

PHOTOSUBSTITUTION REACTION OF CYANOAROMATICS WITH ALIPHATIC AMIDES

Moriya Tsuji, Kimio Higashiyama, Takayasu Yamauchi, Hajime Kubo, and Shigeru Ohmiya*

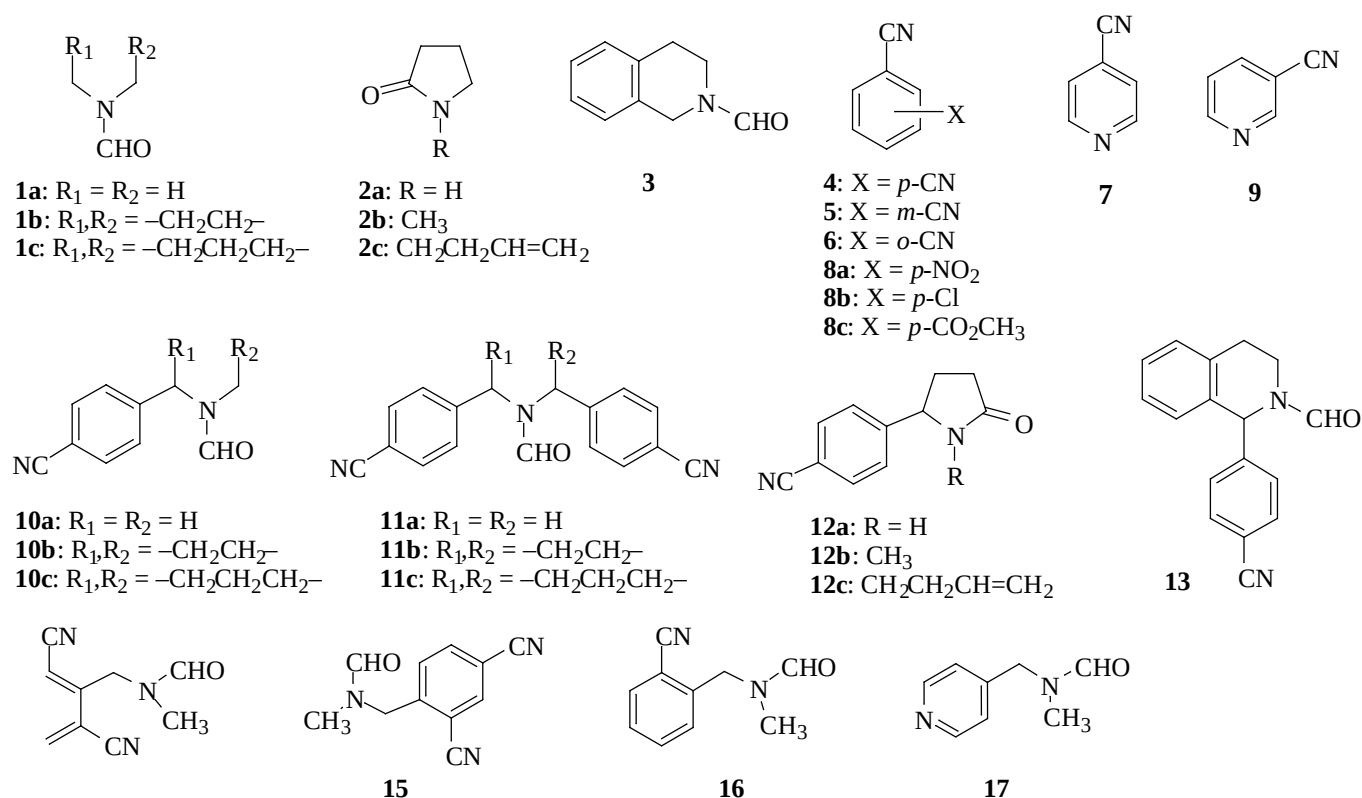
Institute of Medicinal Chemistry, Hoshi University, Ebara 2-4-41, Shinagawa-ku, Tokyo 142-8501, Japan

E-mail: ohmiya@hoshi.ac.jp

Abstract – Photoreaction of *p*- (4) and *o*-dicyanobenzene (6) and 4-cyanopyridine (7) with formamides (1 and 3) and 1-alkyl-2-pyrrolidone (2) produced α -aryl amides (10, 12, 13, 16, and 17). This reaction is attributable to a substitution of the carbon adjacent to the nitrogen of the amide for the cyano group in 4 and 7.

