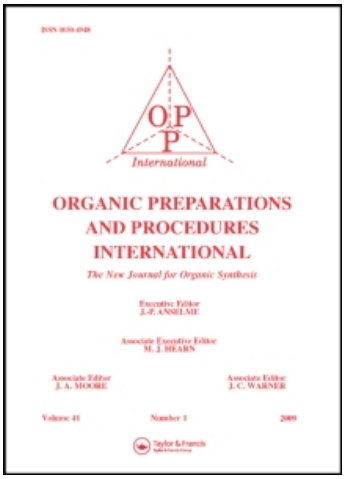

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SYNTHESIS OF α-(DIMETHYLAMINOMETHYLENE)KETONES BY USE OF METHOXYBIS(DIMETHYLAMINO)METHANE (BREDERECK'S REAGENT)

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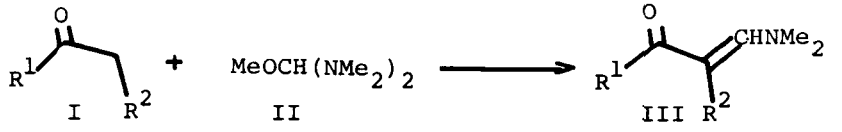
The preparation of alkoxybis(dimethylamino)methanes and their use in aminoformylation was first described by Bredereck and coworkers.[1] The order of reactivity of these N,N-dimethylformamide equivalents in the aminoformylation of active methylene compounds is as follows.

$$HC(NMe_2)_3 > \underline{t}\text{-}BuOCH(NMe_2)_2 > MeOCH(NMe_2)_2 > (MeO)_2CHNMe_2$$

Like Vilsmeier reagents,[2] these aminoorthoesters can be represented as their dissociated or ion-pair hybrids, which helps explain the order of reactivity. Nitrogen provides more anchimeric assistance than oxygen during dissociation as well as more stabilization of the resulting partial positive charge. In addition, the order of reactivity corresponds to the basicity of the anionic species of the ion pair, an indication of its potential role during formylation. Despite this dissociation, ketones possessing base labile functionality[3] undergo aminoformylation without side-reaction.



This work was initiated to provide a better understanding of the scope, limitations and synthetic utility of one of these reagents, methoxybis(dimethylamino)methane (II) in the aminoformylation of activated methylene compounds. The aminoformylation of ketones Ia-g, each with only one activated methylene position, proceeded in high yield to give IIIa-g. The presence of a tertiary basic nitrogen would appear to have no effect on the reaction. The more sterically hindered ketones Ih-j also underwent facile aminoformylation. As might be expected, 6-amino-α-tetralone (Ik) was both N and C formylated. The reagent is not sufficiently reactive to formylate the vinylogous amides resulting from monoformylation of ketones Il-n. Thus despite a sufficient excess of II only monoformylation occurred. With the neutral N-benzoyl-4-piperidone (Io) however, diformylation predominated.

Formylation of lactones Ip and Iq proceeded without concommitant ester or lactam formation, while aliphatic nitriles, esters and aldehydes (Ir, Is and It respectively) failed to react with II even at 120°. The doubly activated methylene positions of keto ester Iu and diester Iv underwent facile formylation. While conventional formylation of 2-pentanone (Iw) affords a 4:1 ratio of methyl to methylene (kinetic to thermodynamic) product,[8] reaction of Iw with II provided a 20:1 ratio of methyl to methylene aminoformylation at 110°C (85% yield). The aminoformylation of ethyl levulinate Ix occurred at the C-5 methyl and C-3 methylene positions only. At ambient temperature a 4:1 ratio of C-3 (IIIx') to C-5 (IIIx'')formylation was observed. At 0° this

preference was reversed, with a ratio of C-3 to C-5 of 4.5 to 5.5. Exposure of 3-methylcyclohexanone Iy to II at 80° gave a 1:1 mixture of C-2 (IIIy') and C-6 (IIIy'') aminoformylated products. Even at lower temperatures a 1:1 ratio of products was observed. Evidently the C-3 methyl has no effect on the course of the reaction.

