CONVENIENT SYNTHESIS OF A SIMPLE COUMARIN FROM SALICYLALDEHYDE AND WITTIG REAGENT (III)[1]: SYNTHESIS OF NITROCOUMARINS

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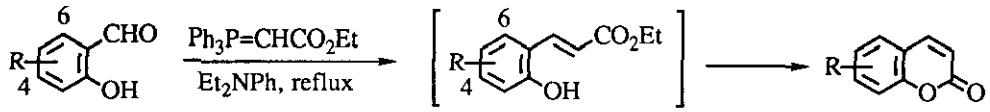
Abstract---Reaction of nitrosalicylaldehydes (**1**) with carbethoxymethylenetriphenylphosphorane in Et_2NPh, in Ph_2O, and in the absence of solvent (neat) at 210-215°C was investigated. Reaction of 3-nitrosalicylaldehyde (**1d**) in Et_2NPh afforded the benzoxazole (**6**) and the aminocoumarin (**3e**) along with the expected coumarin (**3d**). It was clarified that the origin of carbon-unit introduced for the formation of the benzoxazole ring came from the alkyl group of solvent.

Recently, we reported a convenient method for synthesis of a simple 3,4-unsubstituted coumarin (**3**) by the Wittig reaction of salicylaldehydes (**1**) having a methoxy, hydroxy, bromo and carbomethoxy group with carbethoxymethylenetriphenylphosphorane (phosphorane) in *N, N*-diethylaniline (Et_2NPh) under reflux.[1, 2] Therein, we presented that i) an electron-donating group at C_4 on salicylaldehyde (**1**) accelerated the formation of



1 **2** **3**

Scheme 1

coumarin (**3**) from *trans*-cinnamate (**2**) and an electron-withdrawing group at C_4 on **1** retarded the formation of **3**; ii) a substituent group at C_6 on **1** facilitated the formation of **3** irrespective of its electronic character. Then, we planned to investigate the Wittig reaction of **1** having a nitro group, which is a strong electron-withdrawing group, with phosphorane.

Herein, we describe the results including an unusual behavior of 3-nitrosalicylaldehyde (**1d**) in Et_2NPh.

Results and Discussion

Reaction of nitrosalicylaldehyde (**1**) with phosphorane in Et_2NPh under reflux (at 210-215°C) was examined. The results are summarized in Table I. In order to improve yields of **3**, reaction in the absence of solvent and in diphenyl ether (Ph_2O) at 210-215°C was also examined. Yields were improved slightly in reaction in the absence of solvent and total-yields containing **2** and **3** were high in reaction in Ph_2O, as indicated in Table I. Thus, **1a** as well as other 6-substituted salicylaldehydes[1, 2] afforded the corresponding coumarin (**3a**)[3] for a short reaction time and in a high yield, supporting the mechanism that a substituent group at C_6 on **1** could facilitate generally the formation of **3** regardless of its electronic character, *i.e.* an electron-withdrawing group or an electron-donating group.[2] However, other salicylaldehydes (**1b-d**) produced coumarins (**3b-d**), respectively, in low yields accompanied with by-product(s), which were formed by participation of Et_2NPh.

