Asian Journal of Chemistry; Vol. 25, No. 10 (2013), 5360-5362

ASIAN JOURNAL OF CHEMISTRY

http://dx.doi.org/10.14233/ajchem.2013.14220

Synthesis, Characterization and Pesticide Activities of Some Novel Tutin Derivatives

JUN CUI and MENGLOU LI*

College of Forestry, Northwest A & F University, Yangling 712100, Shaanxi Province, P.R. China

*Corresponding author: Tel: +86 29 87082125; E-mail: limenglou@hotmail.com

(*Received*: 22 June 2012; *Accepted*: 5 April 2013) AJC-13205

Seven novel tutin acylation derivatives (T1-T7) were synthesized to determine their pesticide activity against *Mythimna separata*. The structural assignments of these semisynthetic compounds were examined based on their IR, ESIMS and ^{1}H- and ^{13}C-NMR spectra data. Compared with tutin, those derivatives possessing potent anti-feedant activity and the most potent was 2-(3,5-dichlorobenzoyloxy)-tutin (T7).

Key Words: Tutin, Acylation derivatives, Sesquiterpene lactone, Pesticide activity.

INTRODUCTION

Tutin, a low poisonous compound isolated from an indigenous Chinese shrub *Coriaria sinica* Maxim, shows a distinct of pharmacological effects including antagonist of the glycine receptor and convulsant effects[1], acted as an antiepileptic drugs and was widely used to study epileptogenic mechanisms[2]. Animal toxicity studies showed that tutin possess neurotoxic properties, poisonous and antifeedant activity against multiple pests and revealed pronounced medicinal value as antibacterial and antifungal agent[3]. Recently, tutin has received a great deal of attention, not only for being a main ingredient of *Coriaria lactone* (CL), but also because many biologically active natural and synthetic products have particular scaffold[4].

As a sesquiterpene lactone, the structure of tutin has many similarities to that of picrotoxin[5]. The structure of tutin contains a lactone moiety, two epoxy moieties, an olefin bond and two hydroxyl groups. In previous study, the hydroxyl group on 2-position of tutin was acylated to prepare novel and potent pesticide compounds and the derivatives were more potent than the parent. It is evident that the substituents on the C-2 hydroxyl group have a great influence on pesticide activity[4]. Based on the facile acylated reaction, lots of secondary metabolites of plants were modificated to become potent pesticide, such as abamectin, flufenoxuron and indoxacarb *etc*.[6] The acylated substituents like methoxybenzoyl, dinitrobenzoyl and chloronicotinoyl *etc*. play a significant role in the increasingly biological activity of botanical pesticides like abamectin, tebufenozide and nicotinoyl[7].

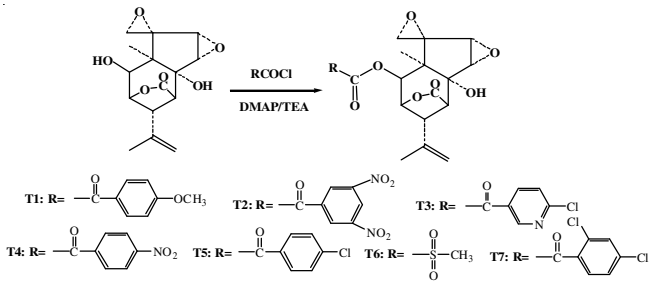
Encouraged by these findings and in continuation of our previous work aimed at the synthesis of a variety of novel *Coriaria lactone* analogues for biological and pesticidal evaluation, we prepared seven new derivatives (T1-T7) with above acylated substituents at the 2-position of tutin and the pesticide activity of these derivatives and tutin against *Mythimna separata* were determined.

