Aryl–Aryl Coupling Reaction Using a Novel and Highly Active Palladium Reagent Prepared from $Pd(OAc)_2$, 1,3-Bis[diphenylphosphino]propane (DPPP), and Bu_3P

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A palladium-assisted coupling reaction of aryl triflate with arene was investigated, and a novel Pd reagent prepared from equimolar $Pd(OAc)_2$, 1,3-Bis[diphenylphosphino]propane (DPPP), and Bu_3P was developed. This method is useful for intramolecular biaryl coupling reactions, not only between aryl triflate and arene (triflate-amide), but also between aryl halide and arene (halo-amide).

Key words biaryl coupling; aryl triflate-arene coupling; aryl halide-arene coupling; palladium; bidentate ligand

Palladium-assisted aryl–aryl coupling reactions are used to synthesize condensed aromatic compounds.[1)] We recently accomplished a convenient synthesis of several benzo[*c*]-phenanthridine alkaloids[2)] and arnottin I[3)] using a biaryl coupling reaction of the appropriate halo-amides (**A**, X=I or Br) and halo-esters (**B**, X=I or Br), under ordinary Heck reaction conditions. Subsequently, we investigated a biaryl cyclization reaction of amides possessing a triflate group as a leaving group instead of a halogen group in order to examine a diversity of leaving group for a biaryl coupling reaction. However, this method was ineffective for the intramolecular biaryl coupling reaction of a triflate-amide, as described below. After considerable experimentation, we developed a novel combination system, consisting of $Pd(OAc)_2$, DPPP (1,3-bis[diphenylphosphino]propane), and Bu_3P in the presence of a base. Here, we describe the results of an aryl–aryl coupling reaction under such reaction conditions.[4)]

First, the biaryl coupling reaction of triflate-amide (**1a**), which was prepared from 2-hydroxy-*N*-methyl-*N*-phenylbenzamide[5)] and Tf_2O in NEt_3–CH_2Cl_2, to phenanthridone (**2a**) by $Pd(OAc)_2$, PPh_3, and Ag_2CO_3[2)] was examined under several reaction conditions. As shown in Table 1, the coupling reaction did not proceed, even with equimolar Pd reagent (see runs 1—4). Suzuki's method, which was efficient for synthesizing gilvocarcin V employing sodium pivalate as a base,[6)] always gave a small amount of the hydrolysis product, 2-hydroxy-*N*-methyl-*N*-phenylbenzamide, along with the desired cyclization product **2a** (see run 5), but without a reliable yield. Therefore, we sought to develop a novel, more efficient method.

Since bidentate ligands such as DPPP have lower cone angles[7a)] and P–Pd–P angles[7b)] than monodentate ligands, and coordinate to the Pd in the square–planar Pd complex in an obligatory *cis* arrangement, in contrast to the *trans* arrangement of monodentate ligands in the complex,[8)] we felt that DPPP would be less bulky than a monodentate ligand, such as PPh_3 and suitable for a biaryl coupling (electrophilic reaction of palladium(II) complex with aryl ring, deprotonation, and reductive elimination of palladium) process for steric reasons.[1d,h,8)] Moreover, since the Pd reagent prepared from $Pd(OAc)_2$–Bu_3P is highly active,[9)] we assumed that the zerovalent Pd prepared from Bu_3P would have strong oxidative addition ability. We examined the cyclization reaction of **1a** using DPPP (see runs 6—8) and the desired product (**2a**) was obtained in yield of 10—21%. Moreover, using Bu_3P, **2a** was obtained in a yield of 27% (see run 9). Surprisingly, however, the DPPP–Bu_3P combination system afforded **2a** in excellent yield (see run 10). Although the coupling reaction proceeds even in the presence of 0.3 equivalent of $Pd(OAc)_2$, several equivalents of Bu_3P were necessary to obtain the desired product in good yield (see runs 11—13 in Table 1 and run 2 in Table 2). Using equimolar $Pd(OAc)_2$, DPPP, Bu_3P, and Hünig base in *N*,*N*-dimethylformamide (DMF), the reaction proceeded quickly, and the coupling product (**2a**) was obtained in excellent yield (see run 17). However, using less equimolar palladium reagent, the coupling reaction did not proceed in a satisfactory yield even in the presence of organic bases (see runs 19—21). Application of our novel method to halo-amides (**1b**,[10)] **c**[10)]) gave **2a** in excellent yield (see runs 22—25 in Table 1).

