A Simple Route to *N*-ω-Chloroalkylisatins from Cyclic *t*-Anilines, Oxalyl Chloride and DABCO

Ying Cheng,*[a] Yu-Hua Zhan,[a] Otto Meth-Cohn*[b]

[a] Chemistry Department, Beijing Normal University, Beijing 100875, China
E-mail: yincheng@public2east.net.cn

[b] Chemistry Department, University of Sunderland, Sunderland SR1 3SD, U.K.
E-mail: otto.meth-cohn@sunderland.ac.uk

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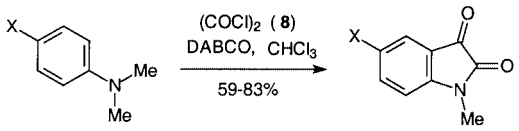
Abstract: *para*-Substituted *N*-phenylpyrrolidines, -piperidines, -perhydroazepines and -morpholines react with oxalyl chloride and DABCO to give the pharmaceutically useful intermediates, *N*-ω-haloalkylisatins, under mild conditions and generally good yields.

Key words: cyclic *t*-anilines, oxalyl chloride, DABCO, *N*-ω-haloalkylisatins

N-ω-Haloalkylisatins **1** are important intermediates in the syntheses of pharmacologically important isatin derivatives. These include anaphylactic asthma inhibitors **2**,[1] gastroduodenal ulcer inhibitors **3**,[2] cholinesterase inhibitors **4**[3] and acetylcholinesterase inhibitors **5**[4] (which are useful in the treatment of neurodegenerative and cognitive dysfunction conditions such as Alzheimer's disease) and compounds **6**[5] used in treating central nervous system disorder (Figure).

Methods for the synthesis of the *N*-ω-haloalkylisatins[1,4,6] are limited to the monoalkylation of isatins by dihaloalkanes. This method has serious limitations due to the lack of available isatins as starting materials and to poor yields due to side-reactions. Very recently, we reported[7] that 5-substituted *N*-methylisatins **9** could be prepared in high yield from *para*-substituted *N*,*N*-dimethylanilines **7** and oxalyl chloride (**8**), catalysed by DABCO (Scheme 1), via *o*-oxalylation, ring-closure and demethylation.



7 9

Scheme 1

We have now discovered that this method is also applicable to *para*-substituted *N*-phenylheterocycles such as pyrrolidines, piperidines, morpholines and perhydroazepines **10**–**13**, with ring-opening of the heterocycle to give 5-substituted *N*-ω-chloroalkylisatins **17**–**20** as the sole products. The formation of **17**–**20** can be explained by a similar mechanism to that invoked for the formation of *N*-methylisatins **9**[7] (Scheme 2).

N-Methylisatins were prepared using DABCO in refluxing chloroform under nitrogen. The reactions of *para*-substituted *N*-phenylheterocycles **10**–**13** with the oxalyl