EXPERIMENTAL

Melting points were measured on a XT-5 micro melting point apparatus and were uncorrected. Proton (^{1}H) and carbon (^{13}C) nuclear magnetic resonance (NMR) spectra were recorded on a Bruker Avance DRX-500 Fourier transformer spectrometer at 500 MHz. Chemical shifts were reported in δ (ppm) values downfield from tetramethylsilane (TMS) as internal standard. The IR spectra obtained on a Thermo Nicolet IR200 Spectrometer. Mass spectrometry (MS) analysis was recorded on Q-TOF MicroTM spectrometer and only prominent absorption bands were listed. Thin layer chromatography (TLC) was carried out on silica gel 60 GF_{254} (Qingdao Marine Chemical, Ltd., China) plates and spots were visualized by spraying with 5 % H_2SO_4 in ethanol reagent followed by heating at 120 ºC. Acetonitrile and pyridine were purified according to the standard procedures and freshly distilled prior to use. All other reagents used were obtained from commercial sources and were of the highest grade available.

Preparation of acylation derivatives of tutin: Tutin (200 mg, 0.68 mmol) was added to the solution of dry CH_2Cl_2 (30 mL) by fully stirring and dissolving and acyl chloride in CH_2Cl_2 (0.2 mmol/mL, 5 mL) was then added drop by drop in the presence of 4-dimethylamino pyridine and triethylamine. The mixture was refluxed with stirring for 6 h and monitored by TLC analysis. The reaction mixture was poured into ice water (10 mL) and extracted with ethyl acetate (3 × 10 mL). The combined organic layer was washed with 10 % aqueous

$NaHCO_3$ solution and dried over anhydrous Na_2SO_4. After evaporation *in vacuo*, the resulting solid was subjected to a silica-gel column chromatography with AcOEt-hexane (9:1, 8:2) as the eluent to give compounds T1-T7 (**Scheme-I**) in almost quantitative yield.



Scheme-I: Semisynthetic route to compounds

2-(4-Methoxybenzoyl)-tutin (T1): White powders, m.p. 212-215 ºC; IR (KBr, ν_{max}, cm^{-1}): 3377, 2967, 1780, 1607, 1529, 1025, 1020, 757; ^1H NMR($CDCl_3$): δ 1.38 (s, 3H, H-7), 1.98 (s, 3H, H-10), 2.97 (d, *J* = 6.0 Hz, 1H, H-14), 3.21 (d, *J* = 5.2 Hz, 1H, H-5), 3.26 (d, *J* = 3.8 Hz, 1H, H-11), 3.29 (s, 1H, H-OH), 3.49 (s, 1H, H-4), 3.82 (d, *J* = 3.8 Hz, 1H, H-12), 3.88 (s, 3H, H-17), 3.91 (d, *J* = 6.0 Hz, 1H, H-14), 5.10 (d, *J* = 6.0 Hz, 2H, H-9), 5.39 (d, *J* = 2.3 Hz, 1H, H-3), 5.47 (s, 3H, H-2), 6.97 (m, 2H, H-2'), 7.96 (m, 2H, H-3'). ^{13}C NMR ($CDCl_3$): δ 19.9 (C-10), 22.9 (C-7), 44.8 (C-1), 48.8 (C-4), 50.1 (C-5), 52.5 (C-14), 55.5 (C-17), 59.8 (C-12), 60.4 (C-11), 65.2 (C-13), 75.0 (C-2), 77.9 (C-6), 80.1 (C-3), 113.2 (C-9), 114.1 (C-3'), 121.4 (C-1'), 132.0 (C-2'), 139.9 (C-8), 164.0 (C-4'), 166.5 (C-16), 174.3 (C-15). ESIMS *m/z*: 429 ($[M+H]^+$).

