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N-[(N-Nitrosoalkylamino)methyl]carbamates as New and Convenient Diazoalkane-generating Agents

Hirotugu Yamashita, Keiichi Ito, Yoshiyasu Terao, and Minoru Sekiya

Shizuoka College of Pharmacy[1]

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A superior method for generation of diazomethane and several other gaseous diazoalkanes has been provided by alkali treatment of N-[(N-nitrosoalkylamino)methyl]-carbamates, especially their isopropyl esters, which react smoothly in high yields (81—82% for diazomethane).

Keywords——isopropyl N-[(N-nitrosomethylamino)methyl]carbamate; alkyl N-[(N-nitrosoalkylamino)methyl]carbamate; N-[(N-nitrosobenzylamino)methyl]amide; diazomethane; diazoalkane; phenyldiazomethane; N-nitrosoamine

The conventional diazomethane-generating agents such as N-methyl-N-nitroso-*p*-toluenesulfonamide,[2] N,N′-dimethyl-N,N′-dinitrosoterephthaldiamide[3] N-methyl-N-nitrosourea,[4] N-methyl-N-nitrosourethane,[5] and N-methyl-N′-nitro-N-nitrosoguanidine[6] are unstable, and some of them are potentially explosive. The commercial reagents are not pure, having a stimulative odor of decomposing nitrogen oxides. This is a disadvantage of these N-nitrosoamide type reagents. In contrast to these reagents, N-[(N-nitrosomethylamino)methyl]benzamide (I), recently reported from this laboratory,[7] is of stable N-nitrosoamine type. This reagent is of indefinitely long storage life and generates diazomethane in comparable yield on treating with alkaline solution. Its alkyl analogs can also serve as the useful agents generating other diazoalkanes.

$$\underset{\text{I}}{2C_6H_5CONHCH_2N(NO)CH_3} \xrightarrow{OH^-} 2CH_2N_2 + (C_6H_5CONH)_2CH_2 + CH_2O + H_2O \qquad (1)$$

In continuing research we intended to know how change of the benzamide residue of I by other varied amide groups influences the reaction. In the present work in this respect we have found a carbamate derivative as much more excellent diazomethane-generating agent.

Initial examination included control experiment of phenyldiazomethane preparation, because of its simpler operation, from N-[(N-nitrosobenzylamino)methyl]amides (IIa—i) possessing varied amide residues (see Table I), which were prepared by the method similar to the previously reported route,[7,8] condensation of benzylamine hydrochloride, formaldehyde and amide followed by N-nitrosation with sodium nitrite.

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$$RCONH_2 + CH_2O + C_6H_5CH_2\overset{+}{N}H_3\cdot\bar{C}l \longrightarrow$$

$$RCONHCH_2\overset{+}{N}H_2CH_2C_6H_5 \xrightarrow{NaNO_2} RCONHCH_2\underset{\underset{NO}{|}}{N}CH_2C_6H_5$$
$$Cl^- \qquad\qquad\qquad\qquad \text{II}$$

Phenyldiazomethane preparation from IIa—i was processed under uniform condition of heating them in diethyleneglycol solution of potassium hydroxide, whereupon generating phenyldiazomethane was transferred into petroleum ether layered over. Content of phenyldiazomethane in the petroleum ether solution was determined by conversion into benzyl benzoate, which was weighed as distilling pure liquid. As shown in Table I, substitution

TABLE I. Preparation[a] of Phenyldiazomethane from N-[(N-Nitrosobenzylamino)methyl]amides

$$RCONHCH_2\underset{\underset{NO}{|}}{N}CH_2C_6H_5 \longrightarrow C_6H_5CHN_2$$

Compd. No.	R	Yield[b] (%)
IIa		43
IIb	CH_3O- 	39
IIc	H	27
IId	CH_3	35
IIe	Cl_3C	19
IIf	F_3C	14
IIg		12
IIh	C_2H_5O	37
IIi	$(CH_3)_2CHO$	36

a) A mixture of substrate (0.05 mol), a solution of KOH in diethyleneglycol (5.6 g in 20 ml) and petr. ether (80 ml) was stirred under refluxing of petr. ether for 40 min.
b) Determined by conversion into benzyl benzoate.

