ONE-POT SYNTHESIS OF NEW 1,3-IMIDAZOLIDINES POSSESSING THREE ARYL GROUPS VIA A 1,3-DIPOLAR CYCLOADDITION REACTION

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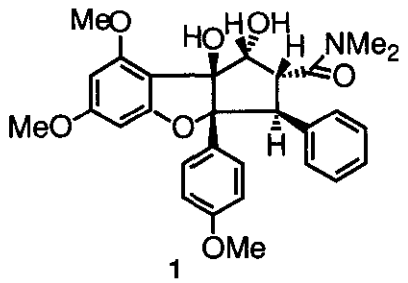
Abstract- Tri-aryl-substituted imidazolidines (**3**) were readily synthesized by heating a mixture of arylaldehyde (**7**), diethyl ketomalonate (**8**), and benzyl(or substituted benzyl)-amine (**6**) in benzene in the presence of a catalytic amount of *p*-toluene-sulfonic acid.

Rocaglamide (**1**)[1] and podophyllotoxin (**2**)[2] exhibit significant antileukemic activity against P388 lymphocytic leukemia in mice. In order to search new lead compounds having potential for antileukemic activity, we are interested in development of



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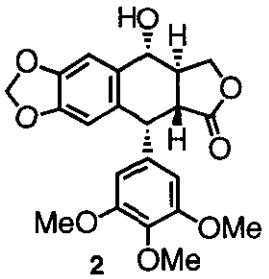

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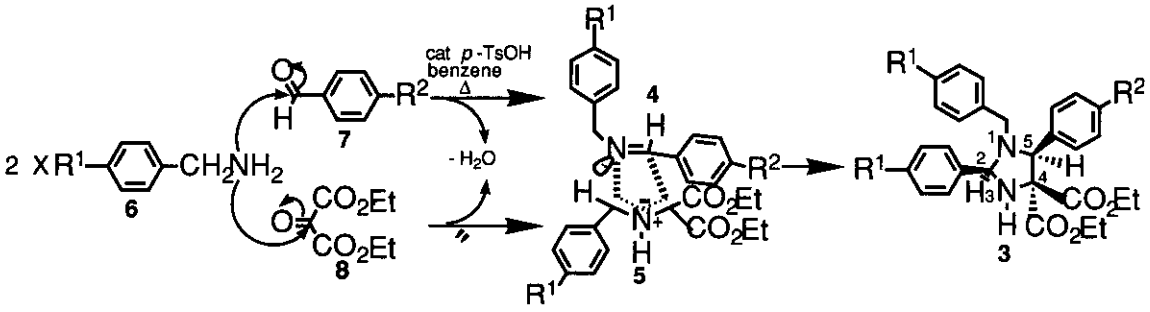
a facile synthesis of new compounds (**3**) possessing three aryl groups such as rocaglamide (**1**). Recently, we paid attention to a 1,3-dipolar cycloaddition reaction between bis-aryl groups-substituted imines (**4**) and azomethine ylides (**5**) bearing mono-aryl group. Grigg and his co-workers reported that the azomethine ylides, generated thermally from the imines of diethyl aminomalonate and arylaldehydes, dimerize to give the corresponding imidazolidines as the major product.[3] Hence, in

order to avoid this undesired dimerization reaction, we planned simultaneous formation of the arylideneimines (**4**) and the azomethine ylides (**5**) *in situ* followed by their 1,3-dipolar cycloaddition reaction[4] to furnish the desired imidazolidine derivatives (**3**) as shown in Scheme 1. Thus, one-pot synthesis of compounds (**3**) was attempted according to the following two similar manners (Methods A and B).



Scheme 1

Method A- After removing water from a catalytic amount of *p*-toluenesulfonic acid monohydrate in refluxing benzene, benzaldehyde (**7**: R^2=H), diethyl ketomalonate (**8**), and benzylamine (**6**: R^1=H) were successively added. The mixture was refluxed with continuous removal of water generated under N_2 for 3 h to give an imidazolidine derivative (**3**: R^1=R^2=H) in 67% yield (Entry 1 in Table 1).