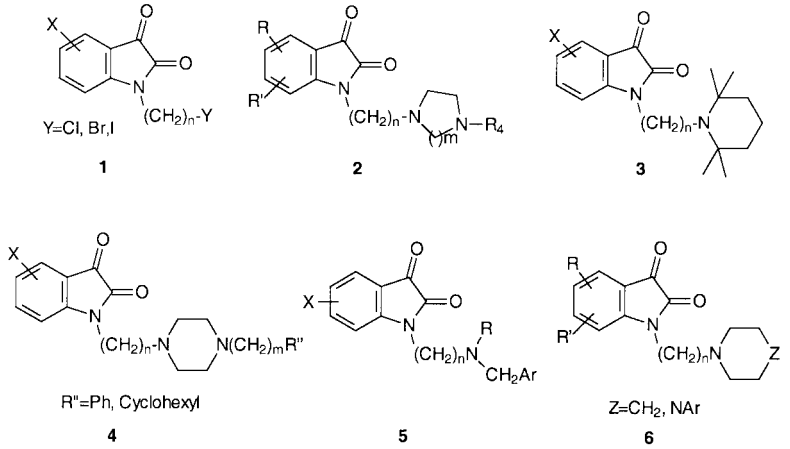


Figure Some pharmacologically important isatin derivatives **1**–**6**

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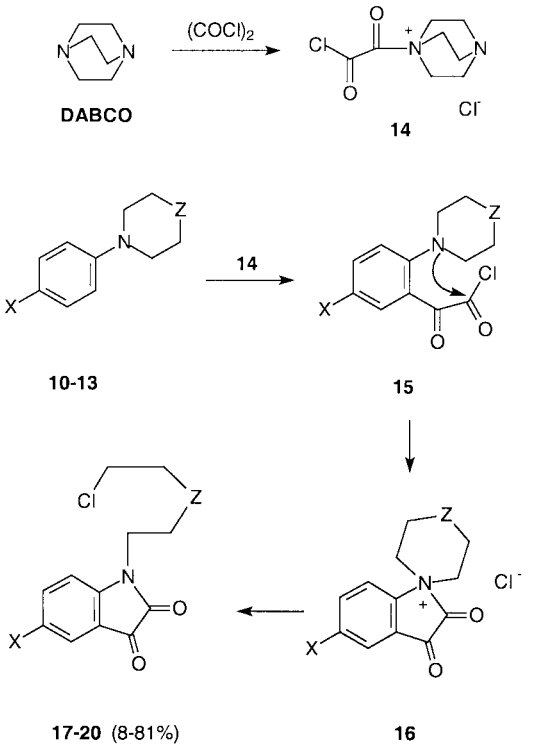
chloride/DABCO salt **14** required long reaction times and/or gave poor yields under these conditions, while with acetonitrile as the solvent, the reaction temperature and time were decreased significantly. Furthermore, the yield of products, particularly when the *para*-substituted *N*-

Table 1 Reactions Between *para*-Substituted *N*-Phenylheterocycles and Oxalyl Chloride/DABCO

N-Phenyl-Heterocycle	Solvent	Temp (°C)	Time (h)	Product[a]	Yield(%)	Mp (°C)
10a	CH_2Cl_2	70	10	**17a**	79	79–80
10a	MeCN	30	2	**17a**	81	
10b	$CHCl_3$	64	10	**17b**	60	86–87
10b	toluene	90–100	46	**17b**	37	
10b	MeCN	30	6	**17b**	72	
10c	$CHCl_3$	35	11	**17c**	41	90–92
10c	MeCN	35	5	**17c**	44	
10d	$CHCl_3$	64	11	**17d**	37	85–86
10d	$Cl_2CHCHCl_2$	110	23	**17d**	48	
10d	MeCN	80–85	9	**17d**	37	
10e	$ClCH_2CH_2Cl$	82	47	**17e**	36	77–78
10e	MeCN	82	10	**17e**	40	
11a	$CHCl_3$	64	16	**18a**	48	48–50
11a	MeCN	60	11	**18a**	59	
11b	$CHCl_3$	64	19	**18b**	35	95–97
11b	MeCN	60	11	**18b**	44	
11d	$CHCl_3$	64	40	**18d**	27	84–86
11d	MeCN	65	11	**18d**	30	
12a	$CHCl_3$	64	8	**19a**	50	45–47
12a	MeCN	48	11	**19a**	52	
12b	$ClCH_2CH_2Cl$	85	16	**19b**	42	69–71
12b	MeCN	65	11	**19b**	42	
12d	$CHCl_3$	64	24	**19d**	16	70–72
12d	MeCN	65	11	**19d**	33	
13a	$CHCl_3$	64	18	**20a**	25	74–76
13a	MeCN	56	11	**20a**	47	
13b	$CHCl_3$	64	38	**20b**	22	87–89
13b	MeCN	58	10	**20b**	52	
13c	$CHCl_3$	64	48	**20c**	0	–
13d	$CHCl_3$	64	48	**20d**	0	170–171
13d	MeCN	85	20	**20d**	9	
13e	MeCN	82	11	**20e**	8	113–114

[a] Satisfactory microanalyses obtained: C ±0.34, H ±0.35, N ±0.36. Exceptions: **17b**, C –0.68; **18b**, C –0.47; **20a**, C –0.47.