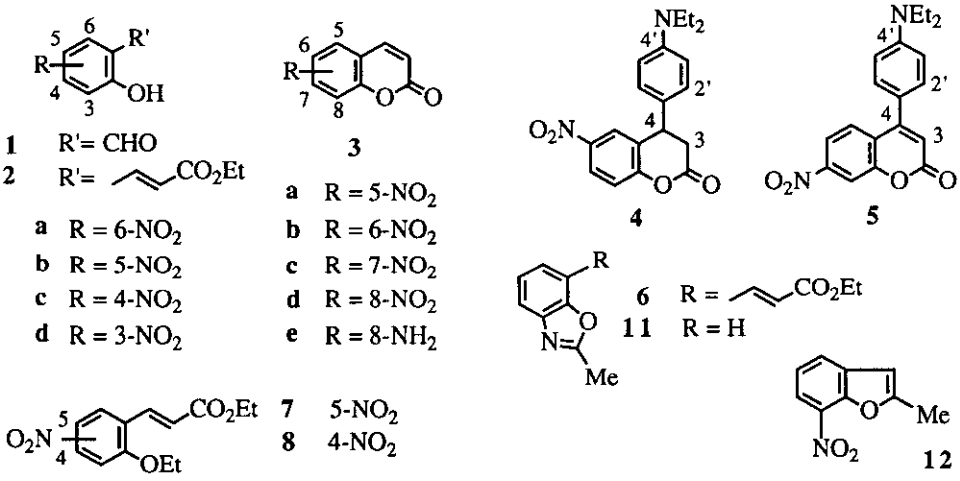
Reaction of 5-nitrosalicylaldehyde (**1b**) and 4-nitrosalicylaldehyde (**1c**) with phosphorane in Et_2NPh afforded the diethylaniline adducts (**4** and **5**) along with the coumarins (**3b**[4] and **3c**[5]), respectively. It should be noted that the cinnamate (**2c**) remains even after reflux for 6 h, indicating that an electron-withdrawing group such as a nitro group at C_4 on cinnamate retards the formation of coumarin ring from cinnamate in comparison with an electron-donating group at C_4 on cinnamate.[1, 2]

Reaction of 3-nitrosalicylaldehyde (**1d**) with phosphorane in Et_2NPh provided two unexpected products, the benzoxazole (**6**) and the aminocoumarin (**3e**)[6] besides the expected nitrocoumarin (**3d**).[7] On the other hand, reaction of **1d** with phosphorane in Ph_2O provided **2d** and **3d**, and neither **6** nor **3e** was produced, suggesting that Et_2NPh would serve as a reducing agent for conversion of **3d** to **3e** and be responsible for the formation of benzoxazole ring. In fact, a solution of **3d** in Et_2NPh was heated for 3h under reflux to produce **3e** in 17% yield along with recovery of the starting material (**3d**) in 69% yield. Moreover, heating of **2d** in Et_2NPh gave **3d**, **3e**, and **6** in 8%, 10%, and 45% yields, respectively, and heating of **2d** in Me_2NPh instead of Et_2NPh gave the benzoxazole (**9**) and the benzoxazolone (**10**) in 30% and 34% yields, respectively, as shown in Scheme 3.

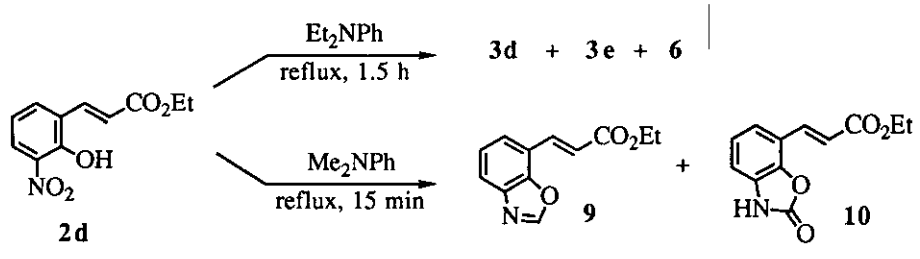
Table I. The Results of Reaction of Salicylaldehyde (1) with Carbethoxymethylene-triphenylphosphorane at 210-215°C

Run	Salicylaldehyde (1)	Solvent	Reaction Time	Products (%) [a]	
				2 / 3	Other(s)
1	6-NO_2 (**1a**)	Et_2NPh	0.75 h	0 / 88	
2	6-NO_2 (**1a**)	None	1.5 h	0 / 55	
3	6-NO_2 (**1a**)	Ph_2O	1 h	0 / 86	
4	5-NO_2 (**1b**)	Et_2NPh	3 h	0 / 28	**4** (14)
5	5-NO_2 (**1b**)	None	3 h	0 / 43	**7** (3)
6	5-NO_2 (**1b**)	Ph_2O	6 h	12 / 77	
7	4-NO_2 (**1c**)	Et_2NPh	6 h	17 / 13	**5** (7)
8	4-NO_2 (**1c**)	None	6 h	14 / 32	**8** (6)
9	4-NO_2 (**1c**)	Ph_2O	6 h	20 / 44	
10	3-NO_2 (**1d**)	Et_2NPh	2.5 h	0 / 10	**6** (42), **3e** (13)
11	3-NO_2 (**1d**)	None	6 h	2 / 35	
12	3-NO_2 (**1d**)	Ph_2O	6 h	52 / 24	