Table 1. One-pot synthesis of imidazolidine derivatives (**3**)

Entry	Method[a)]	Time(h)	Product		Yield(%)[b)]	mp(°C)
			R^1	R^2		
1	A	3	H	H	67	147
2	B	5	Me	H	58	104-106
3	A	2	Me	Me	62	oil
4	B	4	MeO	MeO	67	"
5	A	5	Cl	Cl	30	"

a) See text and experimental part. b) Isolated

Method B- After removing water from *p*-toluenesulfonic acid monohydrate in hot benzene, benzaldehyde (**7**: R^2=H) and *p*-methylbenzylamine (**6**: R^1=Me) were added. The mixture was refluxed for 30 min and then compound (**8**) was added. The whole mixture was refluxed for 5 h to afford compound (**3**: R^1=Me, R^2=H) in 58% yield (Entry 2 in Table 1). Other reactions (Entries 3-5) were similarly carried out to give the C2,C5-substituents *cis* products (**3**: R^1=R^2=Me, OMe, and Cl) as shown in Table 1. The corresponding C2,C5-substituents *trans* stereoisomer was not obtained in all reactions. The structures of two crystalline compounds (**3**: R^1=R^2=H and R^1=Me, R^2=H) were determined by their single crystal X-ray analyses[5] as illustrated in Figure 1.

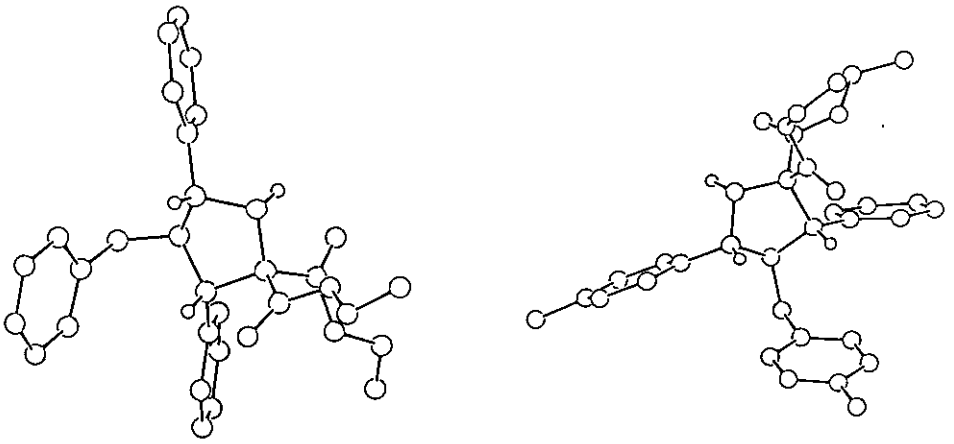


Figure1. Perspective view of the crystallographic structure of compounds (**3**: R^1=R^2=H and R^1=Me, R^2=H).

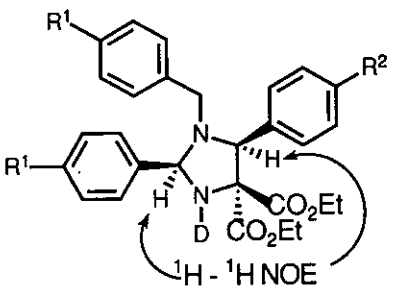


Figure 2. ^{1}H -^{1}H NOE Experiments (400 MHz, $CDCl_3$-D_2O) of compounds (**3**)

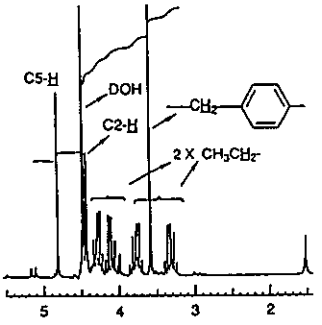


Figure 3. ^{1}H Nmr (200 MHz, $CDCl_3$-D_2O) signals of the methylene protons region of two sets of ethoxycarbonyl groups of compound (**3** : R^1 = R^2 = H).

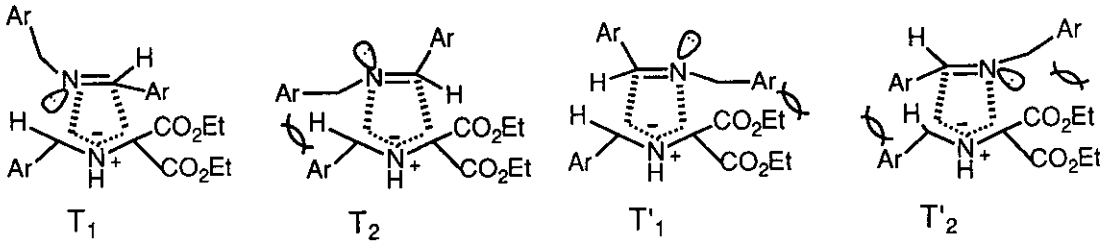


Figure 4. Plausible transition states for 1,3-dipolar cycloaddition reaction between **4** and **5**.

