Benzhydryl 7β-(2-Thienylacetamido)-3-(chloromethyl)-3-cephem-4-carboxylate (4b). The reaction was carried out and the crude product was purified as outlined above to afford a pale yellow solid in 60% yield: mp 143-148 °C; IR (mineral oil) 1781, 1723, 1659, 1376 cm^{-1}; R_f 0.43 (1:9 ethylacetate/benzene); ^1H NMR ($CDCl_3$) δ 3.45, 3.60 (2d, 2 H, C-2, J = 18.6 Hz), 3.86 (s, 2 H, side chain methylene), 4.38 (s, 2 H, C-3 chloromethyl), 4.99 (d, 1 H, C-6, J = 5.1 Hz), 5.88 (m, 1 H, C-7), 6.34 (d, 1 H, NH, J = 9.0 Hz), 6.97 (s, 1 H, benzylic methine), 7.02 (m, 2 H, thienyl), 7.37 (m, 11 H, thienyl and phenyl); MS FAB⁻ 537.5 (M - H, 4.5).

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18-Crown-6 as a Catalyst in the Dialkylation of *o*-Nitrophenacyl Derivatives†

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α,α-Dialkyl *o*-nitrophenacyl derivatives (**3**, Scheme I) are intermediates in a facile synthesis of polysubstituted indolines and related heterocycles.[1] Previously reported syntheses of **3** are lengthy and give low overall yields.[2,3] Hence, it was of interest to develop an efficient, simple, and general synthesis of these compounds.

The use of enolate chemistry to alkylate the benzylic carbon of the *o*-nitrophenacyl moiety with a variety of carbon electrophiles should be relatively straightforward due to the acidity of the benzylic hydrogens. However, our attempts to dialkylate with alkylating agents such as ethyl iodide and benzyl bromide in the presence of bases such as sodium ethoxide, lithium diisopropylamide, and potassium *tert*-butoxide gave low yields of dialkylated products, along with impurities which were not successfully separated. Monoalkylated products **2** were obtained in excellent yields (83-98%) with 1.1 equiv of potassium *tert*-butoxide and alkyl halide. Attempts to dialkylate the monoalkylated products through the use of potassium *tert*-butoxide and *n*-butyllithium, however, gave inseparable mixtures of products.

Use of 18-crown-6 to increase the reactivity of bases and nucleophiles is well-known,[4,5] but there are very few examples of its use for alkylations.[6,7] We have found that dialkylated products **3** are obtained in good yields (60-97%) under 18-crown-6 catalysis. The dialkylations were carried out in one step on 1 equiv of 2-(2-nitrophenyl)-1-phenylethanone (**1a**),[8] methyl *o*-nitrophenylacetate (**1b**),[9] or *o*-nitrophenylacetonitrile (**1c**) with 2.2 equiv of potassium *tert*-butoxide and the alkyl halide in the presence of 0.25 equiv of 18-crown-6. The dialkylation also can be carried out in a stepwise manner on monoalkyl derivatives in good yields (85-97%) in the presence of 18-crown-6. The stepwise procedure permits the introduction of two different alkyl side chains. The monoalkyl derivatives **2** can be prepared with or without 18-crown-6 with no significant difference in yields. The results are summarized in Tables I-IV.

With the ketone **1a**, the steric limits of *C*,*C*-dialkylation appear to have been exceeded when ethyl iodide and allyl bromide were used as the electrophiles. The products showed the expected mass spectral molecular weights but had no carbonyl bands in the infrared spectra, suggesting that *C*,*O*-dialkylation had occurred. The ^1H NMR spectra suggest that the products are mixtures of *E* and *Z* enol *O*-alkylates **4a** and **4b**. It was possible, however, to monoalkylate first with a bulky substituent, followed by a second alkylation with a small (methyl) substituent, as illustrated by the stepwise preparation of an ethyl methyl derivative **3b** in 85% overall yield. The steric limitations observed in the dialkylation of **1a** did not occur with the ester **1b** or the nitrile **1c**, which readily afforded both the *C*,*C*-diethyl (**3c** and **3i**), *C*,*C*-diallyl (**3j**), and *C*,*C*-dibenzyl (**3f**) derivatives in excellent yield.