[a] Isolated yield.



Scheme 2



Scheme 3

These results strongly indicate that the origin of carbon-unit introduced for the formation of the benzoxazole ring came from a used solvent, Et_2NPh or Me_2NPh.[8] Structures of benzoxazole derivatives (**6**, **9**, and **10**) were elucidated on the basis of their elemental analyses and spectral data depicted in Experimental.

In this connection, heating of *o*-nitrophenol in Et_2NPh under reflux (at 210-215°C) gave 2-methylbenzoxazole (**11**)[9] in about 45% yield, although a yield was variable, whereas neither heating of *o*-nitrophenol in Et_2NPh at 150°C nor heating in triethylamine under reflux (at 90°C) gave **11**. Therefore, these facts seem to suggest that an *o*-nitrophenol moiety group is essential and a reaction temperature is crucial for the formation of oxazole ring.

Recently, Oguchi *et al.* reported that photo-irradiation of *o*-nitrophenetole produced **11** through a radical mechanism.[10] Then, heating of *o*-nitrophenetole in Et_2NPh under reflux was examined, and no **11** was produced and the starting material was recovered quantitatively, indicating at least that a present benzoxazole formation does not proceed through *o*-nitrophenethole from *o*-nitrophenol.

Studies on the mechanism and the generality of this new method for synthesis of the benzoxazole from *o*-nitrophenol derivative are now under investigation.

Preparation of Salicylaldehydes (1)

The Duff reaction of *m*-nitrophenol with hexamethylenetetramine in 75% polyphosphoric acid gave 6-nitrosalicylaldehyde (**1a**)[11] and 4-nitrosalicylaldehyde (**1c**)[12] in 34% and 12% yields, respectively. **1c** was also prepared alternatively according to the literature.[12] On that occasion, alkaline hydrolysis of 1-acetoxy-2-dibromomethyl-5-nitrobenzene with 8% Na_2CO_3 aqueous solution produced **1c** in much better yield (72% yield) than the reported acidic hydrolysis with conc. H_2SO_4.[12] 3-Nitrosalicylaldehyde (**1d**)[13] was prepared by ozonolysis of 2-methyl-7-nitrobenzo[*b*]furan (**12**).[14] Thus, ozonolysis of **12** in methylene chloride at -78°C followed by alkaline hydrolysis[15] gave **1d** in 80% yield.[16]

EXPERIMENTAL

Melting points were measured on a micro melting point hot-stage apparatus (Yanagimoto) and are uncorrected. Ir spectra were recorded in Nujol on a JASCO A-102 spectrophotometer and ^1H- and ^{13}C-nmr spectra in deuteriochloroform on a Hitachi R-1500 (60 MHz) or Varian VXR-500 (500 MHz) spectrometer unless otherwise stated. Nmr data are reported in parts per million down field from tetramethylsilane as an internal standard (δ 0.0) and coupling constants are given in hertz. Ms was taken on a VG-70SE spectrometer. Column

chromatography was carried out on silica gel (Merck, silica gel 60, No. 9385). All experiments were carried out in an argon atmosphere and the extract was washed with brine, dried over anhydrous $MgSO_4$, then filtered, and the filtrate was evaporated to dryness under reduced pressure, unless otherwise noted. The synthetic samples were identified by comparison of spectral (^{1}H-nmr and Ir) data with those of commercial or synthetic authentic samples or by comparison with physical data in the cited references.