TABLE II. Preparation[a] of Diazoalkanes from Alkyl N-[(N-Nitrosoalkylamino)methyl]carbamates

$$ROCONHCH_2\underset{\underset{NO}{|}}{N}CH_2R' \longrightarrow R'CHN_2$$

Compd. No.	R	R′	Method[a] and yield (%)[b]				
			A	B	C	D	E
IIIa	CH_3	H	72				
IIIb	C_2H_5	H	70				
IIIc	$(CH_3)_2CH$	H	81	82	81	77	55
IIId	C_4H_9	H	61				
IIIe	$C_6H_5CH_2$	H	64				
IV	$(CH_3)_2CH$	CH_3	22	30	51	50	30
V	$(CH_3)_2CH$	C_2H_5				31	
VI	$(CH_3)_2CH$	C_3H_7				26	
VII	$(CH_3)_2CH$	$(CH_3)_2CH$				14	

a) Ethereal solution of substrate (0.05 mol in 70 ml) was added to the following preheated alkali solution; 4.2 g KOH in 18 ml diethyleneglycol for method A, 3.2 g CH_3ONa in 15 ml MeOH for method B, 5.8 g BuONa in 30 ml BuOH for method C, 4.2 g KOH in 30 ml BuOH for method D, 15 ml of 50% KOH in H_2O for method E. Topping ether containing diazoalkane was collected.
b) Determined by back-titration of excess benzoic acid added to ethereal distillate.

by the other amide residues did not give higher yield of phenyldiazomethane relative to that from IIa, but it was noted that the carbamate derivatives, IIh and IIi, were quickly brought into solution and reacted more rapidly than the others.

Then, diazomethane preparation was checked using the carbamate derivatives, alkyl N-[(N-nitrosomethylamino)methyl]carbamates (IIIa—e) (alkyl=methyl, ethyl, isopropyl, butyl, and benzyl) (see Table II), similarly prepared. The reaction was processed by addition of an ethereal solution of IIIa—e into a preheated diethyleneglycol solution of potassium hydroxide (method A), rapid reaction being controlled by rate of the addition, and topping ether containing diazomethane was collected in an ice-cooled receiver. Accurate content of diazomethane in the ethereal solution was determined by back-titration of excess amount of benzoic acid added. The diazomethane solution was almost anhydrous and free from alcohol. As can be seen from the results listed in Table II, highest yield of diazomethane (81%) was obtained by the use of the isopropyl carbamate derivative (IIIc). In the above method A with IIIc, in place of diethyleneglycol solution of potassium hydroxide several other alkali solutions can be also used as shown in Table II with the yields of diazomethane, *i.e.*, 82% by sodium methoxide in methanol (method B), 81% by sodium butoxide in butanol (method C), 77% by potassium hydroxide in butanol (method D), 55% by potassium hydroxide in water (method E).

Probably owing to much higher solubility of the carbamate derivatives in organic solvents relative to the benzamide derivative, I, the selected methods with IIIc are more advantageous; high yield of diazomethane (81—82%), which is not accessible otherwise, and rapidity of the reaction.

In the procedure of the above methods, carbamate or cyanate was isolated as another product. Conversion into the latter from the former is known[9] as base-catalyzed. So the following reaction may proceed through a path resembling that reported previously[7] in the reaction of I.

$$\underset{\text{III}}{ROCONHCH_2\underset{|}{N}(NO)CH_3} \longrightarrow CH_2N_2 + ROCONH_2 + CH_2O \qquad (2)$$

Actually formaldehyde in Eq. 2 rapidly vanishes by its further conversion in such strong alkaline medium.

Further examination included preparation of another gaseous diazoalkanes from the nitroso compound of the isopropyl carbamate type, $(CH_3)_2CHOCONHCH_2N(NO)R$ (IV—VII). Best yield of diazoethane (50—51%) was obtained by the methods C and D as shown in Table II. 1-Diazopropane, 1-diazobutane and 1-diazo-2-methylpropane obtained by the method D were 31%, 26% and 14% yield, respectively, which were determined by the same way as for diazomethane.

The recorded yields of diazoalkanes in the present paper are most reliable in improvement of their analytical procedure. In our reexperiments of the previously reported[7] diazoalkane preparation from N-[(N-nitrosoalkylamino)methyl]benzamides yields of diazoalkanes[10] were somewhat lower than the reported data, finding the reported procedure (determined as *p*-nitrobenzoate) inadequate.