Next, our novel procedure was applied to the coupling reactions of triflates (**1d**, **3**). 2-Trifluoromethanesulfonyloxy-*N*-methyl-*N*-phenylbenzamide (**1d**) was synthesized by amidation of 3-methoxysalicylic acid with monomethylaniline in the presence of P_2O_5, followed by triflylation with Tf_2O, and 2-trifluoromethanesulfonyloxy-5-methoxy-*N*-methyl-*N*-(1-naphthyl)benzamide (**3**) was synthesized by amidation of salicylic acid with *N*-methyl-1-naphthylamine[11)] using the same procedure used to synthesize **1d**. The results for the coupling reactions of **1d** shown in Table 1 (see runs 26 and 27) and **3** shown in Table 2 indicate that our method is very useful for coupling reactions between aryl triflates and arenes. More-

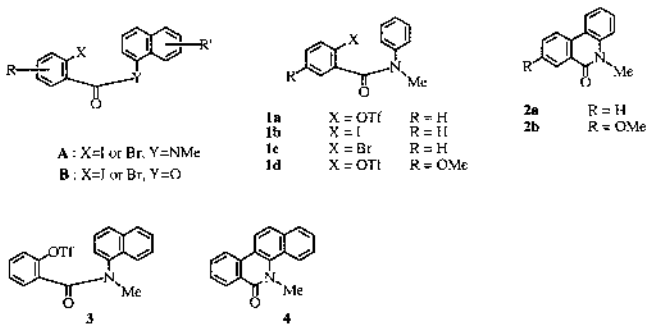

Chart 1

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Table 1. Results of Coupling Reaction of *N*-Methyl-*N*-phenyl-2-substituted Benzamides (**1**) to *N*-Methylphenanthridones (**2**)[a]

	Run	Pd (eq)		Ligand (L/Pd)[b]		Bu_3P (eq)	Base	Solvent	Time	Yield (%)	
										2	**1**
1a	1	$Pd(OAc)_2$	(0.2)	PPh_3	(2)	—	Ag_2CO_3	DMF	3 h	NR[c]	
	2	$Pd(OAc)_2$	(1.0)	PPh_3	(2)	—	Ag_2CO_3	Benzene	3 h	NR	
	3	$Pd(OAc)_2$	(1.0)	PPh_3	(2)	—	Ag_2CO_3	DMF	5 h	NR	
	4	$Pd(PPh_3)_4$	(0.05)	—		—	Ag_2CO_3	Benzene	11 h	NR	
	5	$(Ph_3P)_2PdCl_2$	(0.27)	—		—	NaOPiv	DMA[d]	1 h	69[e]	—
	6	$Pd(OAc)_2$	(1.0)	DPPP	(1)	—	Ag_2CO_3	Xylene	190 h	10	77
	7	$Pd(OAc)_2$	(1.0)	DPPP	(1)	—	Ag_2CO_3	DMF	190 h	21	24
	8	$Pd(OAc)_2$	(1.0)	DPPP	(1)	—	iso-Pr_2NEt	DMF	4 h	15	59
	9	$Pd(OAc)_2$	(1.0)	—		1.0	Ag_2CO_3	DMF	96 h	27	62
	10	$Pd(OAc)_2$	(1.0)	DPPP	(1)	1.0	Ag_2CO_3	DMF	5 h	93	—
	11	$Pd(OAc)_2$	(0.3)	DPPP	(1)	0.3	Ag_2CO_3	DMF	100 h	26	61
	12	$Pd(OAc)_2$	(0.3)	DPPP	(1)	1.0	Ag_2CO_3	DMF	55 h	58	15
	13	$Pd(OAc)_2$	(0.3)	DPPP	(1)	3.0	Ag_2CO_3	DMF	2 h	71	—
	14	$Pd(OAc)_2$	(0.5)	DPPP	(1)	0.5	Ag_2CO_3	DMF	70 h	31	56
	15	$Pd(OAc)_2$	(1.0)	DPPP	(1)	1.0	Ag_2CO_3	Benzene	11 h	37	62
	16	$Pd(OAc)_2$	(1.0)	DPPP	(1)	1.0	Ag_2CO_3	Xylene	9 h	59	35
	17	$Pd(OAc)_2$	(1.0)	DPPP	(1)	1.0	iso-Pr_2NEt	DMF	30 min	92	—
	18	$Pd(OAc)_2$	(1.0)	DPPP	(1)	1.0	—	DMF	30 min	77	—
	19	$Pd(OAc)_2$	(0.3)	DPPP	(1)	0.3	iso-Pr_2NEt	DMF	5 h	17	63[f]
	20	$Pd(OAc)_2$	(0.5)	DPPP	(1)	0.5	iso-Pr_2NEt	DMF	3 h	72	6
	21	$Pd(OAc)_2$	(0.3)	DPPP	(1)	0.3	Cy_2NMe	DMF	5 h	16	45[g]
1b	22	$Pd(OAc)_2$	(1.0)	DPPP	(1)	1.0	Ag_2CO_3	DMF	15 min	93	—
	23	$Pd(OAc)_2$	(1.0)	DPPP	(1)	1.0	iso-Pr_2NEt	DMF	15 h	98	—
1c	24	$Pd(OAc)_2$	(1.0)	DPPP	(1)	1.0	Ag_2CO_3	DMF	20 min	93	—
	25	$Pd(OAc)_2$	(1.0)	DPPP	(1)	1.0	iso-Pr_2NEt	DMF	15 h	90	—
1d	26	$Pd(OAc)_2$	(1.0)	DPPP	(1)	1.0	Ag_2CO_3	DMF	3.5 h	76	—
	27	$Pd(OAc)_2$	(1.0)	DPPP	(1)	1.0	iso-Pr_2NEt	DMF	30 min	88	—