The single electron transfer (SET) process in organic photochemistry has attracted much attention with the aim of discovering synthetically useful processes.¹ Aromatic compounds, especially those with electron-withdrawing substituent such as a cyano group, are strong oxidants in their singlet excited states. They photochemically react with a variety of substrates, such as alkylbenzenes, alkylalkenes, amines, and ethers, to yield substitution products.² The reaction proceeds *via* an SET process, followed by proton transfer and combination of the resulting radicals to produce addition products, which are aromatized by oxidation or elimination of hydrogen cyanide, all of which comprises a substitution reaction.² We examined the possibility of using aliphatic amides as an electron donor in an SET process because the process may also be applicable to the reaction of cyanoaromatics with aliphatic amides, leading to introduction of an aryl group onto the carbon atom adjacent to the nitrogen of amides. In this report, we present the results concerning photoreaction of cyanoaromatics with cyclic and aliphatic amides.

Photoreaction was carried out by internal irradiation of a solution of aliphatic amides (1-3) and dicyanobenzenes (4-9) in acetonitrile (CH₃CN) with a 160 W low-pressure mercury lamp under argon atmosphere at ambient temperature for 8 h. Column chromatography on silica gel was used to separate the reaction mixture. As shown in Table 1, photoreaction was successfully achieved. The products were attributable to a substitution of the carbon adjacent to the nitrogen in amide compounds for a cyano group or a hydrogen in cyanoaromatics.



Scheme 1

Table 1. Photosubstitution Products from Irradiation of Aromatics (**4-7**) and Amides (**1-3**)

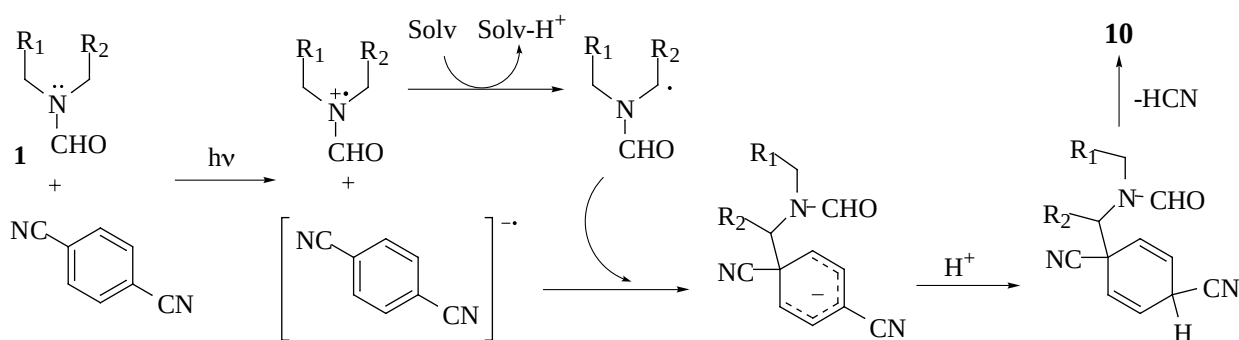
Aromatics	Amides	Products (yields % ^a)	
4	1a	10a (28)	11a (2.5)
	1b	10b (40)	11b (3.5)
	1c	10c (49)	11c (2)
	2a	12a (44)	
	2b	12b (41)	
	2c	12c (12)	
	3	13 (7)	
5	1a	14 (19)	15 (6.5)
6	1a	16 (31)	
7	1a	17 (14)	

^a Isolated yields based on consumed aromatics.

Irradiation of *p*-dicyanobenzene (**4**) with *N,N*-dimethylformamide (**1a**) yielded mainly the mono-substituted product *N*-(4-cyanophenylmethyl)-*N*-methylformamide (**10a**), together with trace amounts of disubstituted product *N,N*-bis(4-cyanophenylmethyl)formamide (**11a**). Similarly, photoreaction of **4** with formamides (**1b**, **1c**, and **3**) gave monosubstitution products (**10b**, **10c**, and **13**) respectively, as the major products. Lactams, 2-pyrrolidones (**2a-2c**), gave a single product, 5-aryl-2-pyrrolidones (**12a-12c**) respectively, after irradiation with **4**. Irradiation of *o*-dicyanobenzene (**6**) and 4-cyanopyridine (**7**) in the

presence of **1a** also resulted in substitution products (**16** and **17**), whereas *m*-dicyanobenzene (**5**) gave dicyano products (**14** and **15**), which arose from substitution of a hydrogen on the aromatic ring with the α -carbon of the amide. Cyanoaromatics (**8**) having other electron withdrawing group, such as nitro, chloro, or methoxycarbonyl group, showed no reaction to irradiation in the presence of amide (**1a**), whereas irradiation with 3-cyanopyridine produced complex products.