The stereochemistry of two aryl groups at C2 and C5 in these molecules proved to be *cis* configuration. In the ^1H-^1H NOE (400 MHz, $CDCl_3$-D_2O) experiment of the compounds (**3**: R^1= R^2=H and R^1=Me, R^2=H), irradiation of C2-H causes clear enhancement of the C5-H signal and *vice versa*, as shown in Figure 2. Thus, we confirmed the structures of other products (**3**: R^1=R^2=Me, OMe, and Cl) on the basis of their ^1H nmr analyses and ^1H-^1H NOE experiments. The NOE aspect (C2-H↔C5-H) of compounds (**3**: R^1=R^2=Me, OMe, and Cl) is consistent with that of compounds (**3**: R^1=R^2=H and R^1=Me, R^2=H). Interestingly, on the ^1H nmr spectra of all compounds (**3**), four diastereotopic methylene protons (located far away from two chiral centers!) of two sets of ethoxycarbonyl groups are shown to be four double quartet peaks (Figure 3). This may be due to the restricted rotaion of two sets of ethoxycarbonyl groups based on their steric hindrance to C5-aryl group. Both arylideneimines (**4**) and azomethine ylides (**5**) may predominantly adopt rather stable *anti* configuration than labile *syn* configuration owing to the severe aza 1,3-allylic strain.[6] Although there are possible two sets of transition states (T_1 and T_2 *vs.* T'_1 and T'_2) in the 1,3-dipolar cycloaddition reaction between **4** and **5** (Figure 4), the T_1 and T_2 set must be much more stable than the T'_1 and T'_2 set from the viewpoints of favorable electronic factor[7] in the former and unfavorable steric factor[8] in the latter. The energy level of T_1 must be lower than that of T_2 bearing the steric repulsion between $ArCH_2$ at the imine nitrogen atom and aryl group of the azomethine ylide. Thus, this 1,3-dipolar cycloaddition reaction in the one-pot system may proceed regio- and stereoselectively *via* the most stable transition state T_1 among T_1,T_2,T'_1, and T'_2 to give the desired imidazolidine derivatives (**3**) possessing three aryl groups.[9] Compounds (**3**: R^1=R^2=Me and Cl) exhibited a marginal antitumor activity [T/C=116% (dose: 200 mg/kg) for R^1=R^2=Me and T/C=119% (dose: 50 mg/kg) for R^1=R^2=Cl] against P388 limphocytic leukemia in mice.[10]

EXPERIMENTAL

Melting points were determined on a Yanagimoto micro melting point apparatus and are uncorrected. The ir spectra were recorded on a Perkin-Elmer 1720 infrared fourier transform spectrophotometer. ^1H and ^{13}C nmr spectra were determined on a JEOL JNM FX200 (200 MHz) or a JEOL JNM-GSX400 (400 MHz) spectrometer in $CDCl_3$ solution and chemical shifts are reported in δ (ppm) relative to tetramethylsilane. Mass spectral determinations were carried out on a JEOL JMS-D300 mass spectrometer. Elemental analyses were obtained on a Yanaco CHN MT-3 CORDER. Column chromatography was performed on silica gel (Wakogel C-200 and Katayama 60 K070). All reactions were monitored by Kieselgel 60 F_{254} plates (Merck). All organic extracts were dried over anhydrous sodium sulfate.