Experimental

All melting points are uncorrected. Ultraviolet (UV) spectra were recorded on a Hitachi EPS-3T spectrophotometer. Infrared (IR) spectra were obtained by a Hitachi EPI-G2 spectrophotometer. Nuclear magnetic resonance (NMR) spectra were taken with a Hitachi R-24 spectrometer using tetramethylsilane as internal standard.

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10) For example yields of diazomethane and diazoethane, determined by the same titration method as described in the present paper, were 66—69% and 44—46%, respectively.

N-[(N-Nitrosoalkylamino)methyl]amides and Alkyl N-[(N-Nitrosoalkylamino)methyl]carbamates——General Procedure: Five N-[(N-nitrosobenzylamino)methyl]amides (IIb, c, e—g, see Table I) and eleven alkyl N-[(N-nitrosoalkylamino)methyl]carbamates (IIh, i, IIIa—e, IV—VII, see Tables I and II) used for the preparation of diazoalkanes were newly prepared by the following general procedure similar to that previously described.[7,8] Into a solution of 0.3 mol of primary amine hydrochloride in 100 ml of EtOH (250 ml in the runs using benzylamine hydrochloride) 27 g of 35% formaline and then a solution of 0.3 mol of amide or alkyl carbamate in 150 ml of EtOH (600 ml of 90% EtOH in the run using *p*-methoxybenzamide) were added with stirring at 35—40°. The mixture was further stirred at the same temperature for 1 hr, followed by concentration under reduced pressure. Recrystallization of the resulting residue gave N-(benzylaminomethyl)amide hydrochloride or alkyl N-(alkylaminomethyl)carbamate hydrochloride. In the run with methyl N-(methylaminomethyl)carbamate hydrochloride a crude product uncrystallized was directly used for the next nitrosation without purification. Yields, melting points and analytical data of these hydrochlorides are recorded in Table III.

Table III. N-(Alkylaminomethyl)amide and -carbamate Hydrochlorides

$R^1CONHCH_2\overset{+}{N}H_2R^2\cdot\bar{C}l$

R^1	R^2	Yield (%)	Appearances (Recryst. solvent)	mp (°C)	Formula	Analysis (%) Calcd. (Found) C	H	N
p-$CH_3OC_6H_4$	$C_6H_5CH_2$	71	Leaflets (EtOH)	169—171	$C_{16}H_{19}ClN_2O_2$	62.64 (62.51	6.24 6.16	9.13 9.14)
Cl_3C	$C_6H_5CH_2$	48	Leaflets (EtOH)	149—151	$C_{10}H_{12}Cl_4N_2O$	37.77 (37.68	3.80 3.62	8.81 8.80)
F_3C	$C_6H_5CH_2$	57	Leaflets (EtOH)	154—156	$C_{10}H_{12}ClF_3N_2O$	44.67 (44.58	4.51 4.41	10.42 10.47)
	$C_6H_5CH_2$	49	Leaflets (EtOH)	161—163	$C_{14}H_{16}ClN_3O$	60.54 (60.47	5.81 5.82	15.31 14.98)
C_2H_5O	$C_6H_5CH_2$	78	Leaflets (EtOH)	144—146	$C_{11}H_{17}ClN_2O_2$	53.99 (54.19	7.00 7.07	11.45 11.44)
$(CH_3)_2CHO$	$C_6H_5CH_2$	73	Leaflets (EtOH)	155—157	$C_{12}H_{19}ClN_2O_2$	55.70 (55.87	7.40 7.40	10.83 10.89)
C_2H_5O	CH_3	79	Prisms (EtOH)	135—136	$C_5H_{13}ClN_2O_2$	35.61 (35.35	7.77 7.70	16.61 16.46)
$(CH_3)_2CHO$	CH_3	78	Leaflets (EtOH)	164—165	$C_6H_{15}ClN_2O_2$	39.46 (39.47	8.28 8.34	15.34 15.26)
C_4H_9O	CH_3	78	Leaflets (EtOH)	124—125	$C_7H_{17}ClN_2O_2$	42.75 (42.51	8.71 8.66	14.24 14.26)
$C_6H_5CH_2O$	CH_3	89	Leaflets (EtOH)	122—124	$C_{10}H_{15}ClN_2O_2$	52.07 (51.85	6.55 6.56	12.14 11.72)
$(CH_3)_2CHO$	C_2H_5	73	Leaflets (EtOH)	145—146	$C_7H_{17}ClN_2O_2$	42.75 (42.56	8.71 8.72	14.24 14.13)
$(CH_3)_2CHO$	C_3H_7	65	Leaflets (EtOH)	140—142	$C_8H_{19}ClN_2O_2$	45.60 (45.13	9.09 8.95	13.29 13.14)
$(CH_3)_2CHO$	C_4H_9	85	Plates (EtOH)	146—148	$C_9H_{21}ClN_2O_2$	48.10 (47.93	9.42 9.47	12.46 12.50)
$(CH_3)_2CHO$	$(CH_3)_2CHCH_2$	62	Leaflets (EtOH–AcOEt)	133—134	$C_9H_{21}ClN_2O_2$	48.10 (47.37	9.42 9.35	12.46 12.32)