2-(3,5-Dinitrobenzoyl)-tutin (T2): White powders, m.p. 205-209 ºC; IR (KBr, ν_{max}, cm^{-1}): 3371, 2985, 1765, 1460, 1348, 1278, 1098, 875; ^1H NMR (DMSO): δ 1.19 (s, 3H, H-7), 1.89 (s, 3H, H-10), 3.03 (d, *J* = 6.2 Hz, 1H, H-11), 3.18 (d, *J* = 5.3 Hz, 1H, H-14), 3.43 (s, 1H, H-OH), 3.69 (d, *J* = 6.2 Hz, 1H, H-12), 3.83 (d, *J* = 3.8 Hz, 1H, H-5), 4.81 (s, 1H, H-14), 4.92 (s, 1H, H-4), 5.04 (s, 1H, H-2), 5.16 (d, *J* = 6.0 Hz, 1H, H-9), 5.50 (s, 1H, H-3), 6.18 (s, 1H, H-9), 8.88 (d, *J* = 2.6 Hz, 1H, H-2'), 8.92 (d, *J* = 6.0 Hz, 1H, H-2'), 9.03 (q, *J* = 4.0 Hz, 1H, H-4'). ^{13}C NMR (DMSO): δ 20.6 (C-10), 23.1 (C-7), 45.0 (C-1), 49.4 (C-4), 49.5 (C-5), 52.9 (C-14), 59.1 (C-12), 60.2 (C-11), 64.6 (C-2), 65.6 (C-13), 77.3 (C-6), 79.3 (C-3), 123.2 (C-9), 123.3 (C-1'), 129.5 (C-2'), 132.7 (C-8), 148.9 (C-3'), 163.3 (C-4'), 173.7 (C-16), 175.1 (C-15). ESIMS *m/z*: 489 ($[M+H]^+$).

2-(6-Chloronicotinoyl)-tutin (T3): White powders, m.p. 203-206 ºC; IR(KBr, ν_{max}, cm^{-1}): 3386, 2924, 2856, 1780, 1625, 1585, 1107, 758; ^1H NMR (DMSO): δ 1.17 (s, 3H, H-7), 1.90 (s, 3H, H-10), 2.98 (d, *J* = 6.2 Hz, 1H, H-11), 3.19 (d, *J* = 5.4 Hz, 1H, H-14), 3.32 (d, *J* = 3.8 Hz, 1H, H-4), 3.41 (s, 1H, H-OH), 3.68 (d, *J* = 6.2 Hz, 1H, H-12), 3.84 (d, *J* = 3.8 Hz, 1H, H-5), 4.92 (s, 1H, H-14), 5.06 (s, 1H, H-2), 5.12 (d, *J* = 6.0 Hz, 1H, H-9), 5.50 (s, 1H, H-3), 6.16 (s, 1H, H-9), 7.73 (d, *J* = 10.4 Hz, 10.4 Hz 1H, H-5'), 8.27 (m, 1H, H-3'), 8.87 (q, *J* = 7.1 Hz, 1H, H-2'). ^{13}C NMR (DMSO): δ 20.5 (C-10), 23.1 (C-7), 45.0 (C-1), 49.4 (C-4), 49.5 (C-5), 52.7 (C-14), 59.1 (C-12), 60.2 (C-11), 65.6 (C-13), 76.2 (C-2), 77.3 (C-6), 79.6 (C-3), 110.8 (C-9), 126.6 (C-1'), 140.8 (C-8), 142.2 (C-3'), 151.3 (C-2'), 155.3 (C-4'), 164.5 (C-5'), 165.9 (C-16), 174.9 (C-15). ESIMS *m/z*: 434 ($[M+H]^+$).

2-(4-Nitrobenzoyloxy)-tutin (T4): White powders, m.p. 215-218 ºC; IR (KBr, ν_{max}, cm^{-1}): 3380, 2996, 2857, 1748, 1635, 1457, 1274, 870; ^1H NMR ($CDCl_3$): δ 1.29 (s, 3H, H-7), 1.98 (s, 3H, H-10), 2.98 (d, *J* = 5.8 Hz, 1H, H-14), 3.08 (d, *J* = 6.5 Hz, 1H, H-11), 3.34 (s, 1H, H-OH), 3.47 (d, *J* = 3.8 Hz, 1H, H-5), 3.52 (s, 1H, H-4), 3.73 (d, *J* = 6.5 Hz, 1H, H-12), 3.91 (d, *J* = 5.8 Hz, 1H, H-14), 5.02 (s, 1H, H-2), 5.14 (d, *J* = 6.0 Hz, 1H, H-9), 5.23 (d, *J* = 3.8 Hz, 1H, H-3), 6.12 (s, 1H, H-9), 8.14 (m, 2H, H-2'), 8.42 (m, 2H, H-3'). ^{13}C NMR ($CDCl_3$): δ 21.9 (C-10), 23.0 (C-7), 44.9 (C-1), 49.2 (C-4), 50.2 (C-5), 52.3 (C-14), 59.7 (C-11), 60.2 (C-12), 64.9 (C-13), 76.0 (C-2), 77.6 (C-6), 79.8 (C-3), 112.9 (C-9), 123.0 (C-3'), 131.2 (C-2'), 136.9 (C-1'), 139.8 (C-8), 151.9 (C-4'), 166.3 (C-16), 174.6 (C-15). ESIMS *m/z*: 444 ($[M+H]^+$).