Thus, irradiation of cyanoaromatics (**4-7**) with aliphatic amides (**1-3**) brought about a substitution reaction, in analogy with the photoreaction between cyanoaromatics and electron donors, such as alkylbenzenes, alkylalkenes and ethers, to produce α -aryl amides (**10-17**). The photoreaction of aliphatic amides-cyanoaromatics systems might be expected to proceed *via* an SET process. A possible reaction mechanism is shown in Scheme 2. It is interesting that the photoreaction of cyclic amides (**2**) provided the annular substitution to give monosubstituted pyrrolidones (**12**) exclusively.



Scheme 2

EXPERIMENTAL

General Procedures

Melting points were determined on a Yanagimoto micro-melting point apparatus and are uncorrected. IR spectra were measured with a JEOL FT/IR spectrophotometer and are given in cm^{-1} . ^1H NMR spectra were determined with a JEOL JNM-LA270 spectrometer with tetramethylsilane as an internal standard.³ EI-MS spectra were measured with a JEOL D600 instrument. A Riko 160 W low-pressure mercury lamp was used as the irradiation source. Analytical grade CH_3CN was used for photoreactions.

General procedure for the photochemical reactions. A solution of the amide (60 mmol) and the dicyanobenzene (20 mmol) in CH_3CN (150 mL) was flushed with argon for 30 min and then irradiated for 8 h with a 160 W low pressure mercury lamp under argon at ambient temperature. After removal of the solvent under reduced pressure, the reaction mixture was subjected to repeated column chromatography on silica gel with solvent systems of CH_2Cl_2 -MeOH.

Photoreaction of 1a with 4. Products (**10a**, 0.49 g, 28%) and (**11a**, 66 mg, 2.5%) were obtained and the starting **4** (1.28 g, 50%) was recovered. *N*-(4-Cyanophenylmethyl)-*N*-methylformamide (**10a**); a pale

yellow oil (*Anal.* Calcd for $C_{10}H_{10}N_2O$: C, 68.95; H, 5.79; N, 16.08. Found: C, 68.85; H, 5.75; N, 16.23). IR ($CHCl_3$): 1670 (C=O), 2230 (CN). 1H NMR δ : 2.92, 2.81 (total 3H, each s, N-CH₃), 4.59, 4.51 (total 2H, each s, N-CH₂), 7.40, 7.35 (total 2H, each d, $J = 8.2$ Hz, ArH-2,6), 7.63, 7.71 (total 2H, each d, $J = 8.2$ Hz, ArH-3,5), 8.21, 8.30 (total 1H, each s, CHO). MS m/z : 174 (M^+). *N,N*-Bis(4-cyanophenylmethyl)-formamide (**11a**); colorless solid from C_6H_6 , mp 151-153 °C (*Anal.* Calcd for $C_{17}H_{13}N_3O$: C, 74.16; H, 4.76; N, 15.26. Found: C, 74.14; H, 4.95; N, 15.41). IR ($CHCl_3$): 1670 (C=O), 2230 (CN). 1H NMR δ : 4.38, 4.47 (total 4H, each s, N-CH₂), 7.27, 7.30 (total 4H, each d, $J = 7.3$ Hz, ArH-2,6), 7.63, 7.71 (total 4H, each d, $J = 7.3$ Hz, ArH-3,5), 8.45 (1H, s, CHO). MS m/z : 275 (M^+), 246 ($M^+ - CHO$).