Into a saturated aqueous solution of the above obtained hydrochloride at the reaction temperature (see below), 2 ml of 35% HCl was added and then a solution of 8.3 g (0.12 mol) of sodium nitrite in 30 ml of H_2O was added dropwise with vigorous stirring. The adequate reaction temperatures are as follows: 0—5° for the preparation of IIc; 20—25° for IIh, i, IIIa—e, IV—VII; 40—45° for IIf; 50—55° for IIe, g; 55—60° for IIb. Stirring at this temperature was continued for additional 30 min. After cooling, the products were isolated from the reaction mixtures either by filtration or by extraction with ether. Yields, melting points and analytical data of the obtained N-nitroso compounds are recorded in Table IV and their spectral data in Table V.

Preparation of Phenyldiazomethane from N-[(N-Nitrosobenzylamino)methyl]amides (IIa—i)——General Procedure: To a solution of 5.6 g (0.1 mol) of KOH dissolved in 20 ml of diethyleneglycol 0.05 mol of finely pulverized N-[(N-nitrosobenzylamino)methyl]amide was added and then 80 ml of petr. ether was layered

Table IV. N-[(N-Nitrosoalkylamino)methyl]amides and -carbamates

$R^1CONHCH_2\underset{\underset{NO}{|}}{N}R^2$

Compd. No.	R^1	R^2	Yield (%)	Appearances (Recryst. solvent)	mp (°C)	Formula	Analysis (%) Calcd. (Found) C	H	N
IIb	p-$CH_3OC_6H_4$	$C_6H_5CH_2$	81	Prisms (EtOH)	88—90	$C_{16}H_{17}N_3O_3$	64.20 (64.09	5.72 5.73	14.04 14.02)
IIc	H	$C_6H_5CH_2$	58	Prisms (benzene)	60—62	$C_9H_{11}N_3O_2$	55.95 (55.86	5.74 5.73	21.75 21.82)
IIe	Cl_3C	$C_6H_5CH_2$	31	Prisms ($isoPr_2O$)	80—83	$C_{10}H_{10}Cl_3N_3O_2$	38.67 (38.60	3.25 3.19	13.53 13.53)
IIf	F_3C	$C_6H_5CH_2$	52	Needles (petr. ether)	48—50	$C_{10}H_{10}F_3N_3O_2$	45.95 (45.99	3.87 3.85	16.10 16.08)
IIg		$C_6H_5CH_2$	58	Needles (AcOEt)	99—100	$C_{14}H_{14}N_4O_2$	62.21 (62.03	5.22 5.21	20.73 20.84)
IIh	C_2H_5O	$C_6H_5CH_2$	81	Needles (ligroin)	59—61	$C_{11}H_{15}N_3O_2$	55.69 (55.70	6.37 6.33	17.71 17.79)
IIi	$(CH_3)_2CHO$	$C_6H_5CH_2$	39	Prisms (ligroin)	64—66	$C_{12}H_{17}N_3O_3$	57.36 (57.21	6.82 6.72	16.72 16.68)
IIIa	CH_3O	CH_3	40	Prisms (ether)	48—49	$C_4H_9N_3O_3$	32.65 (32.68	6.17 6.09	28.56 28.06)
IIIb	C_2H_5O	CH_3	93	Needles (ether)	38—40	$C_5H_{11}N_3O_3$	37.26 (37.04	6.88 6.84	26.07 25.87)
IIIc	$(CH_3)_2CHO$	CH_3	61	Needles (ligroin)	66—67	$C_6H_{13}N_3O_3$	41.14 (41.21	7.48 7.46	23.99 23.80)
IIId	C_4H_9O	CH_3	84	Needles (ether)	32—34	$C_7H_{15}N_3O_3$	44.43 (44.63	7.99 7.97	22.21 21.82)
IIIe	$C_6H_5CH_2O$	CH_3	74	Plates ($isoPr_2O$)	57—58	$C_{10}H_{13}N_3O_3$	53.80 (53.73	5.87 5.85	18.83 18.81)
IV	$(CH_3)_2CHO$	C_2H_5	86	Prisms (ether)	41—42	$C_7H_{15}N_3O_3$	44.43 (44.53	7.99 7.92	22.21 22.31)
V	$(CH_3)_2CHO$	C_3H_7	80	Prisms ($isoPr_2O$)	30—32	$C_8H_{17}N_3O_3$	47.28 (47.50	8.43 8.45	20.68 20.77)
VI	$(CH_3)_2CHO$	C_4H_9	81	Needles (petr. ether)	53—55	$C_9H_{19}N_3O_3$	49.75 (49.82	8.81 8.81	19.34 19.25)
VII	$(CH_3)_2CHO$	$(CH_3)_2CHCH_2$	61	Needles (petr. ether)	55—56	$C_9H_{19}N_2O_3$	49.75 (49.62	8.81 8.90	19.34 19.34)