2-(4-Chlorobenzoyloxy)-tutin (T5): White powders, m.p. 223-226 ºC; IR (KBr, ν_{max}, cm^{-1}): 3351, 1788, 1621, 1460, 1256, 1014, 854, 671; ^1H NMR ($CDCl_3$): δ 1.18 (s, 3H, H-7), 1.98 (s, 3H, H-10), 3.02 (d, *J* = 6.2 Hz, 1H, H-11), 3.20 (d, *J* = 5.4 Hz, 1H, H-14), 3.46 (s, 1H, H-OH), 3.50 (s, 1H, H-4), 3.62 (d, *J* = 4.8 Hz, 1H, H-5), 3.70 (d, *J* = 6.2 Hz, 1H, H-12), 4.86 (s, 1H, H-14), 5.09 (s, 1H, H-2), 5.16 (d, *J* = 6.0 Hz, 1H, H-9), 5.49 (s, 1H, H-3), 6.16 (s, 1H, H-9), 7.56 (d, *J* = 8.6 Hz, 2H, H-3'), 8.14 (d, *J* = 8.6 Hz, 2H, H-2'). ^{13}C NMR ($CDCl_3$): δ 20.5 (C-10), 23.1 (C-7), 44.9 (C-1), 49.2 (C-5), 50.1 (C-4), 52.9 (C-14), 56.3 (C-11), 59.2 (C-12), 63.7 (C-13), 75.0 (C-2), 78.6 (C-6), 80.2 (C-3), 110.3 (C-9), 129.0 (C-3'), 131.3 (C-1'), 131.5 (C-2'), 138.2 (C-4'), 146.9 (C-8), 167.2 (C-16), 174.1 (C-15). ESIMS *m/z*: 433 ($[M+H]^+$).

2-Methane sulfonyloxy- tutin (T6): White powders, m.p. 231-234 ºC; IR (KBr, ν_{max}, cm^{-1}): 3376, 2952, 1736, 1618, 1452, 1362, 1152, 1088; ^1H NMR (DMSO): δ 1.18 (s, 3H, H-7), 1.90 (s, 3H, H-10), 2.98 (d, *J* = 6.5 Hz, 1H, H-11), 3.18 (d, *J* = 5.3 Hz, 1H, H-14), 3.24 (s, 3H, H-4), 3.35 (s, 1H, H-4), 3.47 (s, 1H, H-OH), 3.70 (d, *J* = 6.5 Hz, 1H, H-12), 3.81 (d, *J* = 4.0 Hz, 1H, H-5), 4.02 (s, 1H, H-3), 4.87 (s, 1H, H-14), 5.12 (d, *J* = 6.0 Hz, 1H, H-9), 5.42 (s, 1H, H-2), 6.13 (s, 1H, H-9). ^{13}C-NMR (DMSO): δ 21.6 (C-10), 22.7 (C-7), 36.2 (C-16), 45.0 (C-1), 47.4 (C-14), 50.3 (C-5), 51.2 (C-4), 56.8 (C-11), 59.8 (C-12), 64.7 (C-13), 73.2 (C-2), 77.9 (C-6), 79.8 (C-3), 111.2 (C-9), 143.6 (C-8), 174.9 (C-15). ESIMS *m/z*: 373 ($[M+H]^+$).