Photoreaction of 1b with 4. Products (**10b**, 0.78 g, 40 %) and (**11b**, 66 mg, 3.5%) were obtained and the starting **4** (1.31 g, 51%) was recovered. 2-(4-Cyanophenyl)-1-formylpyrrolidine (**10b**); a pale yellow oil (M^+ , m/z 200.0950. $C_{12}H_{12}N_2O$ requires 200.0949). IR ($CHCl_3$): 1670 (C=O), 2230 (CN). 1H NMR ($CDCl_3$) δ : 1.89-2.10 (4H, m, 4-CH₂ and 3-CH₂), 3.65-3.73 (2H, m, 5-CH₂), 4.98, 5.09 (total 1H, each dm, $J = 8.1$ Hz, 2-CH), 7.30, 7.33 (total 2H, each d, $J = 8.1$ Hz, ArH-2,6), 7.61, 7.67 (total 2H, each d, $J = 8.1$ Hz, ArH-3,5), 8.13, 8.40 (total 1H, each s, CHO). MS m/z : 200 (M^+). 2,5-Bis(4-cyanophenyl)-1-formylpyrrolidine (**11b**); colorless crystals from C_6H_6 , mp 110-112 °C (M^+ , m/z 301.1215. $C_{19}H_{15}N_3O$ requires 301.1215). IR ($CHCl_3$): 1690 (C=O), 2230 (CN). 1H -NMR ($CDCl_3$) δ : 1.84-2.60 (4H, m, 3-CH₂ and 4-CH₂), 5.30, 5.42 (total 2H, each m, 2- and 5-CH), 7.35, 7.40 (total 2H, each d, $J = 8.2$ Hz, ArH-2,6), 7.65 (total 2H, each d, $J = 8.2$ Hz, ArH-3,5), 8.21 (1H, s, CHO). MS m/z : 301 (M^+).

Photoreaction of 1c with 4. Products, (**10c**, 1.0 g, 49 %) and (**11c**, 58 mg, 2 %) were obtained and the starting **4** (1.32 g, 52 %) was recovered. 2-(4-Cyanophenyl)-1-formylpiperidine (**10c**); a pale yellow oil (M^+ , m/z 214.1097. $C_{13}H_{14}N_2O$ requires 214.1106). IR ($CHCl_3$): 1670 (C=O), 2230 (CN). 1H NMR ($CDCl_3$) δ : 1.53-1.85 (4H, m, 4- and 5-CH₂), 1.91 (1H, m, 3-CH_{ax}), 2.40 (1H, m, 3-CH_{eq}), 3.02, 2.74 (total 1H, ddm, $J = 12.7$ and 3.5 Hz, and ddm, $J = 13.5$ and 3.8 Hz, respectively, 6-CH_{ax}), 3.53, 4.27 (total 1H, dm, $J = 12.7$ Hz, and dm, $J = 13.5$ Hz, respectively, 6-CH_{eq}), 5.77, 4.84 (total 1H, each m, 2-CH_{eq}), 7.37, 7.40 (total 2H, each d, $J = 8.4$ Hz, ArH-2,6), 7.66, 7.70 (total 2H, each d, $J = 8.4$ Hz, ArH-3,5), 8.28, 8.19 (total 1H, each s, CHO). MS m/z : 214 (M^+), 185 ($M^+ - CHO$). 2,6-Bis(4-cyanophenyl)-1-formylpiperidine (**11c**); colorless crystals from C_6H_6 , mp 117-118 °C (M^+ , m/z 315.1383. $C_{20}H_{17}N_3O$ requires 315.1371). IR ($CHCl_3$): 1660 (C=O), 2230 (CN). 1H NMR ($CDCl_3$) δ : 1.74 (1H, m, 4-CH_{ax}), 1.97 (4H, m, 3- and 5-CH₂), 2.48 (1H, m, 4-CH_{eq}), 4.36 (1H, dm, $J = 10.6$ Hz, 2-CH), 5.95 (1H, dm, $J = 4.6$ Hz, 6-H), 7.44, 7.47 (total 4H, each d, $J = 8.6$ Hz, ArH-2,6), 7.72, 7.75 (total 4H, each d, $J = 8.6$ Hz, ArH-3,5), 7.86 (1H, s, CHO). MS m/z : 315 (M^+), 286 ($M^+ - CHO$).