	Z —	CH_2	CH_2CH_2	O
OCH_3	**10a**	**11a**	**12a**	**13a**
	17a	**18a**	**19a**	**20a**
CH_3	**10b**	**11b**	**12b**	**13b**
	17b	**18b**	**19b**	**20b**
F	**10c**			
	17c			
Cl	**10d**	**11d**	**12d**	**13d**
	17d	**18d**	**19d**	**20d**
Br	**10e**			**13e**
	17e			**20e**

Scheme 2

phenylmorpholines were utilised, was improved (Table 1).

Methoxy- and methyl-substituted t-anilines **10**–**13** gave higher yields of isatins than their halogen substituted analogues, probably due to the electron-withdrawing effect of the latter substituents on the oxalyl-ring-closure and ring-opening reactions. However, the fluoro-substituted *t*-aniline **10c** was more reactive than the chloro- or bromo-substituted analogues indicating that the reaction sequences are not so trivially explained. If the reaction of fluoro derivative **10c** with oxalyl chloride was carried out above 60 °C, the reaction mixture became very dark. The conversions of the halo *t*-anilines **10d** and **10c** into isatins were not complete even after long reaction times.

The pyrrolidines **10** gave the highest yields of isatins compared to their piperidine **11**, perhydroazepine **12**, and morpholine **13** analogues due probably to the easier ring-opening of the strained spiro-5,5-intermediate. Combination of these two effects, as expected, resulted in the highest yield of isatin from *N*-(*p*-methoxyphenyl)pyrrolidine (81%), while the *N*-(*p*-halophenyl)morpholines gave the lowest yields.

We believe that this method is the simplest route for the preparation of *N*-chloroalkylisatins, requiring only simple, cheap starting materials and reagents, and mild conditions.

Melting points or boiling points and pressure are uncorrected. ^1H NMR and ^{13}C NMR were obtained on a Bruker Avance 500. IR spectra were recorded using a Avatar 360 FT-IR spectrometer. Mass spectra were recorded on a KYKY-ZHT-5 instrument and elemental analyses were performed on a GMBH Vario EL instrument.

para-Substituted *N*-Phenylheterocycles 10–13; General Procedure

To a solution of **7** (50 mmol) in anhyd toluene (20 mL) were added *N*,*N*-diisopropylethylamine (1.42 g, 11 mmol) and a dibromoalkane (55 mmol) (The $BrCH_2CH_2OCH_2CH_2Br$ was displaced by $TsOCH_2CH_2OCH_2CH_2OTs$ when *para*-substituted *N*-phenylmorpholines were prepared). The mixture was refluxed for 18–24 h under N_2. After cooling, the mixture was poured into H_2O (100 mL) and the toluene layer was separated. The aqueous solution was extracted with Et_2O (3×50 mL) and the organic layers were combined and dried ($MgSO_4$). After removal of the solvent, the product was obtained by distillation or chromatography on silica gel eluting with variable amounts of hexane–EtOAc (Table 2).

Table 2 *para*-Substituted *N*-Phenylheterocycles **10**–**13** Prepared

Product	Yield (%)	Mp (°C) or Bp (°C)/Torr	
		Found	Reported
10a	83	45–46	46–47[8]
10b	80	38–40	39–40[9]
10c	61	58–60/0.2	122/13[10]
10d	64	85–87	85–86[11]
10e	78	103–105	103[12]
11a	79	77–79/0.15	37[13,a]
11b	86	97–98/1	57–60/0.5[9]
11d	74	68–71	69[14]
12a	23	94–96/0.3	87/0.2[15]
12b	30	76–80/0.2	62/0.12[15]
12d	24	84–85/0.3	75/0.2[15]
13a	54	71–73	71–73[16]
13b	70	95/0.5[b]	91/0.4[17]
13d	45	71–73	71–72[18]
13e	55	115–117	112–113[19]

[a] Melting point.
[b] Melting point 44–45 °C.