In summary, dialkylation with potassium *tert*-butoxide in the presence of 18-crown-6 has been shown to provide a versatile method for making a variety of α,α-dialkyl *o*-nitrophenacyl derivatives **3** in one or two steps from commercially available starting materials.

Experimental Section

All melting points were determined on Thomas Hoover capillary melting point apparatuses and are uncorrected. Infrared spectra (IR, liquids neat and solids in KBr) were determined on either a Perkin-Elmer Series 1600 FT IR or a Nicolet 5DXC FT IR. Nuclear magnetic resonance spectra (NMR, in $CDCl_3$) were determined either on a 200-MHz Bruker AC-200 or on a 300-MHz General Electric GN-OMEGA. Chemical ionization mass spectra (CIMS) were determined on a Finnigan 4000 spectrometer. All new compounds were characterized by IR, NMR, CIMS, and elemental analyses by either M-H-W laboratories, Phoenix, AZ, or Midwest Microlab, Indianapolis, IN.

General Procedures. Monoalkylation. The *o*-nitrophenacyl starting material **1a-c** (1.00 mmol), freshly distilled alkyl halide (1.10 mmol), and dry tetrahydrofuran (THF, 15 mL) were placed in a dry two-necked flask under an atmosphere of nitrogen. The resulting solution was stirred and cooled to -78 °C in a dry ice/acetone bath, and potassium *tert*-butoxide (1.10 mmol) was added. Stirring was continued for 2 h while the resulting mixture was allowed to warm to room temperature. The mixture was then cooled again to -78 °C and quenched by rapid addition of satu-

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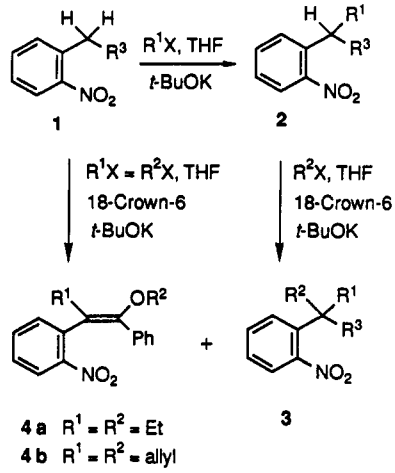
Scheme I



1 2 3

4a $R^1 = R^2 = Et$
4b $R^1 = R^2 =$ allyl

1a R^3 = COPh, 1b R^3 = COOMe, 1c R^3 = CN

	R1	R^3
2a	Me	COPh
2b	Et	COPh
2c	allyl	COPh
2d	Bn	COPh
2e	Me	COOMe
2f	Et	COOMe
2g	Bn	COOMe
2h	Bn	COOEt

	R^1	R^2	R^3
3a	Me	Me	COPh
3b	Et	Me	COPh
3c	Me	Me	COOMe
3d	Et	Me	COOMe
3e	Et	Et	COOMe
3f	Bn	Bn	COOMe
3g[a]	Me	Me	COOMe
3h	Me	Me	CN
3i	Et	Et	CN
3j	allyl	allyl	CN

(a) 5-Methoxy derivative of 3c.