a) All reactions were carried out under an argon atmosphere using $Pd(OAc)_2$, ligand, and Bu_3P in the ratio indicated in the table and 2 mol equivalents of base under reflux unless otherwise noted. *b*) Molar ratio between ligand and $Pd(OAc)_2$. *c*) No reaction occurred and starting material was recovered in a yield of more than 80%. *d*) Heating at 140 °C. *e*) Hydrolysis product, 2-hydroxy-*N*-methyl-*N*-phenylbenzamide, was obtained in 28% yield. *f*) *N*-Methylbenzanilide was obtained in 17% yield. *g*) *N*-Methylbenzanilide was obtained in 37% yield. DPPP: 1,3-bis(diphenylphosphino)propane.

Table 2. Results of Coupling Reaction of 2-[(Trifluoromethanesulfonyl)oxy]-*N*-methyl-*N*-(1-naphthyl)benzamide (**3**) to *N*-Methylbenzo[*c*]phenanthridone (**4**) in DMF under Reflux[a]

Run	$Pd(OAc)_2$ (eq)	Ligand (L/Pd)[b]	Bu_3P (eq)	Base	Time	Yield (%)
1	1.0	DPPP (1)	1.0	Ag_2CO_3	20 min	97
2	0.3	DPPP (1)	3.0	Ag_2CO_3	3 h	70
3	1.0	DPPP (1)	1.0	iso-Pr_2NEt	20 min	96

a) All reactions were carried out under an argon atmosphere using $Pd(OAc)_2$, ligand, and Bu_3P in the ratio indicated in the table, and 2 mol equivalents of base. *b*) Molar ratio between ligand and $Pd(OAc)_2$.

Table 3. Results of Coupling Reactions of *N*-Methyl-*N*-phenyl-2-substituted Benzamides (**1**) to *N*-Methylphenanthridones (**2**)[a]

	Run	$Pd(OAc)_2$ (eq)	Ligand (L/Pd)[b]		Bu_3P (eq)	Base[c]	Time	Yield (%)	
								2	**1**
1a	1	1.0	DPPE	(1)	1.0	iso-Pr_2NEt	30 min	81	—
	2	1.0	DPPB	(1)	1.0	iso-Pr_2NEt	30 min	89	—
	3	1.0	DPPB	(1)	1.0	Ag_2CO_3	30 min	81	—
	4	1.0	DPPH	(1)	1.0	iso-Pr_2NEt	30 min	93	—
	5	1.0	DPPH	(1)	1.0	Ag_2CO_3	30 min	63	—
	6	1.0	(*R*)-BINAP	(1)	1.0	iso-Pr_2NEt	30 min	78	—
	7	1.0	(*R*)-BINAP	(1)	1.0	Ag_2CO_3	30 min	62	7
1d	8	1.0	DPPB	(1)	1.0	iso-Pr_2NEt	30 min	75	—
	9	1.0	DPPB	(1)	1.0	Ag_2CO_3	30 min	87	—
	10	1.0	DPPH	(1)	1.0	iso-Pr_2NEt	30 min	93	—
	11	1.0	(*R*)-BINAP	(1)	1.0	iso-Pr_2NEt	30 min	57	—