***N*-ω-Chloroalkylisatins 17–20; General Procedure**

Oxalyl chloride (1.75 mL, 2.55 g, 20 mmol) was added dropwise to a solution of DABCO (11 mmol) in the appropriate solvent (10 mL) (see Table 1) cooled in an ice-bath under N_2 to form a pale yellow solid salt. To this salt was added slowly with ice-bath cooling, the *para*-substituted *N*-phenylheterocycle **10** (10 mmol) in the same solvent (50 mL) and the mixture was stirred for the period of time and at the temperature shown in Table 1. After removal of solvent, the residue was neutralized with 10% aq $NaHCO_3$. The products were extracted with $CHCl_3$ (3 × 100 mL) and dried ($MgSO_4$). After removal of solvent, the isatins were purified by chromatography on silica gel, eluting with variable amounts of hexane–EtOAc (Table 3).

Table 3 Spectroscopic Data of Isatins **17**–**20**

Product	IR ν (cm^{-1})	^1H NMR ($CDCl_3$/TMS) δ, *J* (Hz)	^{13}C NMR ($CDCl_3$/TMS) δ	MS (EI) (rel. intensity, %)
17a	1730, 1616, 1599, 1490	7.18 (1 H, s), 7.17(1 H, d, *J* = 7.6), 6.87 (1 H, d, *J* = 7.9), 3.84 (3 H, s, OCH_3), 3.77 (2 H, t, *J* = 6.5, NCH_2), 3.63 (2 H, t, *J* = 5.8, CH_2Cl), 1.90 (4 H, m, CH_2CH_2)	184.2, 158.7, 157.0, 145.0, 125.1, 118.5, 111.5, 110.2, 56.4, 44.6, 39.7, 29.9, 24.9	149 (95), 162 (100), 176 (39), 177 (38), 267 (M^+, 60)/269 (20)
17b	1739, 1621, 1594, 1490	7.44 (1 H, s), 7.42 (1 H, d, *J* = 8.2), 6.84 (1 H, d, *J* = 8.0), 3.77 (2 H, t, *J* = 6.5, NCH_2), 3.62 (2 H, t, *J* = 5.9, CH_2Cl), 2.36 (3 H, s, CH_3), 1.89 (4 H, m, CH_2CH_2)	184.0, 158.7, 148.9, 139.2, 134.0, 126.3, 118.1, 110.3, 44.6, 39.7, 29.9, 24.9, 21.0	133 (100), 146 (90), 160 (37), 251 (M^+, 60)/253 (20)
17c	1741, 1728, 1618, 1606, 1485, 1464	7.29–7.37 (2 H, m), 6.91–6.94 (2 H, m), 3.79 (2 H, t, *J* = 6.6, NCH_2), 3.63 (2 H, t, *J* = 5.9, CH_2Cl), 1.89 (4 H, m, CH_2CH_2)	183.1, 160.7, 158.7, 158.4, 147.1, 125.2, 125.0, 118.7, 113.1, 112.9, 111.7, 111.6, 44.5, 39.9, 29.8, 24.8	137 (37), 150 (100), 255 (M^+, 9)/257 (3)
17d	1751, 1735, 1605, 1592, 1474, 1445	7.61 (1 H, s), 7.60 (1 H, d, *J* = 10.8), 6.91 (1 H, d, *J* = 8.2), 3.80 (2 H, t, *J* = 6.5, NCH_2), 3.63 (2 H, t, *J* = 5.8, CH_2Cl), 1.91 (4 H, m, CH_2CH_2)	182.7, 158.1, 149.3, 138.2, 130.1, 125.9, 118.9, 111.8, 44.5, 39.9, 29.8, 24.8	153(85), 166 (100)/168 (55), 180 (22), 271 (M^+, 7)/273 (4)/275 (2)