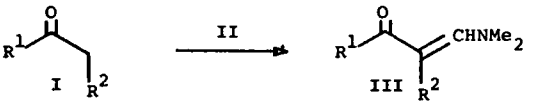
Our spectral data (Table 2) confirm the observations of Trost and his group.[4a] The carbonyl absorptions indicate substantial contribution of the dipolar resonance form[4b] yet the N-methyl PMR signals appear as sharp singlets, an indication that the barrier of rotation about the C-N bond is less than that of a typical amide.

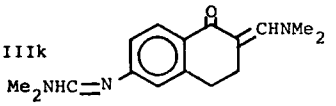
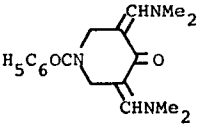
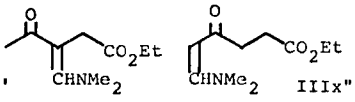
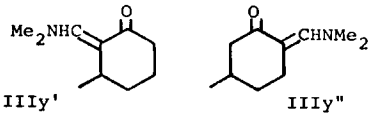
In all cases, the yields cited are for analytically pure material which has been distilled and/or crystallized. Except where noted only a single, monoformylated product was observed. The pertinent data are summarized in Tables 1 and 2.

EXPERIMENTAL

General Procedure.[5] Preparation of 1-dimethylaminomethylene-3,3-dimethylbutanone (IIIg). A solution of pinacolone (40.0 g, 0.40 mol) and methoxybis(dimethylamino)methane[1a] (II) (80ml) was heated under N_2 at 110° for 18 h. Concentration in vacuo[6] followed by distillation (68-73° 0.1 mm) of the residue provided 39.0 g (63%) of a yellow oil which solidified on standing at room temperature.

Table 1



	SM		Product				
Cmpd	R^1	R^2	Cmpd	R^1	R^2	mp (bp)[a]	Yield[b]
Ia	C_6H_5	Me	IIIa	C_6H_5	Me	70-2[c]	95
Ib	4-pyridyl	H	IIIb	4-pyridyl	H	115-7	96
Ic	3-pyridyl	H	IIIc	3-pyridyl	H	62-70	74
Id	2-pyridyl	H	IIId	2-pyridyl	H	125-7	79
Ie	4-pyridyl	Me	IIIe	4-pyridyl	Me	oil	67
If	C_6H_5	CH_2NMe_2	IIIf	C_6H_5	CH_2NMe_2	oil	61
Ig	Me_3C	H	IIIg	Me_3C	H	(68-73/0.1)	63
Ih	Me_3C	C_6H_5	IIIh	Me_3C	C_6H_5	54.5-5.5	78
Ii	$pMeOC_6H_4$	$pMeOC_6H_4$	IIIi	$pMeOC_6H_4$	$pMeOC_6H_4$	119-20	82
Ij	4-pyridyl	C_6H_5	IIIj	4-pyridyl	C_6H_5	(150-60/0.1)	60
Ik	6-amino-α-tetralone		IIIk			130.5-1.5	37
Il	$-(CH_2)_2NMeCH_2-$		IIIl	$-(CH_2)_2NMeCH_2-$		(110-20/0.1)	68
Im	$-(CH_2)_2CH(Me_3C)CH_2-$		IIIm	$-(CH_2)_2CH(Me_3C)CH_2-$		(135-42/0.1)	82
In	$-(CH_2)_{10}-$		IIIn	$-(CH_2)_{10}-$		(98-105/0.1)[c]	75
Io	$-(CH_2)N(COC_6H_5)CH_2-$		IIIo			161-3	90
Ip	$-O(CH_2)_3-$		IIIp	$-O(CH_2)_3-$		45-55	60
Iq	$-O(CH_2)_2-$		IIIq	$-O(CH_2)_2-$		96-7.5	55
Ir	(butyronitrile)		-	-	-	-	-
Is	EtO	Et	-	-	-	-	-
It	H	Et	-	-	-	-	-
Iu	CH_3	CO_2Et	IIIu	CH_3	CO_2Et	oil[g]	87
Iv	EtO	CO_2Et	IIIv	EtO	CO_2Et	(130-40/0.1)[h]	84
Iw	Pr	H	IIIw'	Pr	H	(90-7/0.1)[d]	85
			IIIw''	Me	Et	-	4
Ix	Me	CH_2CO_2Et	 IIIx' IIIx"			oil[e]	86
Iy	$-(CH_2)_3CHMe-$		 IIIy' IIIy"			(99-104/0.1)[f]	67