a) All reactions were carried out under reflux in DMF. *b*) Molar ratio between ligand and Pd. *c*) Two mol equivalents of base was added. DPPE: 1,2-bis(diphenylphosphino)ethane, DPPB: 1,4-bis(diphenylphosphino)butane, DPPH: 1,6-bis(diphenylphosphino)hexane, (*R*)-BINAP: (*R*)-2,2′-bis(diphenylphosphino)-1,1′-binaphthyl.

over, other bidentate ligands were also effective for the coupling reaction of **1a** and **1d** using equimolar $Pd(OAc)_2$ as shown in Table 3.

Consequently, our novel combination system consisting of equimolar $Pd(OAc)_2$, DPPP, and Bu_3P and two molar equivalents of a base is very efficient and powerful for the intramolecular aryl–aryl coupling reaction of not only triflate-amides (**1a**, **d**, **3**), but also halo-amides (**1b**, **c**). Mechanistic and synthetic studies of benzo[*c*]phenanthridine alkaloids are currently under way using our novel method.[12)]

Experimental

Melting points were measured on a micro melting point hot-stage apparatus (Yanagimoto) and are given uncorrected. IR spectra were recorded from samples in KBr pellets with JASCO A-102 or JASCO FT/IR 350 spectrophotometer, and ^{1}H-NMR spectra were recorded in deuteriochloroform on a Hitachi R-1500 (60 MHz) unless otherwise stated. NMR data are reported in parts per million downfield from tetramethylsilane as an internal standard (δ 0.0) and coupling constants are given in Hertz. Mass spectra were obtained 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. $Pd(OAc)_2$ was treated with boiling benzene and the mixture was filtered while hot. The hot filtrate was then concentrated to dryness to give purified $Pd(OAc)_2$.[13)]

2-Trifluoromethanesulfonyloxy-*N*-methyl-*N*-phenylbenzamide (1a) To a mixture of 2-hydroxy-*N*-methyl-*N*-phenylbenzamide[5)] (0.97 g, 4.3 mmol) and dry NEt_3 (1.30 g, 12.8 mmol) in dry CH_2Cl_2 (14 ml) at −15 °C was added triflic anhydride (1.81 g, 6.4 mmol) in dry CH_2Cl_2 (4 ml). The whole was stirred for 30 min at the same temperature. The mixture was diluted with CH_2Cl_2 (20 ml) and washed with aqueous sat. $NaHCO_3$ (20 ml) and brine (20 ml). The organic layer was dried over anhydrous Na_2SO_4. The residue dissolved in hexane–AcOEt (2 : 1) was subjected to column chromatography on silica gel. Elution with hexane–AcOEt (2 : 1) gave **1a** (1.45 g, 94%) as colorless needles, mp 69—70 °C (from hexane). IR cm^{-1}: 1650, 1150. ^{1}H-NMR (60 MHz) δ: 3.49 (3H, s, NCH_3), 7.16—7.34 (9H, m, aromatic protons). FAB-MS *m*/*z*: 360 (M^++1). *Anal.* Calcd for $C_{15}H_{12}F_3NO_4S$: C, 50.14; H, 3.37; N, 3.90. Found: C, 49.91; H, 3.57; N, 4.06.

General Procedure for the Coupling Reaction of 2-Trifluoromethanesulfonyloxy-*N*-methyl-*N*-phenylbenzamide (1a) (Runs 1—5 in Table 1) Reaction of **1a** (0.3 mmol) with $Pd(OAc)_2$, PPh_3, and a base in dry solvent (8 ml) was carried out using $Pd(OAc)_2$ and PPh_3 in a ratio 1 : 2 and 2 mol equivalent of a base under reflux and under the reaction conditions indicated in Table 1. The reaction mixture was diluted with ether, and the precipitates were removed by filtration. The filtrate was washed with brine. The residue dissolved in hexane–AcOEt (4 : 1) was subjected to column chromatography on silica gel. Elution with hexane–AcOEt (4 : 1) gave the hydrolysis product, 2-hydroxy-*N*-methyl-*N*-phenylbenzamide, and then, the cyclized product (**2a**).[2a)] Elution with hexane–AcOEt (3 : 1) gave the starting material (**1a**).