17e	1735, 1599, 1472, 1441	7.74 (2 H, m), 6.86 (1 H, d, *J* = 8.9), 3.79 (2 H, t, *J* = 6.5, NCH_2), 3.62 (2 H, t, *J* = 5.8, CH_2Cl), 1.89 (4 H, m, CH_2CH_2)	182.5, 157.9, 149.8, 141.0, 128.7, 119.2, 117.0, 112.2, 44.5, 39.9, 29.8, 24.8	197 (100)/199 (80), 210 (75)/212 (73), 315 (M^+, 9)/317 (10)/319 (4)
18a	1747, 1722, 1632, 1595, 1491, 1470	7.16 (1 H, s), 7.15(1 H, dd, *J* = 8.2, 2.7), 6.81 (1 H, d, *J* = 8.2), 3.81 (3 H, s, OCH_3), 3.71 (2 H, t, *J* = 7.2, NCH_2), 3.54 (2 H, t, *J* = 6.5, CH_2Cl), 1.83 (2 H, m, CH_2), 1.73 (2 H, m, CH_2), 1.53 (2 H, m, CH_2)	184.2, 158.6, 156.9, 145.1, 125.0, 118.5, 111.5, 110.2, 56.4, 45.0, 40.4, 32.4, 27.0, 24.5	149 (60), 162 (100), 176 (50), 177 (49), 190 (75), 218 (80), 281 (83)/283 (53)
18b	1737, 1725, 1620, 1597, 1492	7.44 (1 H, s), 7.41 (1 H, d, *J* = 8.0), 6.81 (1 H, d, *J* = 8.0), 3.74 (2 H, t, *J* = 7.2, NCH_2), 3.56 (2 H, t, *J* = 6.5, CH_2Cl), 2.36 (3 H, s, CH_3), 1.86 (2 H, m, CH_2), 1.76 (2 H, m, CH_2), 1.56 (2 H, m, CH_2)	184.1, 158.7, 149.1, 139.1, 133.9, 126.5, 118.1, 110.3, 45.0, 40.3, 32.4, 27.0, 24.5, 21.0	146 (100), 175 (24), 265 (M^+, 15)/267 (5)
18d	1752, 1735, 1605, 1475, 1446	7.59 (1 H, s), 7.58 (1 H, d, *J* = 9.2), 6.89 (1 H, d, *J* = 8.1), 3.76 (2 H, t, *J* = 7.2, NCH_2), 3.56 (2 H, t, *J* = 6.5, CH_2Cl), 1.86 (2 H, m, CH_2), 1.75 (2 H, m, CH_2), 1.56 (2 H, m, CH_2)	182.9, 158.0, 149.5, 138.1, 130.0, 125.9, 118.8, 111.7, 45.0, 40.6, 32.3, 26.9, 24.5	166 (100)/168 (40), 285 (M^+, 9)/287 (7)/289 (2)
19a	1732, 1618, 1598, 1491	7.17 (1 H, s), 7.16 (1 H, d, *J* = 7.3), 6.83 (1 H, d, *J* = 8.9), 3.83 (3 H, s, OCH_3), 3.72 (2 H, t, *J* = 7.2, NCH_2), 3.52 (2 H, t, *J* = 6.5, CH_2Cl), 1.80 (2 H, m, CH_2), 1.74 (2 H, m, CH_2), 1.52 (2 H, m, CH_2), 1.42 (2 H, m, CH_2)	184.4, 158.6, 156.8, 145.2, 125.1, 118.4, 111.5, 110.1, 56.4, 45.3, 40.5, 32.7, 27.5, 26.8, 26.6	149 (35), 162 (100), 177 (40), 295 (M^+, 16)/297 (10)
19b	1744, 1725, 1619, 1596, 1491	7.43 (1 H, s), 7.41(1 H, d, *J* = 8.1), 6.81 (1 H, d, *J* = 8.0), 3.73 (2 H, t, *J* = 7.3, NCH_2), 3.55 (2 H, t, *J* = 6.6, CH_2Cl), 2.36 (3 H, s), 1.79 (2 H, m, CH_2), 1.73 (2 H, m, CH_2), 1.52 (2 H, m, CH_2), 1.42 (2 H, m, CH_2)	184.2, 158.7, 149.2, 139.1, 133.9, 126.2, 118.1, 110.3, 45.3, 40.4, 32.8, 27.6, 26.8, 26.6, 21.0	133 (54), 146 (100), 175 (45), 279 (M^+, 45)/281 (15)