over. The mixture was vigorously stirred under refluxing of petr. ether for 40 min. After cooling, the resulting red-colored petr. ether layer was separated easily by decantation. By addition of 50 ml of H_2O to the diethyleneglycol layer additional small amount of phenyldiazomethane was liberated, which was extracted with petr. ether. The combined petr. ether solution was washed with H_2O and dried over anhydrous $MgSO_4$. Filtration gave petr. ether solution of phenyldiazomethane, content of which was determined by its conversion into benzyl benzoate as follows. To a solution of sufficient excess of benzoic acid in ether the above phenyldiazomethane solution was added dropwise with stirring. After the color of the solution completely disappeared, excess of benzoic acid was removed by washing with aqueous $KHCO_3$ solution. The resulting solution was dried over anhydrous $MgSO_4$, filtered and evaporated. Distillation of the residual oil under reduced pressure gave benzyl benzoate, bp 194—199° (26 mmHg). Yields of phenyldiazomethane, calculated from the weighed amount of the isolated benzyl benzoate, are listed in Table I.

Preparation of Diazomethane, Diazoethane, 1-Diazopropane, 1-Diazobutane, and 1-Diazo-2-methylpropane from Alkyl N-[(N-Nitrosoalkylamino)methyl]carbamates (IIIa—e, IV—VII)——Diazomethane, diazoethane, 1-diazopropane, 1-diazobutane, and 1-diazo-2-methylpropane were prepared from alkyl N-[(N-nitrosomethylamino)methyl]carbamates (IIIa—e), isopropyl N-[(N-nitrosoethylamino)methyl]carbamate (IV), isopropyl N-[(N-nitrosopropylamino)methyl]carbamate (V), isopropyl N-[(N-nitrosobutylamino)methyl]carbamate (VI), and isopropyl N-[(N-nitrosoisobutylamino)methyl]carbamate (VII), respectively, by the following general procedure.