2-Trifluoromethanesulfonyloxy-5-methoxy-*N*-methyl-*N*-phenylbenzamide (1d) A mixture of 2-hydroxy-5-methoxybenzoic acid (2.0 g, 11.9 mmol), *N*-methylaniline (1.66 g, 15.5 mmol), P_2O_5 (0.56 g, 3.96 mmol) in dry xylene (40 ml) was refluxed for 6 h. The reaction mixture was diluted with AcOEt and then, washed with 10% HCl, aqueous 5% $NaHCO_3$ solution and brine. The residue in hexane–AcOEt (3 : 1) was subjected to column chromatography on silica gel. Elution with hexane–AcOEt (3 : 1) gave 2-hydroxy-5-methoxy-*N*-methyl-*N*-phenylbenzamide (1.84 g, 60%) as a colorless amorphous solid. IR cm^{-1}: 3300—3650, 1580. ^{1}H-NMR (60 MHz) δ: 3.20 (3H, s, NCH_3), 3.49 (3H, s, OCH_3), 6.17 (1H, m, OH), 6.79—6.83 (2H, m, aromatic protons) 7.05—7.41 (4H, m, aromatic protons). FAB-MS *m*/*z*: 258.1130 (Calcd for $C_{15}H_{16}NO_3$: 253.1130).

To a mixture of 2-hydroxy-5-methoxy-*N*-methyl-*N*-phenylbenzamide (0.80 g, 3.11 mmol) and dry NEt_3 (0.94 g, 9.33 mmol) in dry CH_2Cl_2 (16 ml) at −21 °C was added triflic anhydride (1.31 g, 4.66 mmol) in dry CH_2Cl_2 (4 ml). The whole was stirred for 1.5 h at the same temperature. The mixture was diluted with CH_2Cl_2 (20 ml) and washed with aqueous sat. $NaHCO_3$ and brine. The organic layer was dried over anhydrous Na_2SO_4. The residue dissolved in hexane–AcOEt (3 : 1) was subjected to column chromatography on silica gel. Elution with hexane–AcOEt (3 : 1) gave **1d** (0.97 g, 80%) as colorless needles, mp 100—103 °C (from hexane–benzene). IR cm^{-1}: 1650, 1145. ^{1}H-NMR (60 MHz) δ: 3.49 (3H, s, NCH_3), 3.73 (3H, s, OCH_3), 6.89—6.92 (3H, m, aromatic protons), 7.07—7.27 (5H, m, aromatic protons). FAB-MS *m*/*z*: 390 (M^++1). *Anal.* Calcd for $C_{16}H_{14}F_3NO_5S$: C, 49.36; H, 3.62; N, 3.60. Found: C, 49.39; H, 3.82; N, 3.53.

General Procedure for the Coupling Reaction of *N*-Methylbenzanilides 1 Using Bidentate Ligands (Runs 6—27 in Table 1 and Runs 1—11 in Table 3) Reaction of **1** (0.3 mmol) with $Pd(OAc)_2$, a bidentate ligand, and/or Bu_3P and a base in dry solvent (8 ml) was carried out using $Pd(OAc)_2$, a bidentate ligand, and/or Bu_3P in the ratios indicated in Tables 1 and 3, and 2 mol equivalents of a base under reflux. The reaction mixture was diluted with ether and the precipitates were removed by filtration. The filtrate was washed with brine. The residue dissolved in hexane–AcOEt (4 : 1) was subjected to column chromatography on silica gel. In the cases of **1a**—**c**, elution with hexane–AcOEt (4 : 1) gave the cyclized product (**2a**)[2a)] and further elution with hexane–AcOEt (3 : 1) gave the starting material (**1a**). In the case of **1d**, elution with hexane–AcOEt (4 : 1) gave 8-methoxy-*N*-methylphenanthridine-6(5*H*)-one (**2b**) as colorless needles, mp 134—134.5 °C (from hexane). IR cm^{-1}: 1650. ^{1}H-NMR (60 MHz) δ: 3.79 (3H, s, NCH_3), 3.95 (3H, s, OCH_3), 6.87—7.48 (4H, m, aromatic protons), 7.98 (1H, d, J=8.1 Hz, C_9-H), 8.02 (1H, d, J=8.1 Hz, C_{10}-H), 8.20 (1H, s, C_7-H). FAB-MS *m*/*z*: 240 (M^++1). *Anal.* Calcd for $C_{15}H_{13}NO_2$: C, 75.30; H, 5.48; N, 5.85. Found: C, 75.13; H, 5.71; N, 5.91.