2-(3,5-Dichlorobenzoyloxy)-tutin (T7): White powders, mp 206-209 ºC; IR (KBr, ν_{max}, cm^{-1}): 3365, 1771, 1653, 1542, 1172, 1018, 975; ^1H NMR ($CDCl_3$): δ 1.19 (s, 3H, H-7), 1.98 (s, 3H, H-10), 2.96 (d, *J* = 6.2 Hz, 1H, H-11), 3.12 (d, *J* = 5.3 Hz, 1H, H-14), 3.28 (s, 1H, H-OH), 3.63 (d, *J* = 6.2 Hz, 1H, H-12), 3.82 (d, *J* = 4.0 Hz, 1H, H-5), 4.65 (s, 1H, H-4), 4.82 (d, *J* = 5.3 Hz,1H, H-14), 5.04 (s, 1H, H-2), 5.18 (d, *J* = 6.0 Hz, 1H, H-9), 5.49 (s, 1H, H-3), 6.20 (s, 1H, H-9), 7.70 (d, *J* = 8.4 Hz 1H, H-5'), 7.89 (s, 1H, H-3'), 8.19 (d, *J* = 8.4 Hz, 1H, H-6'). ^{13}C NMR($CDCl_3$): δ 21.3 (C-10), 23.0 (C-7), 45.1 (C-1), 49.9 (C-5), 50.3 (C-4), 51.2 (C-14), 58.2 (C-11), 60.7 (C-12), 64.2 (C-13), 76.0 (C-2), 77.1 (C-6), 79.2 (C-3), 110.9 (C-9), 127.3 (C-5'), 129.8 (C-3'), 130.3 (C-1'), 133.2 (C-6'), 135.9 (C-2'), 142.1 (C-8), 143.2 (C-4'), 166.0 (C-16), 174.1 (C-15). ESIMS *m/z*: 467 ($[M+H]^+$).

TABLE-1
PESTICIDE EFFECTS OF TUTIN AND ITS DERIVATIVES AGAINST 3th INSTAR *Mythimna separata*

Compound	T1	T2	T3	T4	T5	T6	T7	Tutin
24 h-antifeeding rate (%)	44.41**	-0.59	48.28**	25.48	8.92	23.52	45.33**	23.55
24 h-relative variability rate (%)	88.58	-102.51	105.01	8.20	-62.12	-0.13	92.48	0.00
24 h-mortality rate (%)	3.33	0.00	6.67	6.67	6.67	0.00	10.00	0.00
48 h-antifeeding rate (%)	55.10*	31.09	46.81*	34.66	23.72	32.64	51.75*	35.99
48 h-relative variability rate (%)	53.10	-13.61	30.06	-3.70	-34.09	-9.31	43.79	0.00
48 h-mortality rate (%)	6.67	0.00	23.33	6.67	20.00	6.62	33.33	0.00

Data were analyzed using one-way ANOVA, where $^{*}P < 0.05$ and $^{**}P < 0.01$ were significantly different from tutin

Pesticide activity test: The pesticide activities of T1-T7 and tutin were determined by presenting them on leaf disks of wheat against the 1-day-old third instar larvae of *Mythimna separata* (Walker) at 24 h and 48 h, using a non-choice leaf disk method under the sub-lethal concentration of 2.0 mg/mL in acetone, with acetone as the control[7]. Thirty larvae were used for each treatment and the entire experiment was repeated twice. The activity was expressed as a percentage of feeding inhibition and was calculated according to the following equation: antifeeding rate (%) = [(CK-T)/CK] × 100, where CK is the consumption of the control disk and T is the consumption of the treated disk. Relative variability rate (%) = [(Xi-Xt)/Xt] × 100 %, where Xi is the antifeeding rate of the derivative and Xt is the antifeeding rate of tutin. One-way ANOVA test were conducted using SPSS (version 13, SPSS Inc., Chicago, IL, USA) to determine the differences in antifeeding rates between these compounds.