a) Expressed in °C and (°C/mm Hg). b) Isolated yields, not optimized. c) See Ref 7. d) Separted by chromatography over silica gel prior to distillation. e) Depending upon rxn conditions a 4:1 or 4.5:5.5 mixture. f) a 1:1 mixture. g) See Ref 9. h) See Ref 10.

Acknowledgement. The services of the Analytical Section are gratefully acknowledged.

Table 2 Partial Spectral Data

Cmpd	PMR[a]	IR[b]
IIIa	2.11(s,3H),3.00(s,6H),6.88(s,1H), 7.35(s,5H)	1675,1630
IIIb	2.90(s,3H),3.10(s,3H), 5.67(d,J = 11Hz,1H),7.84(d,J = 11Hz,1H)	1650
IIIc	3.00(broad s,6H)5.64(d,J = 12Hz,1H), 7.81(d,J = 12Hz,1H)	1645
IIId	3.02(broad s,6H)6.44(d,J = 12Hz,1H), 7.90(d,J = 12Hz,1H	1645
IIIe	2.11(s,3H),3.06(s,6H),6.76(s,1H)	1640
IIIf	2.30(s,6H),3.17(s,6H),7.00(s,1H)	1645,1625
IIIg	2.94(s,6H),5.23(d,J = 12Hz,1H), 7.58(d,J = 12Hz,1H)	1650
IIIh	2.59(s,6H),7.43(s,1H)	1635
IIIi	2.71(s,6H),3.73(s,6H)	1630
IIIj	2.70(s,6H)	1640
IIIk	3.08(s,6H),3.16(s,6H),6.76(m,1H)	1640
IIIl	2.41(s,3H),3.05(s,6H),7.45(m,1H)	1650
IIIm	0.93(s,9H),3.07(s,6H),7.46(m,1H)	1645
IIIn	3.02(s,6H),7.14(s,1H)	1635
IIIo	2.96(broad s,12H),7.41(s,5H), 7.48(s,2H)	1625
IIIp	3.10(s,6H),7.50(m,1H)	1685
IIIq	3.06(s,6H),7.06(m,1H)	1725,1630
IIIu	3.07(s,6H),7.65(s,1H)	1695,1660,1640
IIIv	3.00(s,6H),7.50(s,1H)	1685,1605
IIIw'	2.93(s,6H),5.02(d,J = 13Hz,1H), 7.49(d,J = 13Hz,1H)	1655
IIIw''	2.93(s,6H),7.29(s,1H)	1655
IIIx[c]	2.20(s,2.4H),3.11(s,6H), 5.04(d,J = 13Hz,0.8H),7.31(s,0.2H), 7.52(d,J = 13Hz,0.8H)	1735,1665,1650
IIIy[d]	1.01(d,J = 7Hz,1.5H),1.23(d,J = 6Hz, 1.5H),3.12(s,6H),7.50(m,1H)	1650

(a) Recorded on a Varian T-60 or XL-100 spectrometer, expressed in δ relative to TMS.
(b) Recorded on a Perkin-Elmer model 257 or 457 spectrometer, expressed in $cm.^{-1}$
(c) A mixture of 80% IIIx', 20% IIIx''.
(d) A mixture of 50% IIIy', 50% IIIy''.

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6. In most cases concentration provided a material which on recrystallization from the appropriate solvent gave an analytically pure aminoformylation product. Many of the products were heat labile.

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