Synlett S. Asai et al. Letter

Selective *N*-Monoalkylation of Amide Derivatives with Trialkyl Phosphates

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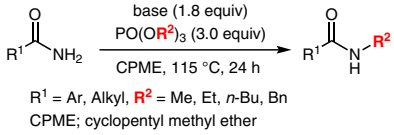


Received: 22.08.2017
Accepted after revision: 25.09.2017
Published online: 23.10.2017
DOI: 10.1055/s-0036-1591494; Art ID: st-2017-u0636-l

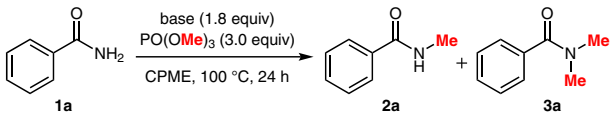
Abstract A highly selective and easily handled monoalkylation of primary amide derivatives by using trialkyl phosphates as alkylating reagents in cyclopentyl methyl ether (CPME) was developed. Various monoalkylated amide derivatives were efficiently synthesized by changing the alkyl moiety (e.g., methyl, ethyl, butyl, or benzyl) of the trialkyl phosphate. These phosphate reagents are relatively stable and easily available, and CPME is a useful solvent in process chemistry.

Key words alkylation, monoalkylation, amides, trialkyl phosphates, cyclopentyl methyl ether

The amide group is widely used as a fundamental functional group in various scientific fields. The *N*-monoalkylated amide backbone is frequently found in pharmaceutical agents[1,2] and in natural products.[3] Although the alkylation of primary amides by using alkyl halides (e.g., MeI, EtBr, BuBr, *i*-PrBr) occurs in the presence of an appropriate base,[4] prevention of overalkylation to give the corresponding *N*,*N*-dialkyl amide is difficult. In particular, *N*-monomethylation by using small and highly reactive methylating agents, such as MeI or Me_2SO_4, is difficult. In addition, such methylating agents are potentially toxic and exhibit mutagenicity. Efficient mono-selective methylations have been achieved by using a copper catalyst and dicumyl peroxide as a methylating agent in chlorobenzene at 120 °C[5] or by a stepwise method through silylmethylation of primary amides with chloro(chloromethyl)dimethylsilane and subsequent desilylation by CsF.[6] Although trialkyl phosphates have also been used as alkylating reagents for alcohols and dimethyl amines to give alkyl ethers[7] and tertiary amines,[8] respectively, harsh reaction conditions were required. Meanwhile, a synthesis of *N*-monoaryl amides from the corresponding primary amides by using pyrimidin-2-yl phosphates as aryl sources in the presence of $CuSO_4{\cdot}5H_2O$, sodium ascorbate, and *t*-BuONa in DMSO at 100 °C was reported.[9] We recently developed a method for the activation of hydroxy groups under basic conditions by using stable and easily available trimethyl phosphate.[10] We now report a novel and highly selective method for the *N*-monoalkylation of primary amides by using trialkyl phosphates as alkylating agents.

We initially examined the effects of the base and solvent on the *N*-monoalkylation of benzamide (**1a**) with trimethyl phosphate [$PO(OMe)_3$] as a methylating agent in cyclopentyl methyl ether (CPME) at 100 or 115 °C for 24 hours (Table 1, entries 1–8). In the presence of 1.8 equivalents of NaOH at 115 °C, benzamide (**1a**) was smoothly transformed into *N*-methylbenzamide (**2a**)[11] in 86% yield, together with a small amount (4%) of the overmethylated *N*,*N*-dimethylbenzamide (**3a**) (entry 8). Whereas NaH, KH, and BuLi also gave acceptable results (entries 1–6), *t*-BuONa, *t*-BuOK, KOH, $LiOH{\cdot}H_2O$, CsOH, and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) were inefficient (entries 11–16). Prolongation of the reaction time from 24 to 48 hours gave a similar result (entries 8 and 9), and the use of a smaller amount (2 equiv) of $PO(OMe)_3$ led to the slightly lower yield of **2a** (entries 9 and 10). The reaction proceeded smoothly in hot CPME or toluene in a highly selective manner (entries 7, 8, 17, and 18), whereas DMSO and DCE were ineffective solvents (entries 19 and 20). As a result, we chose CPME as a solvent, as it gave a slightly higher yield of **2a** than did toluene. Additionally, CPME has recently attracted attention as a useful solvent for process chemistry due to its excellent stability to oxidation (peroxide formation).[12,13] Further detailed optimizations of the reaction conditions are described in the Supporting Information.