Photoreaction of 2a with 4. Products (**12a**, 284 mg, 44 %) was obtained and the starting **4** (2.11 g, 82.5 %) was recovered. 5-(4-Cyanophenyl)pyrrolidin-2-one (**12a**); colorless crystals from C_6H_6 , mp 162-164 °C (*Anal.* Calcd for $C_{11}H_{10}N_2O$: C, 70.95; H, 5.41; N, 15.04. Found: C, 70.01; H, 5.56; N, 14.97). IR

(CHCl₃): 1690 (C=O), 2230 (CN). ¹H NMR (CDCl₃) δ: 1.93 (1H, m, one of 4-CH₂), 2.46 (2H, m, 3-CH₂), 2.63 (1H, m, one of 4-CH₂), 4.83 (1H, t, *J* = 7.1 Hz, 5-CH), 6.83 (1H, br, NH), 7.42 (2H, d, *J* = 8.4 Hz, ArH-2,6), 7.67 (2H, d, *J* = 8.4 Hz, ArH-3,5). MS *m/z*: 186 (M⁺).

Photoreaction of 2b with 4. Products (**12b**, 276 mg, 41 %) was obtained and the starting **4** (2.11 g, 82.5 %) was recovered. 5-(4-Cyanophenyl)-1-methylpyrrolidin-2-one (**12b**); a pale yellow oil (M⁺, *m/z* 200.0950. C₁₂H₁₂N₂O requires 200.0950). IR (CHCl₃): 1690 (C=O), 2230 (CN). ¹H NMR (CDCl₃) δ: 1.84 (1H, m, one of 4-CH₂), 2.53 (3H, m, one of 4-CH₂ and 3-CH₂), 2.70 (3H, s, CH₃), 4.60 (1H, m, 5-CH), 7.33 (2H, d, *J* = 8.4 Hz, ArH-2,6), 7.70 (2H, d, *J* = 8.4 Hz, ArH-3,5). MS *m/z*: 200 (M⁺).

Photoreaction of 2c with 4. Products (**12c**, 127 mg, 12 %) was obtained and the starting **4** (2.03 g, 79.5 %) was recovered. 1-(3-Butenyl)-5-(4-cyanophenyl)pyrrolidin-2-one (**12c**); a pale yellow oil (M⁺, *m/z* 254.1426. C₁₆H₁₈N₂O requires 254.1419). IR (CHCl₃): 1690 (C=O), 2230 (CN). ¹H NMR (CDCl₃) δ: 1.79 (1H, m, one of 4-CH₂), 2.19 (2H, m, butenyl 2-CH₂), 2.45 (1H, m, one of 4-CH₂), 2.51 (2H, m, 3-CH₂), 2.61 (1H, dt, *J* = 13.7 and 7.7 Hz, one of butenyl 1-CH₂), 3.84 (1H, dt, *J* = 13.7 and 7.7 Hz, one of butenyl 1-CH₂), 4.73 (1H, m, 5-CH), 5.05 (2H, m, butenyl 4-CH₂), 5.69 (1H, ddt, *J* = 17.2, 10.2, 6.9 Hz, butenyl 3-CH), 7.33 (2H, d, *J* = 8.4 Hz, ArH-2,6), 7.70 (2H, d, *J* = 8.4 Hz, ArH-3,5). MS *m/z*: 254 (M⁺), 199 (M⁺ - C₄H₇).

Photoreaction of 3 with 4. Product (**13**, 86 mg, 6.7 %) was obtained and the starting **4** (1.94 g, 80 %) was recovered. 1-(4-Cyanophenyl)-2-formyl-1,2,3,4-tetrahydroisoquinoline (**13**); a pale yellow oil (M⁺, *m/z* 262.1092. C₁₇H₁₄N₂O requires 262.1106). IR (CHCl₃): 1670 (C=O), 2230 (CN). ¹H NMR (CDCl₃) δ: 2.80-3.14 (2H, m, 4-CH₂), 3.41, 3.00 (total 1H, ddm, *J* = 4.6, 13.2 Hz, and m, respectively, 3-CH_{ax}), 3.69, 4.25 (total 1H, ddm, *J* = 5.5, 13.2 Hz, and m, respectively, 3-CH_{eq}), 6.68, 5.80 (total 1H, each s, 1-CH), 6.98, 7.07 (total 1H, d, *J* = 7.9 Hz, and d, *J* = 7.6 Hz, respectively, 8-CH), 7.22-7.35 (3H, m, 5-, 6- and 7-CH), 7.38 (2H, d, *J* = 7.9 Hz, ArH-2,6), 7.59, 7.62 (total 2H, each d, *J* = 7.9 Hz, ArH-3,5), 8.19, 8.51 (total 1H, each s, CHO). MS *m/z*: 262 (M⁺), 233 (M⁺ - CHO).