2-Trifluoromethanesulfonyloxy-5-methoxy-*N*-methyl-*N*-(1-naphthyl)-benzamide (3) A mixture of salicylic acid (1.1 g, 8.0 mmol), *N*-methyl-1-naphthylamine (1.56 g, 9.5 mmol), P_2O_5 (0.34 g, 2.4 mmol) in dry xylene (30 ml) was refluxed for 8 h. The reaction mixture was diluted with ether and then, washed with 10% HCl, aqueous 5% $NaHCO_3$ solution and brine. The residue in hexane–AcOEt (4 : 1) was subjected to column chromatography on silica gel. Elution with hexane–AcOEt (4 : 1) gave 2-hydroxy-*N*-methyl-*N*-(1-naphthyl)benzamide (1.1 g, 50%) as a colorless oil. IR cm^{-1} ($CHCl_3$): 3050, 1650. ^{1}H-NMR (60 MHz) δ: 3.52 (3H, s, NCH_3), 6.14 (1H, dt, J=6.3, 1.8 Hz, C_3-H), 6.52 (1H, m, aromatic proton), 6.81—7.21 (4H, m, aromatic protons), 7.35—8.07 (5H, m, aromatic protons), 11.17 (1H, s, OH). FAB-MS *m*/*z*: 278 (M^++1).

To a mixture of 2-hydroxy-5-methoxy-*N*-methyl-*N*-(1-naphthyl)benzamide (0.56 g, 2.02 mmol) and dry NEt_3 (0.61 g, 6.06 mmol) in dry CH_2Cl_2 (15 ml) at −21 °C was added triflic anhydride (0.85 g, 3.03 mmol) in dry CH_2Cl_2 (5 ml). The whole was stirred for 1 h at the same temperature. The mixture was diluted with CH_2Cl_2 (20 ml) and washed with aqueous sat. $NaHCO_3$ and brine. The organic layer was dried over anhydrous Na_2SO_4. The residue dissolved in hexane–AcOEt (3 : 1) was subjected to column chromatography on silica gel. Elution with hexane–AcOEt (3 : 1) gave **3** (0.70 g, 85%) as colorless oil. IR cm^{-1} ($CHCl_3$): 1660, 1150. ^{1}H-NMR (60 MHz) δ: 3.56 (3H, s, NCH_3), 6.95—8.06 (11H, m, aromatic protons). FAB-MS *m*/*z*: 410.0674 (Calcd for $C_{19}H_{14}F_3NO_4S$: 410.0674).

General Procedure for the Coupling Reaction of 2-Trifluoromethanesulfonyloxy-5-methoxy-*N*-methyl-*N*-(1-naphthyl)benzamide (3) to *N*-Methylbenzo[*c*]phenanthridine-6(5*H*)-one (4) (Runs 1—3 in Table 2) Reaction of **3** (0.3 mmol) in dry DMF (8 ml) was carried out using $Pd(OAc)_2$, DPPP, and Bu_3P in the ratio indicated in the Table 2 and 2 mol equivalents of a base under reflux. The reaction mixture was diluted with ether and the precipitates were removed by filtration. The filtrate was washed with 1 N HCl, aqueous sat. $NaHCO_3$ solution and brine. The residue dissolved in hexane–AcOEt (4 : 1) was subjected to column chromatography on silica gel. Elution with hexane–AcOEt (4 : 1) gave **4** as pale yellow needles, mp 148—148.5 °C (from hexane) (lit.[14)] mp 148—149 °C). IR cm^{-1}: 1650. ^{1}H-NMR (60 MHz) δ: 4.02 (3H, s, NCH_3), 7.42—7.91 (6H, m, aromatic protons), 8.13—8.40 (3H, m, aromatic protons), 8.57 (1H, dd, J=7.6, 1.7 Hz, C_7-H). *Anal.* Calcd for $C_{18}H_{13}NO$: C, 83.38; H, 5.05; N, 5.40. Found: C, 83.64; H, 5.22; N, 5.10.

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