1-Benzyl-4,4-Diethoxycarbonyl-2,5-diphenyl-1,3-imidazolidine (3: R^1=R^2

=H). Method A: A solution of *p*-toluenesulfonic acid monohydrate (23 mg, 0.12 mmol) in anhydrous benzene (20 ml) was refluxed in the flask equipped with a Dean-Stark trap under N_2 for 1 h. To the solution were successively added benzaldehyde (**7**: R^2=H, 0.41 ml, 4.03 mmol), diethyl ketomalonate (**8**: 0.61 ml, 4.00 mmol), and benzylamine (**6**: R^1=H, 0.88 ml, 8.06 mmol) at room temperature. The mixture was refluxed for 3 h and then the solvent was removed *in vacuo* to give an oily residue. The residue was dissolved in an appropriate amount of ether and the resultant ether layer was washed with 10% HCl, saturated aqueous $NaHCO_3$, and dried. Evaporation of the ethereal solution *in vacuo* gave an oily residue which was chromatographed on a silica gel column with hexane-ether (4:1) to afford compound (**3**: R^1=R^2=H) (1.24 g, 67% yield) as colorless prisms. mp 147°C (hexane). Ir ν_{max} (KBr) cm^{-1}: 3309, 1727. ^{1}H Nmr δ: 0.72 (t, 3H, J=7.2 Hz), 1.19 (t, 3H, J=7.2 Hz), 3.31 (dq, 1H, J=10.7, 7.2 Hz), 3.39 (br s, 1H), 3.59 (s, 2H), 3.79 (dq, 1H, J=10.6, 7.2 Hz), 4.08 (dq, 1H, J=10.7, 7.2 Hz), 4.32 (dq, 1H, J=10.6, 7.2 Hz), 4.44 (br s, 1H), 4.82 (s, 1H), 6.83-7.72 (m, 15H). ^{13}C Nmr (100 MHz, $CDCl_3$) δ: 13.26, 13.86, 51.99, 61.80, 61.99, 69.54, 75.78, 79.91, 126.93, 127.74, 127.78, 128.12, 128.51, 128.62, 128.65, 128.92, 130.02, 134.81, 138.14, 138.89, 169.63, 170.10. High resolution ms: Calcd for $C_{28}H_{30}N_2O_4$ MW 458.2205, found *m/z* 458.2213(M^+). Anal. Calcd for $C_{28}H_{30}N_2O_4$: C,73.24; H,6.59; N,6.11. Found: C,73.20; H,6.59: N,6.04.

4,4-Diethoxycarbonyl-1-(*p*-methylbenzyl)-2-(*p*-methylphenyl)-5-phenyl-1,3-imidazolidine (3: R^1=Me, R^2=H). Method B: A solution of *p*-toluenesulfonic acid monohydrate (23 mg, 0.12 mmol) in anhydrous benzene (20 ml) was refluxed in the flask equipped with a Dean-Stark trap under N_2 for 1 h. To a solution were added benzaldehyde (**7**: R^2=H, 0.40 ml, 3.94 mmol) and *p*-methylbenzylamine (**6**: R^1=Me, 1.00 ml, 7.86 mmol) at room temperature and then the mixture was refluxed for 30 min. After diethyl ketomalonate (**8**, 0.60 ml, 3.94 mmol) was added, the mixture was refluxed with removing some water for 5 h. The reaction mixture was treated as usual to give an oily residue. The residue was chromatographed on a silica gel column with hexane-ether (5:1) to afford compound (**3**: R^1=Me, R^2=H) (1.12 g, 58% yield) as colorless prisms. mp 104-106 °C. Ir ν max ($CHCl_3$) cm^{-1}: 3300, 1729. ^{1}H Nmr δ: 0.71 (t, 3H, J=7.2 Hz), 1.17 (t, 3H, J=7.2 Hz), 2.26 (s, 3H), 2.38 (s, 3H), 3.30 (dq, 1H, J=10.9, 7.2 Hz), 3.46 (br s, 1H), 3.54 (s, 2H), 3.78 (dq, 1H, J=10.6, 7.2 Hz), 4.06 (dq, 1H, J=10.9, 7.2 Hz), 4.31 (dq, 1H, J=10.9, 7.2 Hz), 4.38 (br s, 1H), 4.78 (s, 1H), 6.72-7.62 (m, 13H). High resolution ms: Calcd for $C_{30}H_{34}N_2O_4$ MW 486.2519, found *m/z* 486.2523(M^+). Anal. Calcd for $C_{30}H_{34}N_2O_4$: C,74.05; H,7.04; N,5.76. Found: C,73.88; H,7.05; N,5.77.

4,4-Diethoxycarbonyl-1-(*p*-methylbenzyl)-2,5-di-(*p*-methylphenyl)-1,3-imidazolidine (3: R^1=R^2=Me). Method A: 62% yield. Pale yellow oil. Ir ν_{max}($CHCl_3$)

cm^{-1}: 3300, 1728. ^1H Nmr δ: 0.73 (t, 3H, J=7.2 Hz), 1.16 (t, 3H, J=7.2 Hz), 2.26 (s, 3H), 2.35 (s, 3H), 2.38(s, 3H), 3.32 (dq, 1H, J=10.6, 7.2 Hz), 3.43 (br s, 1H), 3.53 (s, 2H), 3.79 (dq, 1H, J=10.6, 7.2 Hz), 4.05 (dq, 1H, J=10.9, 7.2 Hz), 4.30 (dq, 1H, J=10.6, 7.2 Hz), 4.37 (br s, 1H), 4.73 (s, 1H), 6.72-7.61 (m, 12H). High resolution ms: Calcd for $C_{31}H_{36}N_2O_4$ MW 500.2675, found *m/z* 500.2645(M^+).