General Procedure for Reaction of Salicylaldehyde (1) with Carbethoxymethylenetriphenylphosphorane in Diethylaniline under Reflux *Reaction of salicylaldehyde* (**1**) (*1 mmol*) *with the* Wittig reagent (1.2 mmol) in Et_2NPh (10 ml) was carried out for the reaction time indicated in Table I.

5-Nitrocoumarin (3a) The raction mixture was diluted with 5% HCl solution and extracted with ether. The residue in CH_2Cl_2 was chromatographed on silica gel. Further elution with the same solvent gave **3a**, 164-164.5°C (lit.,[3] mp 160°C)(pale yellow needles from MeOH).

4-(4-*N*,*N*-Diethylaminophenyl)-6-nitro-3,4-dihydrocoumarin (4) and 6-Nitrocoumarin (3b) The reaction mixture was concentrated under reduced pressure and the residue in hexane-AcOEt (4 : 1) was chromatographed on silica gel. Elution with the same solvent gave **4**. Ir (neat) cm^{-1} : 1785 (C=O), 1520 and 1345 (NO_2). ^{1}H-Nmr (60 MHz, CCl_4) δ : 1.13 (6H, t, *J*=7.0 Hz, 2xNCH$_2$C<u>H</u>$_3$), 2.93 (2H, d, *J*=7.0 Hz, C$_3$-H$_2$), 3.22 (4H, q, *J*=7.0 Hz, 2xNC<u>H</u>$_2$CH$_3$), 4.23 (1H, t, *J*=7.0 Hz, C$_4$-H), 6.54 (2H, d, *J*=9.1 Hz, 2xC3'-H), 6.90 (2H, d, *J*=9.1 Hz, 2xC2'-H), 7.10 (1H, d, *J*=8.8 Hz, C$_8$-H), 7.84 (1H, d, *J*=2.9 Hz, C$_5$-H), 8.07 (1H, dd, *J*=8.8, 2.9 Hz, C$_7$-H). Ms (FAB) *m/z* : 341 (M^++1). Successive elution with the same solvent gave **3b**, mp 187-191°C (lit.,[4] 181-182°C)(colorless prisms from hexane-AcOEt).

4-(4-*N*,*N*-Diethylaminophenyl)-7-nitrocoumarin (5), Ethyl *trans*-2-hydroxy-4-nitrocinnamate (2c), and 7-Nitrocoumarin (3c) The reaction mixture was concentrated under reduced pressure and the residue in hexane-AcOEt (8 : 1) was chromatographed on silica gel. Elution with the same solvent afforded **5**, mp 173-174°C (red needles from AcOEt). *Anal.* Calcd for $C_{19}H_{18}N_2O_4$: C, 67.45; H, 5.36; N, 8.28. Found : C, 67.21; H, 5.34; N, 8.14. Ir cm^{-1} : 1720 (C=O), 1525 and 1350 (NO_2). ^{1}H-Nmr (60 MHz, $CDCl_3$) δ : 1.24 (6H, t, *J*=7.0 Hz, 2xNCH$_2$C<u>H</u>$_3$), 3.46 (4H, q, *J*=7.0 Hz, 2xNC<u>H</u>$_2$CH$_3$), 6.46 (1H, s, C$_3$-H), 6.78 (2H, d, *J*=9.0 Hz, 2xC3'-H), 7.35 (2H, d, *J*=9.0 Hz, 2xC2'-H), 7.95-8.05 (2H, m, C$_5$-H and C$_6$-H), 8.20 (1H, d, *J*=2.3 Hz, C$_8$-H). Ms (EI) *m/z* : 338 (M^+). Elution with hexane-AcOEt (6 : 1) afforded **2c**, mp 234-235°C (yellow prisms from AcOEt-benzene). *Anal.* Calcd for $C_{11}H_{11}NO_5$: C, 55.70; H, 4.67; N, 5.90. Found : C, 55.72; H, 4.70; N, 5.65. Ir cm^{-1} : 3350(OH), 1690 (C=O), 1530 and 1350 (NO_2). ^{1}H-Nmr (60 MHz,