Photoreaction of 1a with 5. Products, **14** (189 mg, 19 %) and **15** (63 mg, 6.5 %) were obtained and the starting **5** (1.92 g, 75 %) was recovered. *N*-(2,6-Dicyanophenylmethyl)-*N*-methylformamide (**14**); colorless crystals from C₆H₆, mp 185-187 °C (Anal. Calcd for C₁₁H₉N₃O : C, 66.32; H, 4.55; N, 21.10, Found : C, 66.46; H, 4.59; N, 20.95). IR (CHCl₃): 1680 (C=O), 2230 (CN). ¹H NMR (CDCl₃) δ: 2.82, 3.05 (total 3H, each s, N-CH₃), 4.81, 4.88 (total 2H, each s, N-CH₂), 7.67, 7.57 (total 1H, each dd, *J* = 7.7, 7.7 Hz, ArH-4), 7.97, 7.91 (total 2H, each d, *J* = 7.7 Hz, ArH-3,5), 8.16, 8.50 (total 1H, each s, CHO). MS *m/z*: 199 (M⁺), 170 (M⁺ - CHO). *N*-(2,4-Dicyanophenylmethyl)-*N*-methylformamide (**15**); a pale yellow oil (M⁺, *m/z* 199.0761. C₁₁H₉N₃O requires 199.0746). IR : 1670 (C=O), 2235 (CN). ¹H NMR (CDCl₃) δ: 3.01, 2.85 (total 3H, each s, N-CH₃), 4.79, 4.69 (total 2H, each s, N-CH₂), 7.60, 7.59 (total 1H, each d, *J* = 8.2 Hz, ArH-6), 7.92, 8.00 (total 1H, each dd, *J* = 8.2, 1.3 Hz, ArH-5), 8.04, 8.09 (total 1H, each d, *J* = 1.3 Hz,

ArH-3), 8.20, 8.31 (total 1H, each s, CHO). MS m/z : 199 (M^+), 170 ($M^+ - \text{CHO}$).

Photoreaction of 1a with 6. Product (**16**, 376 mg, 31 %) was obtained and the starting **6** (1.65 g, 64.5 %) was recovered. *N*-(2-Cyanophenylmethyl)-*N*-methylformamide (**16**); a colorless oil (M^+ , m/z 174.0799. $\text{C}_{10}\text{H}_{10}\text{N}_2\text{O}$ requires 174.0793). IR (CHCl_3): 1670 (C=O), 2225 (CN). ^1H NMR (CDCl_3) δ : 2.96, 2.83 (total 3H, each s, N- CH_3), 4.77, 4.64 (total 2H, each s, N- CH_2), 7.33-7.74 (4H, m, ArH). MS m/z : 174 (M^+).

Photoreaction of 1a with 7. Product (**17**, 155 mg, 14 %) was obtained and the starting **6** (1.31 g, 63 %) was recovered. *N*-(4-Pyridylmethyl)-*N*-methylformamide (**17**); a colorless oil (M^+ , m/z 150.0802. $\text{C}_{11}\text{H}_9\text{N}_3\text{O}$ requires 150.0793). IR (CHCl_3): 1670 (C=O). ^1H NMR (CDCl_3) δ : 2.92, 2.83 (total 3H, each s, N- CH_3), 4.54, 4.43 (total 2H, each s, N- CH_2), 7.17, 7.15 (total 2H, each d, $J = 6.1$ Hz, ArH-3,5), 8.22, 8.28 (total 1H, each s, CHO), 8.58, 8.63 (total 2H, each d, $J = 6.1$ Hz, ArH-2,6). MS m/z : 150 (M^+), 121 ($M^+ - \text{CHO}$).

REFERENCES AND NOTES

1. P. S. Mariano and J. L. Stavinocha, "Synthetic Organic Photochemistry: Synthetic Aspects of Photochemical Electron Transfer Reactions," ed. by W. M. Horspool, Plenum Press, New York, 1984, pp. 145-257; J. Mattay, *Angew. Chem., Int. Ed. Engl.*, 1987, **26**, 825.
2. A. Albini, M. Mella, and M. Freccero, *Tetrahedron*, 1994, **50**, 575.
3. The ^1H NMR spectra of the products showed the signals due to the two rotamers except for those of **11** and **12**.