Table I. α-Monoalkyl-o-nitrophenacyl Derivatives 2

				anal. calcd/found			CIMS (NH_3) (rel intensity)	
compd	R^1X	yield[a] (%)	molecular formula	C	H	N	$[M + H]^+$	$[M + NH_4]^+$
2a	MeI	87[a]	$C_{15}H_{13}NO_3$	70.58	5.13	5.49	255[b]	
		90[c]	255.26	70.69	5.39	5.62	(100)	
b	EtI	90	$C_{16}H_{15}NO_3$	71.36	5.61	5.20	269[b]	
			269.29	71.19	5.66	5.23	(100)	
c	allyl-Br	83	$C_{17}H_{15}NO_3$	72.58	5.37	4.98	282[d]	
			281.30	72.32	5.46	4.75	(24)	
d	BnBr	87	$C_{21}H_{17}NO_3$	76.12	5.17	4.23	332[e]	
			331.35	76.09	5.28	4.21	(0.7)	
e	MeI	84[f]	$C_{10}H_{11}NO_4$	57.41	5.30	6.70	210	227
			209.20	57.37	5.38	6.66	(20)	(100)
f	EtI	96	$C_{11}H_{13}NO_4$	59.18	5.87	6.28	224	241
		98[c,g]	223.22	58.99	5.82	6.24	(5)	(42)
g	BnBr	83	$C_{16}H_{15}NO_4$	67.36	5.30	4.91	286	303
			285.29	67.19	5.29	4.87	(14)	(100)
h	BnBr	85[a]	$C_{17}H_{17}NO_4$	68.21	5.73	4.68	300[h]	
			299.31	68.31	5.61	4.60	(8)	

[a] All compounds are yellow oils, except for **2a**, colorless solid, mp 115–117 °C, and **2h**, colorless solid, mp 60–61 °C. [b] Using CH_4, $M^{+\cdot}$. [c] With 18-crown-6. [d] Using CH_4, also $M^{+\cdot}$ at 281 (21) and $[M - H]^-$ at 280 (100). [e] Using CH_4, also $M^{+\cdot}$ at 331 (23) and $[M - H]^-$ at 330 (100). [f] Compound reported in ref 10. [g] Using EtBr. [h] Using CH_4, also $M^{+\cdot}$ at 299 (100).

Table II. α,α-Dialkyl-o-nitrophenacyl Derivatives 3 and 4

				anal. calcd/found			CIMS (NH_3) (rel intensity)	
compd[a]	yield (%)	mp (°C)	molecular formula	C	H	N	$[M + H]^+$	$[M + NH_4]^+$
3a	83, 71[b]	118–120	$C_{16}H_{15}NO_3$	71.36	5.61	5.20	269[c]	285[d]
			269.29	71.06	5.82	5.16	(100)	(15)
b	76[b]	oil	$C_{17}H_{17}NO_3$	72.06	6.04	4.94	284[e]	
			283.31	72.02	6.06	4.93	(3)	
c	89	oil	$C_{11}H_{13}NO_4$	59.18	5.87	6.28	224	241
			223.22	58.99	5.87	6.27	(17)	(100)
d	82[b]	oil	$C_{12}H_{15}NO_4$	60.75	6.37	5.90	238	255
			237.25	60.56	6.42	5.79	(7)	(62)
e	76	45–46	$C_{13}H_{17}NO_4$	62.14	6.82	5.57	252	269
			251.27	62.24	6.55	5.51	(1)	(3)
f	87	107–108	$C_{23}H_{21}NO_4$	73.58	5.64	3.73	375.5[c]	
			375.41	73.50	5.75	3.70	(25)	
g[f]	89	61–62	$C_{12}H_{15}NO_5$	56.91	5.97	5.53	254	271
			253.25	56.74	5.95	5.45	(6)	(100)
h	95	96–98	$C_{10}H_{10}N_2O_2$	63.15	5.30	14.73	191[g]	
			190.20	63.25	5.55	14.77	(13)	
i	91	oil	$C_{12}H_{14}N_2O_2$	66.03	6.47	12.84	*h*	236
			218.25	66.31	6.57	12.90		(35)
j	85	oil	$C_{14}H_{14}N_2O_2$	69.40	5.83	11.56	*i*	260
			242.27	69.38	5.88	11.61		(16)
4a	60	oil	$C_{18}H_{19}NO_3$	72.70	6.44	4.71	298[j]	
			297.34	72.40	6.34	4.87	(22)	
b	55	oil	$C_{20}H_{19}NO_3$	74.74	5.96	4.36	321[k]	
			321.36	74.42	5.63	4.29	(2)	