Table 1 Effect of the Base

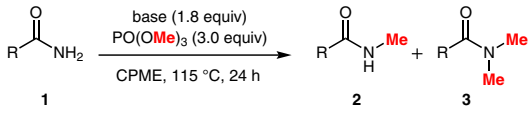


Entry	Base	Solvent	Yield[a]		
			1a	**2a**	**3a**
1	NaH	CPME	17	70	0
2[b]	NaH	CPME	1	57	37
3	KH	CPME	14	78	3
4[b]	KH	CPME	16	77	4
5	BuLi	CPME	25	72	3
6[b]	BuLi	CPME	14	77	4
7	NaOH	CPME	45	55	0
8[b]	NaOH	CPME	3	86	4
9[b,c]	NaOH	CPME	3	83	5
10[b,c,d]	NaOH	CPME	5	78	11
11	*t*-BuONa	CPME	80	7	0
12	*t*-BuOK	CPME	72	13	0
13	KOH	CPME	77	19	0
14	LiOH·H_2O	CPME	81	18	0
15	CsOH	CPME	71	26	2
16	DBU	CPME	100	0	0
17	NaOH	toluene	9	83	2
18[b]	NaOH	toluene	7	83	4
19	NaOH	DMSO	2	40	38
20	NaOH	DCE	89	5	0

[a] Determined by ^{1}H NMR with durene as an internal standard.
[b] At 115 °C.
[c] For 48 h.
[d] $PO(OMe)_3$ (2 equiv) was used.

The substrate scope was next examined. Because the reaction efficiency was sometimes improved by the use of BuLi instead of NaOH, the reaction was performed under both sets of conditions (Table 2).[14] 4-Methoxybenzamide (**1b**) and 4- and 3-methylbenzamides (**1c** and **1d**) were effectively converted into their corresponding *N*-monomethyl derivatives **2b–d** in moderate to high yields (entries 3–8) in the presence of NaOH or BuLi. The reactions of 2-methyl-, 4-chloro-, or 4-nitrobenzamide (**1e–g**, respectively) or thiophene-2-carboxamide (**1h**) proceeded selectively in the presence of NaOH as a base to give the corresponding *N*-monomethylated amides, whereas significant amounts of the corresponding overmethylated *N*,*N*-dimethylated derivatives **3e-h** were obtained in the presence of BuLi (entries 9–16). On the other hand, stearamide (**1i**), an aliphatic amide, underwent *N*-monomethylation in the presence of either NaOH or BuLi (entries 17 and 18).

Table 2 *N*-Monomethylation of Primary Amides



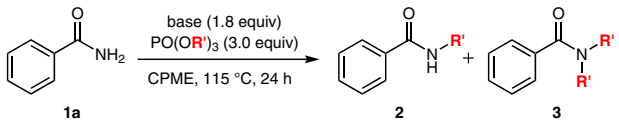
Entry	R	Base	Yield[a]		
			1	**2**	**3**
1	Ph (**1a**)	NaOH	3	86 (79)[b]	4
2		BuLi	14	77	4
3	4-$MeOC_6H_4$ (**1b**)	NaOH	34	52	0
4		BuLi	5	66 (66)[b]	0
5	4-Tol(**1c**)	NaOH	18	76 (80)[b]	0
6		BuLi	15	73	trace
7	3-Tol (**1d**)	NaOH	46	36	0
8		BuLi	8	87 (76)[b]	trace
9	2-Tol (**1e**)	NaOH	54	41 (34)[b]	2
10		BuLi	trace	18	58
11	4-ClC_6H_4 (**1f**)	NaOH	26	69 (73)[b]	2
12		BuLi	6	53	30
13	4-$O_2NC_6H_4$ (**1g**)	NaOH	58	25	0
14		BuLi	12	46 (46)[b]	16
15	2-thienyl (**1h**)	NaOH	trace	85 (81)[b]	8
16		BuLi	3	22	54
17	$(CH_2)_{16}Me$ (**1i**)	NaOH	77	23	0
18		BuLi	34	64 (65)[b]	2

[a] Determined by ^{1}H NMR with durene as an internal standard.
[b] Isolated yield.

The ethylation, butylation, or benzylation of benzamide could also be carried out by using the appropriate trialkyl phosphate[16] in the presence of BuLi as a base to give the *N*-monoalkylated benzamides **2j–l**, respectively, in moderate yields (Table 3, entries 2, 4, and 6). Whereas NaOH was ineffective for the ethylation or butylation reactions (entries 1 and 3), benzylation by tribenzyl phosphate was facilitated by NaOH (entry 5). The formation of the *N*,*N*-dialkylated products **3** was not detected under any of these reaction conditions; the use of alkyl substituents that are bulkier than the methyl group might suppress the second *N*-alkylation.