Table 3 Spectroscopic Data of Isatins **17**–**20** (continued)

Product	IR ν (cm^{-1})	^1H NMR ($CDCl_3$/TMS) δ, *J* (Hz)	^{13}C NMR ($CDCl_3$/TMS) δ	MS (EI) (rel. intensity, %)
19d	1752, 1731, 1608, 1589, 1473, 1447	7.57 (1 H, s), 7.56 (1 H, d, *J* = 8.6), 6.86 (1 H, d, *J* = 8.2), 3.73 (2 H, t, *J* = 7.2, NCH_2), 3.53 (2 H, t, *J* = 6.5, CH_2Cl), 1.78 (2 H, m, CH_2), 1.72 (2 H, m, CH_2), 1.51 (2 H, m, CH_2), 1.41 (2 H, m, CH_2)	182.9, 158.0, 149.6, 138.1, 129.9, 125.8, 118.8, 111.7, 45.2, 40.6, 32.7, 27.5, 26.8, 26.5	153 (40), 166 (100)/168 (40), 299 (M^+, 12)/301 (5)/303 (2)
20a	1730, 1616, 1601, 1491	7.12 (1 H, s), 7.13 (1 H, d, *J* = 9.1), 7.03 (1 H, d, *J* = 8.3), 3.91 (2 H, t, *J* = 5.1, OCH_2), 3.81 (3 H, s, OCH_3), 3.77 (2 H, t, *J* = 5.1, NCH_2), 3.71 (2 H, t, *J* = 5.5, OCH_2), 3.56 (2 H, t, *J* = 5.5, CH_2Cl)	184.1, 159.0, 156.8, 145.9, 125.2, 118.3, 113.0, 109.4, 71.5, 69.4, 56.4, 43.3, 40.9	162 (100), 177 (20), 283 (M^+, 10)/285 (4)
20b	1743, 1729, 1618, 1598, 1492	7.39 (1 H, s), 7.38 (1 H, d, *J* = 9.7), 6.99 (1 H, d, *J* = 7.9), 3.92 (2 H, t, *J* = 5.1, OCH_2), 3.78 (2 H, t, *J* = 5.1, NCH_2), 3.71 (2 H, t, *J* = 5.5, OCH_2), 3.56 (2 H, t, *J* = 5.5, CH_2Cl), 2.33 (3 H, s, CH_3)	184.0, 159.0, 149.7, 139.1, 133.9, 125.8, 118.0, 111.6, 71.6, 69.2, 43.2, 40.8, 21.0	146 (100), 161 (23), 267 (M^+, 17)/269 (7)
20d	1750, 1731, 1607, 1475, 1448	7.57(1 H, s), 7.56(1 H, d, *J* = 7.9), 7.13 (1 H, d, *J* = 8.5), 3.96 (2 H, t, *J* = 4.9, OCH_2), 3.80 (2 H, t, *J* = 5.1, NCH_2), 3.73 (2 H, t, *J* = 5.2, OCH_2), 3.60(2 H, t, *J* = 5.6, CH_2Cl)	182.8, 158.4, 150.3, 138.1, 129.9, 125.3, 118.7, 113.5, 71.6, 69.6, 43.3, 41.2	107 (70), 166 (10), 168 (80), 181 (80)/183 (45), 287 (M^+, 50)/289 (34)/291 (6)
20e	1747, 1731, 1604, 1473, 1440	7.71 (1 H, s), 7.70 (1 H, d, *J* = 7.2), 7.09 (1 H, d, *J* = 9.0), 3.96 (2 H, t, *J* = 5.0, OCH_2), 3.80 (2 H, t, *J* = 5.0, NCH_2), 3.73 (2 H, t, *J* = 5.2, OCH_2), 3.58 (2 H, t, *J* = 5.5, CH_2Cl)	182.6, 158.2, 150.7, 140.9, 128.2, 119.0, 116.9, 113.9, 71.6, 69.5, 43.3, 41.2	107 (80), 155 (60)/157 (55), 210 (100)/212 (98), 225 (85)/227 (82), 331 (M^+, 52)/333 (60)/335 (20)