$CDCl_3$) δ : 1.28 (3H, t, *J*=7.0 Hz, $CO_2CH_2\underline{C}H_3$), 4.22 (2H, q, *J*=7.0 Hz, $CO_2\underline{C}H_2CH_3$), 6.78 (1H, d, *J*=16.4 Hz, CH=$C\underline{H}CO_2$), 7.53-7.84 (3H, m, aromatic protons), 7.85 (1H, d, *J*=16.4 Hz, $C\underline{H}$=$CHCO_2$), 11.25 (1H, s, OH). Ms (EI) *m/z* : 237 (M^+). Elution with hexane-AcOEt (2 : 1) afforded **3c**, mp 205-205.5°C (lit.,[5] 199-202°C)(yellow plates from benzene).

Ethyl *trans*-3-(2-methylbenzoxazole-7-yl)propenoate (6), 8-Aminocoumarin (3e), and 8-Nitrocoumarin (3d) The reaction mixture in hexane-AcOEt (5 : 1) was chromatographed on silica gel. Elution with the same solvent afforded **6**, mp 101-102°C (pale yellow needles from ether). *Anal.* Calcd for $C_{13}H_{13}NO_3$: C, 67.52; H, 5.66; N, 6.06. Found : C, 67.30; H, 5.57; N, 6.36. Ir cm^{-1} : 1700 (C=O). ^{1}H-Nmr (60 MHz, $CDCl_3$) δ : 1.38 (3H, t, *J*=7.0 Hz, $CO_2CH_2\underline{C}H_3$), 2.70 (3H, s, CH_3), 4.32 (2H, q, *J*=7.0 Hz, $CO_2\underline{C}H_2CH_3$), 6.86 (1H, d, *J*=15.8 Hz, CH=$C\underline{H}CO_2$), 7.26-7.75 (3H, m, aromatic protons), 7.81 (1H, d, *J*=15.8 Hz, $C\underline{H}$=$CHCO_2$). ^{13}C-Nmr (125 MHz) δ: 14.4 (CH_3), 14.6 (CH_3), 60.7 (CH_2), 119.0 (C), 121.2 (CH), 122.0 (CH), 124.5 (CH), 126.2 (CH), 138.8 (CH), 142.2 (C), 149.1 (C), 164.2 (C), 167.0 (C). Ms (FAB) *m/z* : 231 (M^++1). Elution with hexane-AcOEt (2 : 1) afforded **3e**, mp 144-145°C (lit.,[6] 145-146°C)(pale yellow needles from benzene). Elution with hexane-AcOEt (1 : 1) afforded **3d**, mp 190-192°C (lit.,[7] 187°C)(pale yellow plates from benzene).

General Procedure for Reaction of 1 with Phosphorane in the Absence of Solvent at 210-215°C Reaction of **1** (1 mmol) with phosphorane (1.2 mmol) was carried out for the reaction time indicated in Table I. After cooling, the reaction mixture was dissolved in $CHCl_3$ and the solution was chromatographed on silica gel.

5-Nitrocoumarin (3a) Elution with hexane-AcOEt (6 : 1) gave **3a**, mp 163-164°C.

