (70 eV): *m*/*z* = 495 (M^+, 2), 440 (3), 394 (28), 338 (100), 335, (2), 320 (15), 292 (13), 235 (18), 57 (42), 41 (14); Anal. Calcd for $C_{23}H_{33}N_3O_9$ (495.52): C, 55.76; H, 6.67; N, 8.48. Found: C, 55.80; H, 6.72; N, 8.56.

Acknowledgement

We gratefully acknowledge financial support from the Research council of the University of Sistan and Baluchestan.

References

[1] Li, C. J. *Chem. Rev*. **2005**, *105*, 3095.
[2] Colacino, E.: Lamaty, F.; Martinez, J.; Parrot, I. *Tetrahedron Lett*. **2007**, *48*, 5317.
[3] Varma, R. S. *Green Chem*. **1999**, *1*, 43.
[4] Balalaie, S.; Hashemi, M. M.; Akhbari, M. *Tetrahedron Lett*. **2003**, *44*, 1709.
[5] Samai, S.; Nandi, G. C.; Kumar, R.; Singh, M. S. *Tetrahedron Lett*. **2009**, *50*, 7096.
[6] Yavari, I.; Maghsoodlou, M. T. *J. Chem. Res*. (*S*). **1998**, 386.
[7] Maghsoodlou, M. T.; Hazeri, N.; Navvabian, H.; Razmjoo, Z.; Marandi, G. *J. Chem. Res*. (*S*). **2005**, 401.
[8] Maghsoodlou, M. T.; Habibi-Khorassani, S. M.; Hazeri, N.; Marandi, G.; Bijanzadeh, H. R. *J. Chem. Res*. (*S*). **2006**, 73.
[9] Maghsoodlou, M. T.; Marandi, G.; Hazeri, N.; Aminkhani, A.; Kabiri, R. *Tetrahedron Lett*. **2007**, *48*, 3197.
[10] Marandi, G.; Maghsoodlou, M. T.; Hazeri, N.; Habibi-Khorassani, S. M.; Akbarzadeh Torbati, N.; Rostami-Charati, F.; Skelton, B. W.; Makha, M. *Mol. Divers*. **2011**, *15*, 197.
[11] Maghsoodlou, M. T.; Marandi, G.; Hazeri, N.; Habibi-Khorassani, S. M.; Mirzaei, A. A. *Mol. Divers*. **2011**, *15*, 227.
[12] Marandi, G.; Maghsoodlou, M. T.; Hazeri, N.; Heydari, R.; Habibi-Khorassani, S. M.; Ebrahimi, A.; Mollaee Poor, S.; Hosseini Mahdiabad, H.; Nassiri, M.; Kabiri, R. *Heteroatom Chem*. **2010**, *21*, 228.
[13] Winterfeldt, E.; Schmann D.; Dillinger, H. J., *Chem. Ber*. **1962**, *102*, 1656.
[14] Oakes, T. R.; David. H. G.; Nagel, F. J. *J. Am. Chem. Soc*. **1969**, *91*, 4761.

[15] Takizawa, T.; Obata, N.; Suzuki, Y.; Yanagida, T. *Tetrahedron Lett*. **1969**, 3407.
[16] Dillinger, H. J.; Fengler, G.; Schumann, D.; Winterfeldt, E. *Tetrahedron* **1974**, *30*, 2553.
[17] Dillinger, H. J.; Fengler, G.; Schumann, D.; Winterfeldt, E. *Tetrahedron* **1974**, *30*, 2561.