[a] The alkyl halides (R^1X, R^2X) used are the same as in Table I. [b] Stepwise dialkylation. [c] Using CH_4, $M^{+\cdot}$ also $[M - H]^-$, 374.45 (100). [d] Using CH_4, $[M + CH_4]^{+\cdot}$. [e] Using CH_4, also $[M - H]^-$, 282 (100). [f] 5-Methoxy derivative of **3c**. [g] Using CH_4, also $M^{+\cdot}$, 190 (100). [h] Using NH_3, $M^{+\cdot}$, 218 (100). [i] Using NH_3, $M^{+\cdot}$, 242 (34). [j] Using CH_4, also $M^{+\cdot}$, 297 (100). [k] Using CH_4, $M^{+\cdot}$, also $[M - H]^-$ 320 (5).

Table III. Spectroscopic Data for α-Monoalkyl-*o*-nitrophenacyl Derivatives 2

compd	IR, cm^{-1} C=O	IR, cm^{-1} NO_2	CIMS (NH_3) (rel intensity) fragments		^{1}H NMR ($CDCl_3$, ppm) benzylic C–H/OCH_3	^{1}H NMR ($CDCl_3$, ppm) R^1
2a	1685	1523	238[a]	207[a]	5.37 (q)	1.58 (3 H, d)
		1348	(15)	(15)		
b	1685	1525	252[a]	239[a,b]	5.26 (t)	2.23 (1 H, 5-line m), 1.90
		1350	(7)	(4)		(1 H, 5-line m), 0.92 (3 H, t)
c	1683	1524	239[a]		5.44 (t)	5.73 (1 H, 10-line m), 5.04–4.99
		1350	(15)			(2 H, 5-line m), 2.93 (1 H, 5-line m), 2.56 (1 H, 5-line m)
d	1719	1523	239[a,c]	192[a]	5.63 (t)	3.46 (1 H, ABd),
		1349	(82)	(22)		3.13 (1 H, ABd)
e	1738	1526	163[d]	148	4.31 (q)	1.58 (3 H, d)
		1352	(44)	(87)	3.64 (3 H, s)	
f	1738	1529	179	163[e]	4.09 (t)	2.20 (1 H, 7-line m),
		1352	(57)	(100)	3.66 (3 H, s)	1.89 (1 H, 7-line m), 0.94 (3 H, t)
g	1736	1527	254		4.52 (ABd)	3.47 (1 H, ABd),
		1352	(16)		3.61 (3 H, s)	3.12 (1 H, ABd)
h	1738	1529	254	237[f]	4.50 (ABd)	3.45 (1 H, ABd),
		1352	(100)	(14)	4.07 (q)[g]	3.13 (1 H, ABd)
					1.11 (t)[g]	

[a] Using CH_4, negative ion. [b] Also 221 (6). [c] Also 300 (14), 282 (15), and 240 (14). [d] Also 163 (44) and 150 (32). [e] Also 161 (43) and 146 (44). [f] Also 208 (15). [g] OCH_2CH_3.