Ethyl *trans*-2-ethoxy-5-nitrocinnamate (7) and 6-Nitrocoumarin (3b) Elution with hexane-AcOEt (7 : 1) afforded **7**, mp 81-82°C (colorless needles from ether-hexane). *Anal.* Calcd for $C_{13}H_{15}NO_5$: C, 58.86; H, 5.70; N, 5.28. Found : C, 58.40; H, 5.77; N, 5.29. Ir cm^{-1} : 1705 (C=O), 1507 and 1340 (NO_2). ^{1}H-Nmr (60 MHz, $CDCl_3$) δ : 1.35 (3H, t, *J*=7.0 Hz, $OCH_2\underline{C}H_3$), 1.53 (3H, t, *J*=7.0 Hz, $CO_2CH_2\underline{C}H_3$), 4.24 (2H, q, *J*=7.0 Hz, $OC\underline{H}_2CH_3$), 4.28 (2H, q, *J*=7.0 Hz, $CO_2\underline{C}H_2CH_3$), 6.60 (1H, d, *J*=16.4 Hz, CH=$C\underline{H}CO_2$), 6.97 (1H, d, *J*=9.4 Hz, C_3-H), 7.96 (1H, d, *J*=16.4 Hz, $C\underline{H}$=$CHCO_2$), 8.22 (1H, dd, *J*=9.4, 2.9 Hz, C_4-H), 8.20 (1H, d, *J*=2.9 Hz, C_6-H). Ms (EI) *m/z* : 265 (M^+). Elution with hexane-AcOEt (5 : 1) gave **3b**, mp 188-190°C.

Ethyl *trans*-2-ethoxy-4-nitrocinnamate (8), Ethyl *trans*-2-hydroxy-4-nitrocinnamate (2c) and 7-Nitrocoumarin (3c) Elution with hexane-AcOEt (7 : 1) afforded **8**, mp 92-93°C (pale yellow needles from ether-hexane). *Anal.* Calcd for $C_{13}H_{15}NO_5$: C, 58.86; H, 5.70; N, 5.28. Found : C, 58.52; H, 5.68; N, 5.17. Ir cm^{-1} : 1715 (C=O), 1520 and 1350 (NO_2). ^{1}H-Nmr (60 MHz, $CDCl_3$) δ : 1.35 (3H, t, *J*=7.0 Hz, $OCH_2\underline{CH_3}$), 1.53 (3H, t, *J*=7.0 Hz, $CO_2CH_2\underline{CH_3}$), 4.22 (2H, q, *J*=7.0 Hz, OCH_2CH_3), 4.30 (2H, q, *J*=7.0 Hz, $CO_2\underline{CH_2}CH_3$), 6.62 (1H, d, *J*=16.4 Hz, $CH=\underline{CH}CO_2$), 7.53-7.94 (3H, m, aromatic protons), 7.97 (1H, d, *J*=16.4 Hz, $\underline{CH}=CHCO_2$). Ms (EI) *m/z* : 265 (M^+). Elution with hexane-AcOEt (6 : 1) gave **2c**, mp 233-235°C and elution with hexane-AcOEt (2 : 1) gave **3c**, mp 204-205°C.

Ethyl *trans*-2-hydroxy-3-nitrocinnamate (2d) and 8-Nitrocoumarin (3d) Elution with hexane-AcOEt (5 : 1) gave **2d**, mp 83-85°C (yellow pillars from benzene). *Anal.* Calcd for $C_{11}H_{11}NO_5$: C, 55.70; H, 4.67; N, 5.90. Found : C, 55.74; H, 4.77; N, 5.63. Ir cm^{-1} : 1715 (C=O), 1540 and 1330 (NO_2). ^{1}H-Nmr (60 MHz, $CDCl_3$) δ : 1.36 (3H, t, *J*=7.0 Hz, $CO_2CH_2\underline{CH_3}$), 4.30 (2H, q, *J*=7.0 Hz, $CO_2\underline{CH_2}CH_3$), 6.62 (1H, d, *J*=16.4 Hz, $CH=\underline{CH}CO_2$), 7.02 (1H, t, *J*=7.9 Hz, C_5-H), 7.83 (1H, dd, *J*=7.9, 1.7 Hz, C_6-H), 7.96 (1H, d, *J*=16.4 Hz, $\underline{CH}=CHCO_2$), 8.15 (1H, dd, *J*=7.9, 1.7 Hz, C_4-H), 11.27 (1H, s, OH, exchangeable with D_2O). Ms (FAB) *m/z* : 238 (M^++1). Elution with hexane-AcOEt (1 : 1) gave **3d**, mp 190-191°C.