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References

(1) Teraji, T.; Oku, T.; Namiki, T. Eur. Patent 10398, **1980**; *Chem. Abstr.* **1980**, *93*, 220773.
(2) Kobayashi, M.; Kitazawa, M. Y. Japanese Patent 62270576, **1987**; *Chem. Abstr*. **1988**, *109*, 110263.
(3) Boar, B. R.; Cross, A. J. WO Patent 9312085, **1993**; *Chem. Abstr*. **1993**, *119*, 225964.
(4) Boar, B. R.; O'shea, D. M.; Tomlinson, I. D. WO Patent 9429272, **1994**; *Chem. Abstr*. **1995**, *122*, 239179.
(5) Gallagher, P. T.; Owton, W. M.; Smith, C. W. Eur. Patent 780388, **1997**; *Chem. Abstr*. **1997**, *127*, 135719.
(6) Rekhter, M. A.; Radul, O. M.; Bukhanyuk, S. M. *Chem. Heterocycl. Compd. (Engl. Trans.)* **1999**, *35*, 792.
(7) Cheng, Y.; Ye, H. L.; Zhan, Y. H.; Meth-Cohn, O. *Synthesis* **2001**, 904.
(8) Venuti, M. C.; Ort, O. *Synthesis* **1988**, 985.
(9) Juaristi, E.; Madrigal, D. *Tetrahedron* **1989**, *45*, 629.
(10) Sellers, C.; Suschitzky, H. *J. Chem. Soc.* **1965**, 6186.
(11) Shim, S. C.; Huh, K. T.; Park, W. H. *Tetrahedron* **1986**, *42*, 259.
(12) Beach, S. F.; Hepworth, J. D.; Sawyer, J.; Hallas, G.; Marsden, R.; Mitchell, M. M.; Ibbitson, D. A.; Jones, A. M.; Neal, G. T. *J. Chem. Soc., Perkin 2* **1984**, 217.
(13) Barton, D. H. R.; Donnelly, D. M. X.; Finet, J.-P.; Guiry, P. J. *J. Chem. Soc., Perkin Trans. 1* **1991**, 2095.
(14) Fielden, R.; Meth-Cohn, O.; Suschitzky, H. *J. Chem. Soc., Perkin Trans. 1* **1973**, 696.
(15) Shim, S. C.; Doh, C. H.; Kim, T. J.; Lee, H. K.; Kim, K. D. *J. Heterocycl. Chem.* **1988**, *25*, 1383.
(16) Stauffer, S. R.; Lee, S.; Stambuli, J. P.; Hauek, S. I.; Hartwig, J. F. *Org. Lett.* **2000**, *2*, 1423.
(17) Birch, A. J.; Hutchinson, E. G.; Rao, G. S. *J. Chem. Soc. (C)* **1971**, 637.
(18) Pearson, A. J.; Gelormini, A. M. *J. Org. Chem.* **1994**, *59*, 4561.
(19) Jones, D. H. *J. Chem. Soc.(C)* **1971**, 132.