Method A: In a flask fitted with a dropping funnel and a condenser set for distillation was placed a solution of 4.2 g (0.075 mol) of KOH in 18 ml of diethyleneglycol and 50 ml of dry ether. The mixture was magnetically stirred and warmed. When the distillation of ether was started, 0.05 mol of alkyl N-[(N-

TABLE V. Spectral Data of $RCONHCH_2N(NO)CH_2R'$

Compd. No.	R	R′	IR ν_{max}^{KBr} cm^{-1} NH	IR ν_{max}^{KBr} cm^{-1} CONH	UV λ_{max}^{EtOH} nm (log ε)		NMR δ (in $CDCl_3$) $-NHCH_2N<$ *syn*	$-NHCH_2N<$ *anti*	$>NCH_2R'$ or $>NCH_3$ *syn*	$>NCH_2R'$ or $>NCH_3$ *anti*
IIb	*p*-$CH_3OC_6H_4$	C_6H_5	3344	1641 1528	254.5 (4.31)	366.0 (1.78)	4.87	5.73	5.48	4.83
IIc	H	C_6H_5	3275	1662 1512	235.5 (3.88)	368.0 (1.80)	4.70	5.57	5.40	4.78
IIe	Cl_3C	C_6H_5	3291	1725 1495	236.0 (4.14)	367.5 (1.80)	4.80	5.68	5.44	4.81
IIf	F_3C	C_6H_5	3286	1722 1550	236.0 (3.96)	368.5 (1.81)	4.66	5.56	5.34	4.72
IIg		C_6H_5	3180	1663 1548	237.0sh (4.03)	368.0 (1.79)	4.88	5.80	5.50	4.85
IIh	C_2H_5O	C_6H_5	3270	1688 1546	236.5 (3.83)	366.0 (1.79)	4.61	5.50	5.42	4.79
IIi	$(CH_3)_2CHO$	C_6H_5	3274	1685 1534	234.0sh (3.91)	365.5 (1.79)	4.60	5.47	5.40	4.80
IIIa	CH_3O	H	3335	1690 1544	230.0 (3.89)	354.0 (1.93)	4.79	5.55	3.88	3.05
IIIb	C_2H_5O	H	3323	1694 1550	228.5 (3.94)	353.0 (1.92)	4.74	5.50	3.87	3.02
IIIc	$(CH_3)_2CHO$	H	3305	1691 1546	227.0 (3.92)	352.5 (1.94)	5.01	5.51	3.87	3.06
IIId	C_4H_9O	H	3326	1690 1543	229.0 (3.80)	353.0 (1.87)	—	5.52	—	3.06
IIIe	$C_6H_5CH_2O$	H	3315	1690 1535	229.0 (3.88)	354.0 (1.90)	4.77	5.10	3.87	3.03
IV	$(CH_3)_2CHO$	CH_3	3314	1690 1547	230.5 (3.87)	356.0 (1.86)	4.69	5.52	4.26	3.63
V	$(CH_3)_2CHO$	C_2H_5	3318	1689 1544	233.0 (3.84)	358.5 (1.87)	4.76	5.49	4.17	3.56
VI	$(CH_3)_2CHO$	C_3H_7	3314	1690 1546	232.0 (3.89)	356.5 (1.86)	4.71	5.50	4.28	3.61
VII	$(CH_3)_2CHO$	$(CH_3)_2CH$	3325	1690 1540	233.0 (3.88)	365.0 (1.84)	4.72	5.47	4.01	3.40

sh: shoulder.
syn, *anti*: relative to nitroso oxygen.

nitrosoalkylamino)methyl]carbamate dissolved in 70 ml of dry ether was slowly added from the dropping funnel so as to keep roughly the initial volume of ether in the flask. The yellow distillate was collected in an ice-cooled receiver containing dry ether. When the dropping funnel was empty, another dry ether was slowly added and distillation was continued until the distilling ether became colorless. Content of diazoalkane in the distilled ethereal solution was determined by the previously described[4] back-titration method in which excess amount of accurately weighed benzoic acid was added to the solution at 0° to react with diazoalkane and the unreacted benzoic acid was titrated with standard 0.2 N NaOH. Yields of diazoalkanes are listed in Table II.

In the above method the following alkali solutions can be also used in place of KOH in diethyleneglycol: 3.2 g of sodium methoxide in 15 ml of MeOH (method B); 1.4 g of sodium dissolved in 30 ml of BuOH (method C); 4.2 g of KOH in 30 ml of BuOH (method D); 15 ml of 50% aqueous KOH (method E).

Productions of potassium cyanate and isopropyl carbamate as another products were confirmed in the run with IIIc by method A and by method E, respectively. Potassium cyanate was obtained as precipitates in the reaction solution on cool, and isopropyl carbamate from the ethereal layer of the reaction solution.

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