General Procedure for Reaction of 1 with Phosphorane in Diphenyl Ether at 210-215°C Reaction of **1** (1 mmol) with phosphorane (1.2 mmol) in Ph_2O (10 ml) was carried out for the reaction time indicated in Table I. The reaction mixture in hexane was chromatographed on silica gel.

5-Nitrocoumarin (3a) Elution with hexane-AcOEt (2 : 1) gave **3a**, mp 162.5-163.5°C.

6-Nitrocoumarin (3b) and Ethyl *trans*-2-hydroxy-5-nitrocinnamate (2b) Elution with hexane-AcOEt (3 : 1) gave **3b**, mp 181.5-182.5°C and elution with hexane-AcOEt (2 : 1) gave **2b**, mp 175-176°C (lit.,[18] mp 170-172°C)(yellow prisms from benzene).

Ethyl *trans*-2-hydroxy-4-nitrocinnamate (2c) and 7-Nitrocoumarin (3c) Elution with hexane-AcOEt (3: 1) gave **2c**, mp 235-237°C and elution with hexane-AcOEt (2 : 1) gave **3c**, mp 203-204.5°C.

Ethyl *trans*-2-hydroxy-3-nitrocinnamate (2d) and 8-Nitrocoumarin (3d) Elution with hexane-AcOEt (4: 1) gave **2d**, mp 82-83°C and elution with hexane-AcOEt (1 : 1) gave **3d**, mp 190-192°C.

Heating of 3d in Et_2NPh at 210-215°C A solution of **3d** (100 mg, 0.52 mmol) in Et_2NPh (5 ml) was refluxed for 3 h. After cooling, the reaction mixture was diluted with hexane and the solution was subjected to

column chromatography on silica gel. *Elution with hexane-AcOEt* (2 : 1) gave **3e** (14 mg, 17% yield), mp 142-143°C. Elution with hexane-AcOEt (1 : 1) gave the starting material (**3d**)(69 mg, 69% yield).

Heating of 2d in Et_2NPh at 210-215°C A solution of **2d** (500 mg, 2.11 mmol) in Et_2NPh (30 ml) was heated for 15 min under reflux. After cooling, the reaction mixture was diluted with hexane and a solution was subjected to column chromatography on silica gel. Elution with hexane-AcOEt (5 : 1) provided **6** (218 mg, 45% yield), *mp* 101-102°C and elution with hexane-AcOEt (2 : 1) provided **3e** (35 mg, 10% yield), mp 143-145°C. Elution with hexane-AcOEt (1 : 1) provided **3d** (33 mg, 8% yield), mp 185-187°C.

Heating of 2d in Me_2NPh under Reflux A solution of **2d** (500 mg, 2.11 mmol) in Me_2NPh (30 ml) was heated for 15 min under reflux. After cooling, the reaction mixture was diluted with a large quantity of ether and the ethereal solution was washed with 5% HCl solution. The residue in CH_2Cl_2 was subjected to column chromatography on silica gel. Elution with hexane-AcOEt (5 : 1) gave ethyl *trans*-3-(benzoxazole-7-yl)propenoate (**9**)(138 mg, 30% yield), mp 91-92°C (pale yellow needles from ether-hexane). *Anal.* Calcd for $C_{12}H_{11}NO_3$: C, 66.35; H, 5.10; N, 6.45. Found : C, 66.54; H, 5.04; N, 6.30. Ir cm^{-1} : 1705 (C=O). ^{1}H-Nmr (60 MHz, $CDCl_3$) δ : 1.37 (3H, t, *J*=7.0 Hz, $CO_2CH_2C\underline{H}_3$), 4.31 (2H, q, *J*=7.0 Hz, $CO_2C\underline{H}_2CH_3$), 6.90 (1H, d, *J*=16.4 Hz, $CH=C\underline{H}CO_2$), 7.20-7.92 (3H, m, aromatic protons), 7.83 (1H, d, *J*=16.4 Hz, $C\underline{H}=CHCO_2$), 8.18 (1H, s, $OC\underline{H}=N$). Elution with hexane-AcOEt (2 : 1) gave ethyl *trans*-3-(2-benzoxazolon-7-yl)propenoate (**10**)(166 mg, 34% yield), mp 182-184°C (colorless needles from benzene). *Anal.* Calcd for $C_{12}H_{11}NO_4$: C, 61.80; H, 4.75; N, 6.01. Found : C, 61.91; H, 4.63; N, 5.91. Ir ($CHCl_3$) cm^{-1} : 3200 (NH), 1780 (OCONH), 1705 (COOEt). ^{1}H-Nmr (60 MHz, DMSO-d_6) δ : 1.29 (3H, t, *J*=7.0 Hz, $CO_2CH_2C\underline{H}_3$), 4.22 (2H, q, *J*=7.0 Hz, $CO_2C\underline{H}_2CH_3$), 6.70 (1H, d, *J*=16.4 Hz, $CH=C\underline{H}CO_2$), 7.05-7.53 (3H, m, aromatic protons), 7.67 (1H, d, *J*=16.4 Hz, $C\underline{H}=CHCO_2$), 11.84 (1H, s, NH).