RESULTS AND DISCUSSION

Seven new derivatives were synthesized by reflux tutin and various acyl chlorides in dichloromethane in the presence of 4-dimethylaminopyridine and triethylamine (**Scheme-I**). The structural assignments of synthetic compounds were examined based on the analytical and spectral data. For instance, the FT-IR spectrum of 2-(4-methoxybenzoyl)-tutin (**T1**) presented different absorption bands at 3377 cm^{-1} assignable to hydroxyl group, 2967 cm^{-1} due to methoxy group, 1780 cm^{-1} due to carbonyl group, 1607 cm^{-1} and 1529 cm^{-1} due to the benzene ring, 1025 cm^{-1} and 1020 cm^{-1} characteristic for epoxy moieties. In the ^{1}H NMR spectrum revealed 24 protons signals, including three methyl singlets (δ 1.38, 1.98, 3.88), one hydroxyl singlets (δ 3.29), four oxygenated methines (δ 3.26, 3.82, 5.39, 5.47), six olefinic protons (δ 2.97, 3.91, 5.10, 5.10, 3.49, 3.21) and four benzene protons in pairs (δ 6.97, 7.96). The ^{13}C NMR spectrum revealed 23 carbon signals, including three methyls, two methylenes, ten methines and eight quaternary carbons (two ester carbonyl, one oxygenated). Moreover, the ESIMS *m/z*: 429 ($[M+H]^{+}$) and mp: 212-215 ºC data strongly supported the acylated structure of compound **T1**.

Pesticide activity of these 7 derivatives and tutin were determined by a conventional leaf disk method against the 1-day old third instar larvae of *Mythimna separate* (Walker) at 24 h and 48 h under the sub-lethal concentrations of tutin 2.0 mg/mL[4]. Compared with tutin, the acylation derivatives showed statistically significant differences existed in antifeedant activity (Table-1). As summarized in Table-1, **T1**, **T3** and **T7** exhibited much higher antifeedant activities toward *M. separate* and the relative variability rate increased 88.58 %-105.01 % and 30.06 %-53.10 % at 24 h and 48 h, respectively. Compounds led to different lethal toxicities with the sub-lethal concentrations except **T2** and tutin. **T6** made a mortality rate of 6.62 % slowly at 48 h. **T4** made mortality rate of 6.67 % stably at both 24 h and 48 h, respectively. However, the mortality rates of **T1**, **T3**, **T5** and **T7** were increased evidently and compound **T7** showed the most potent mortal effect.

ACKNOWLEDGEMENTS

This work was supported by the National Natural Science Foundation of China (No. 30872032). Thanks are also due to Mr. Richmond Wills for his help in manuscript preparation.

REFERENCES

1. J. Fuentealba, B. Munoz, G. Yevenes, G. Moraga-Cid, C. Pérez, L. Guzman, J.M. Rigo and L.G. Aguayo, *Neuropharmacology*, **60**, 453 (2011).
2. H. Zhou, Y.H. Tang and Y. Zheng, *Brain Res.*, **1092**, 207 (2006).
3. L.J. Zhou, L.C. Song, R.T. Ruo, Z.R. Yang and C. He, *J. Sichuan Uni. (Nat. Sci. Ed.)*, **43**, 1165 (2006).
4. M.L. Li, J. Cui, R.H. Qin, J.M. Gao, Y.B. Zhang, X.R. Guo and W. Zhang, *Heterocycles*, **71**, 1155 (2007).
5. Y. Kudo, H. Niwa, A. Tanaka and K. Yamada, *Br. J. Pharmacol.*, **81**, 373 (1984).
6. C. Ioriatti, E. Pasqualini, D. Pasquier and C. Tomasi, *J. Pest. Sci.*, **79**, 163 (2006).
7. M.S. Godoy, G.A. Carvalho, J.C. Moraes, M.G. Junior, A.A. Moraise and L.V. Cosme, *Neotrop. Entomol.*, **33**, 639 (2004).