Table IV. Spectroscopic Data for Dialkyl-*o*-nitrophenacyl Derivatives 3 and 4

compd	IR, cm^{-1} C=O	IR, cm^{-1} NO_2	CIMS (NH_3) (rel intensity) fragments		^{1}H NMR ($CDCl_3$, ppm) OCH_3, R^2, R^1
3a	1679	1524	255[a]	221[a]	1.75 (6 H, s)
		1346	(65)	(23)	
b	1680	1525	234[a]	120[a]	2.20 (2 H, 8-line m), 1.73
		1340	(12)	(8)	(3 H, s), 0.60 (3 H, t)
c	1739	1526	192		3.63 (3 H, s), 1.68 (6 H, s)
		1355	(21)		
d	1738	1529	208	176	3.65 (3 H, s), 2.15 (2 H, q),
		1358	(22)	(100)	1.66 (3 H, s), 0.77 (3 H, t)
e	1723	1523	191	190	3.63 (3 H, s), 2.17 (4 H, q),
		1351	(13)	(100)	0.76 (6 H, t)
f	1737	1528	327[a]	295[a]	3.55 (2 H, ABd), 3.48 (2 H,
		1357	(3)	(6)	ABd), 3.36 (3 H, s)
g[b]	1740	1518	238	222[c]	3.91 (3 H, s), 3.65 (3 H, s),
		1346	(9)	(92)	1.65 (6 H, s)
h	2235[d]	1533	160[a]		1.86 (6 H, s)
		1360	(15)		
i	2235[d]	1534	189	159	2.12 (4 H, 9-line m), 0.98
		1364	(100)	(9)	(6 H, t)
j	2215[d]	1531	225	213[e]	5.68 (2 H, m), 5.19 (4 H,
		1360	(12)	(100)	6-line m), 2.87 (4 H, 8-line m)
4a[f]	1633[g]	1524	236[a]	121[a]	3.59–3.76 (1.5 H, m), 3.22
		1351	(5)	(14)	(0.8 H, q), 2.86 (0.4 H, m),
					2.35 (0.7 H, q), 2.19 (0.5 H, m),
					1.19 (2.5 H, t), 0.90–0.82
					(3.7 H, 9-line m, possibly 3 overlapping t)[h]
b[f]	1630[g]	1523	234[a]	156[a,i]	6.18–5.98 (1.9 H, 9-line m),
		1350	(100)	(14)	5.96–5.64 (0.7 H, m),
					5.48–5.18 (3.7 H, m), 4.98–
					4.80 (3.7, 7-line m)[j]

[a] Using CH_4, anions. [b] 5-Methoxy derivative of **3c**. [c] Also 207 (28), 192 (21). [d] C≡N. [e] Also 171 (33), 130 (17). [f] Mixture of (*E*,*Z*)-*O*-alkylates. [g] Conjugated C=C. [h] These data suggest the presence of *E* and *Z* isomers in the approximate ratio of 4:1. [i] Also 105 (39). [j] These data suggest the presence of *E* and *Z* isomers in the approximate ratio of 3:1.

rated ammonium chloride solution, causing the water to freeze. The mixture was then allowed to warm to room temperature and was extracted with methylene chloride (30 mL). The organic layer was washed once with water and once with aqueous saturated sodium chloride solution (30–40 mL) and dried over anhydrous magnesium sulfate. The solvent was removed by rotary evaporation under an aspirator, and the residue was purified by column chromatography on silica gel (Baker, 60–200 mesh or E. Merck, 230–400 mesh) by using hexane to hexane/ethyl acetate (5/1, v/v) as eluent.

Dialkylation (Direct). The procedure for the monoalkylation as described above was followed, except that the amount of alkyl halide was 2.20 mmol and 18-crown-6 (0.25 mmol) was added.

Dialkylation (Stepwise). The procedure for the monoalkylation as described above was followed, except that the starting material was the monoalkylated product **2a–g** (1.00 mmol) and 18-crown-6 (0.25 mmol) was added.

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Registry No. **1a**, 4212-33-3; **1b**, 30095-98-8; **1c**, 610-66-2; **2a**, 58751-67-0; **2b**, 136764-79-9; **2c**, 136764-80-2; **2d**, 136764-81-3; **2e**, 30096-07-2; **2f**, 136764-82-4; **2g**, 136764-83-5; **2h**, 136764-84-6; **3a**, 136764-85-7; **3b**, 136764-86-8; **3c**, 136764-87-9; **3d**, 136764-88-0; **3e**, 136764-89-1; **3f**, 136764-90-4; **3g**, 136764-91-5; **3h**, 136764-92-6; **3i**, 136764-93-7; **3j**, 136764-94-8; *E*-**4a**, 136764-95-9; *Z*-**4a**, 136764-96-0; *E*-**4b**, 136764-97-1; *Z*-**4b**, 136764-98-2; MeI, 74-88-4; EtI, 75-03-6; allyl-Br, 106-95-6; BnBr, 100-39-0; 18-crown-6, 17455-13-9.