2-Methylbenzoxazole (11) A solution of *o*-nitrophenol (500 mg, 3.59 mmol) in Et_2NPh (15 ml) was reflux for 3 h. After cooling, the reaction mixture in hexane was subjected to column chromatography on silica gel. Elution with hexane-AcOEt (5 : 1) afforded **11**[9] (216 mg, 45% yield).

The Duff reaction of *m*-Nitrophenol Hexamethylenetetramine (7.10 g, 50.7 mmol) was added to a stirred solution of *m*-nitrophenol (7.0 g, 50.3 mmol) in 75% polyphosphoric acid (40 ml) at 100°C and the mixture was stirred for 45 min. After cooling, the reaction mixture was diluted with cold water and extracted with AcOEt. The residue in $CHCl_3$ was chromatographed on silica gel. Elution with hexane-AcOEt (8 : 1) provided **1a** (2.82 g, 34% yield), mp 52-53°C (lit.,[11] mp 54-55°C)(yellow prisms from ether-hexane). Elution

with hexane-AcOEt (6 : 1) provided **1c** (1.01 g, 12% yield), mp 137-138°C (lit.,[12] mp 133-134°C)(pale yellow plates from benzene).

4-Nitrosalicylaldehyde (1c) A solution of 1-acetoxy-2-dibromomethyl-5-nitrobenzene[12] (6.44 g, 18.2 mmol) in 8% Na_2CO_3 aqueous solution (70 ml) was boiled under reflux for 4 h. After cooling, the reaction mixture ws acidified with 10% HCl solution and the solution was extracted with AcOEt. The residue in AcOEt was subjected to column chromatography on silica gel. Elution with hexane-AcOEt (6 : 1) gave **1c** (2.20 g, 72% yield), mp 137-138°C.

3-Nitrosalicylaldehyde (1d) Benzofuran (**12**)[14] (500 mg, 2.82 mmol) was dissolved in dry CH_2Cl_2 (92 ml) and cooled to -78°C. Ozone was bubbled through the solution for 15 min with stirring. The reaction mixture was stirred at -78°C for a further 15 min. Excess ozone was removed by bubbling argon through the solution for about 10 min at -78°C. Me_2S (1 ml, 13.6 mmol) was added with stirring and the whole was stirred at room temperature for 1 h. The reaction mixture was concentrated under reduced pressure. The residue in EtOH (35 ml) and 1% $NaHCO_3$ aqueous solution (36 ml) was warmed at 40-45°C for 5 min. The reaction mixture was poured into water, acidified in 1% HCl solution and then extracted with ether. The residue in AcOEt was subjected to column chromatography on silica gel. Elution with the same solvent gave **1d**, (380 mg, 80% yield), mp 110-111°C (lit.,[13] 109-110°C)(yellow prisms from benzene)

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