The present method could also be applied to *N*-alkylation to give tertiary amides, but only in cases in which the corresponding secondary amide or imide derivatives were used as substrates, whereas a second *N*-alkylation of primary amides was almost entirely suppressed (see Tables 1 and 2). *N*-Methylbenzamide (**2a**) was transformed into *N*,*N*-dimethylbenzamide (**3a**) in 71% yield by using BuLi as a base (entry 2). *N*-Phenylbenzamide (**4a**) reacted efficiently with trimethyl phosphate in the presence of NaOH or BuLi to

Table 3 *N*-Monoalkylation of Primary Amides

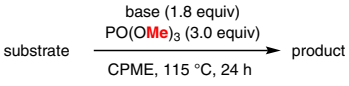


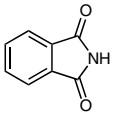
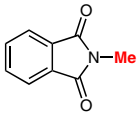
Entry	R′	Solvent	Yield[a]		
			1a	**2**	**3**
1	Et	NaOH	93	7	ND[b]
2		BuLi	7	54 (50)[c]	ND
3	Bu	NaOH	76	11	ND
4		BuLi	4	61 (54)[c]	ND
5	Bn	NaOH	trace	–[d] (43)[c]	ND
6		BuLi	trace	–[d] (56)[c]	ND

[a] Determined by ^{1}H NMR with durene as an internal standard.
[b] ND = not detected.
[c] Isolated yield.
[d] The ^{1}H NMR yield could not be determined because the ^{1}H NMR spectrum of the crude mixture was complicated.

give *N*-methyl-*N*-phenylbenzamide (**5a**) in excellent yield (entries 3 and 4). Phthalimide (**4b**) was similarly converted into *N*-methylphthalimide (**5b**) in good yield (entries 5 and 6).

Table 4 *N*-Methylation of Secondary Amides



Entry	Substrate	Product	Product	Yield[a]
1	BzNHMe	NaOH	$BzNMe_2$ (**3a**)	38 (62)[b]
2		BuLi		71 (18)[b]
3	BzNHPh	NaOH	BzN(Me)Ph (**5a**)	quant
4		BuLi		90 (0)[b]
5	 **4b**	NaOH	 **5b**	66 (14)[b]
6		BuLi		70 (trace)[b]

[a] Isolated yield.
[b] Recovered yield of substrate.

In conclusion, we have accomplished a highly selective *N*-monoalkylation of amides by using trialkyl phosphates in the presence of NaOH or BuLi in CPME, a solvent useful for chemical processes. Although the selectivity is not perfect, the desired *N*-monoalkylated amide derivatives are readily separated from the recovered substrate and overreacted *N*,*N*-dialkyl amides by silica gel column chromatography. Consequently, the present *N*-monoalkylation method is useful from the viewpoint of using stable and easily handled alkylating reagents.

Acknowledgment

We thank the Zeon Corporation for the kind gift of CPME.

Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0036-1591494.

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(11) ***N*-Methylbenzamide (2a)**
Colorless solid; yield: 24.6 mg (79%); mp 80 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.76 (d, *J* = 7.5 Hz, 2 H), 7.51–7.49 (m, 1 H), 7.44 (t, *J* = 7.0 Hz, 2 H), 6.11 (br s, 1 H), 3.03 (d, *J* = 4.5 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.4, 134.7, 131.4, 128.6, 127.0, 27.0. The ^{1}H NMR and ^{13}C NMR spectra were identical to those reported (see Ref. 5).

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(14) ***N*-Monoalkyl Amides 2; General Procedure**
NaOH (14.4 mg, 0.36 mmol, 1.8 equiv) or a 2.65 M solution of *n*-BuLi in hexane (0.14 mL, 0.37 mmol, 1.8 equiv) and the appropriate trialkyl phosphate (0.60 mmol, 3.0 equiv) were added sequentially to a solution of the appropriate amide derivative **1** (0.20 mmol, 1.0 equiv) in CPME (1.0 mL), and the mixture was stirred at 115 °C under argon for 24 h. The reaction was then quenched with brine (2 mL) and the mixture was extracted with EtOAc (3 × 50 mL). The organic layers were combined, dried (Na_2SO_4), and concentrated in vacuo to give a residue that was purified by column chromatography (silica gel).

(15) **4-Methoxy-*N*-methylbenzamide (2b)**
Colorless solid; yield: 30.7 mg (66%); mp 116–118 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.73 (d, *J* = 8.8 Hz, 2 H), 6.92 (d, *J* = 8.8 Hz, 2 H), 6.03 (br s, 1 H), 3.85 (s, 3 H), 3.01 (d, *J* = 5.5 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.9, 162.1, 128.7, 127.0, 113.8, 55.5, 26.9. The ^{1}H NMR and ^{13}C NMR spectra were identical to those reported (see Ref. 5).

(16) Trimethyl, triethyl, and tributyl phosphates are commercially available. Tribenzyl phosphate was synthesized (see Supplementary Information).