4,4-Diethoxycarbonyl-1-(*p*-methoxybenzyl)-2,5-di-(*p*-methoxyphenyl)-1,3-imidazolidine (3: R^1=R^2=OMe). Method B: 67% yield. Pale yellow oil. Ir $\nu_{max}(CHCl_3)$ cm^{-1}: 3300, 1728. ^1H Nmr δ: 0.78 (t, 3H, J=7.2 Hz), 1.18 (t, 3H, J=7.2 Hz), 3.39 (dq, 1H, J=10.6, 7.2 Hz), 3.44 (br s, 1H), 3.50 (s, 2H), 3.75 (s, 3H), 3.81(s, 3H), 3.84 (s, 3H), 3.75-3.90 (m, 1H), 4.06 (dq, 1H, J=10.7, 7.2 Hz), 4.31 (dq, 1H, J=10.6, 7.2 Hz), 4.35 (br s, 1H), 4.71 (s, 1H), 6.65-7.63 (m, 12H). Anal. Calcd for $C_{30}H_{34}N_2O_7$: C,67.87; H,6.61; N,5.11. Found: C,67.14; H,6.55; N,4.99.

4,4-Diethoxycarbonyl-1-(*p*-chlorobenzyl)-2,5-di-(*p*-chlorophenyl)-1,3-imidazolidine (3: R^1=R^2=Cl). Method A: 30% yield. Pale yellow oil. Ir ν_{max} $(CHCl_3)$ cm^{-1}: 3300, 1729. ^1H Nmr δ: 0.79 (t, 3H, J=7.2 Hz), 1.21 (t, 3H, J=7.2 Hz), 3.41 (dq, 1H, J=10.7, 7.2 Hz), 3.46 (br s, 1H), 3.51 (s, 2H), 3.84 (dq, 1H, J=10.7, 7.2 Hz), 4.11 (dq, 1H, J=10.9, 7.2 Hz), 4.34 (dq, 1H, J=10.6, 7.2 Hz), 4.40 (br s, 1H), 4.74 (s, 1H), 6.71-7.59 (m, 12H). High resolution ms: Calcd for $C_{28}H_{27}N_2O_4Cl_3$ MW 560.1036, found *m/z* 559.0977(M^+). Anal. Calcd for $C_{28}H_{27}N_2O_4Cl_3$: C,59.85; H,4.84; N,4.99. Found: C,60.21; H,5.00; N,4.75.

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5. The crystallographic data as follows: Compound (**3**: R^1=R^2=H) $C_{28}H_{30}N_2O_4$, M= 458.56, monoclinic, $P2_{1/n}$, a=10.995(5)Å, b=16.583(4)Å, c=14.355(3)Å, β=106.50 (3)°, V= 2510(3)Å^3, z=4, D_{calc}=1.213 gcm^{-3}, R=0.054; Compound (**3**: R^1=Me, R^2=H) $C_{30}H_{34}N_2O_4$, M=486.61, monoclinic, $P2_{1/a}$, a=11.944(1)Å, b=19.810(4)Å, c=11.682 (2)Å, β= 90.15 (1)°, V=2764.0(7)Å^3, z=4, D_{calc}=1.169 gcm^{-3}, R=0.060.
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7. Electrostatic attraction between the aromatic moiety ("electron rich") at the imine carbon atom and the ethoxycarbonyl moiety ("electron deficient") of the azomethine ylide may be possible. (a) Y. Nagao, W.-M. Dai, and M. Ochiai, *Tetrahedron Lett.*, 1988, *29*, 6133. (b) Y. Nagao, S. Sano, S. Nakagawa, M. Tanaka, M. Shiro, and T. Taga, *Chem. Lett.*, 1992, 915.
8. Steric repulsion between $ArCH_2$-group at the imine nitrogen atom and diethoxycarbonyl groups of the azomethine ylide may be possible.
9. We do not deny entirely that the compounds (**3**) can be obyained under the reaction conditions controlled thermodynamically.
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