A Facile Synthesis of 2-Aza-1,3-butadienes

Hidenori OKAMOTO and Shozo KATO
Tsukuba Research Lab., Tokuyama Soda Co., Ltd., 40 Wadai, Tsukuba, Ibaraki 300-42
(Received August 29, 1990)

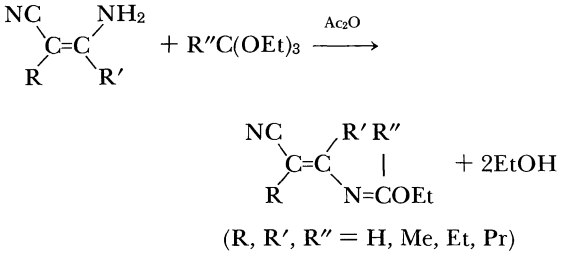
2-Aza-1,3-butadienes bearing alkoxyl substituent were obtained easily by the reaction of ketimines with orthoesters. The reaction proceeded smoothly by the addition of small amount of *p*-toluenesulfonic acid. When acetals were used in place of orthoesters, the corresponding 2-aza-1,3-butadienes were similarly prepared.

Due to the usefulness in various organic syntheses, several reports have been published on 2-aza-1,3-butadienes.[1] However, there have been few reports about 2-aza-1,3-butadienes bearing an alkoxyl group at the end position. For example, Saegusa and co-workers[2] reported that the reaction of vinyl isocyanide with alcohols in the presence of Cu(I) catalyst gives the corresponding 1-alkoxy-2-aza-1,3-butadienes.

$$CH_2{=}CHNC + ROH \xrightarrow{Cu_2O} CH_2{=}CHN{=}CHOR \quad (R = Me, Et, C_6H_{11} \text{ etc.})$$

Aue and co-worker[3] described that thermolysis of 2-methyl-1-azetine affords 1-alkoxy-2-aza-1,3-butadienes via electrocyclic ring opening followed by a 1,5-hydride shift.

Brown and co-worker[4] reported that the reaction of the orthoester with an enamino nitrile gives rise to the corresponding ethoxy derivative. This method, however, is only applicable to the enamines having electron-withdrawing groups.



(R, R′, R″ = H, Me, Et, Pr)

Although a number of reactions of orthoesters with amine compounds have been reported,[5] little has been known of the reaction with ketimines. During the course of our study on ketimine compounds, we found that ketimines easily react with orthoesters and acetals to give 2-aza-1,3-butadienes.

In this paper, we wish to report a facile, extensive synthesis of 2-aza-1,3-butadienes having alkoxyl substituent or dialkylamino substituent.

Results and Discussion

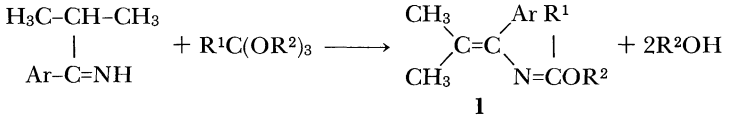
1-Alkoxy-2-aza-1,3-butadienes (**1**) were prepared from 1-aryl-2-methyl-1-propanimines and orthoesters as shown in Scheme 1.

General procedure is as follows. To a flask equipped with distillation head were added 1-aryl-2-methyl-1-propanimines, orthoester and a small amount of *p*-toluenesulfonic acid (PTS). The mixture was heated in an oil bath (120—160 °C) for about 10—20 min until the corresponding alcohol, which was formed during the reaction, was distilled out. The resulting mixture afforded a colorless, pale yellow or yellow liquid after distillation under a reduced pressure.

These results are summarized in Table 1. As can be seen in the Table, 2-aza-1,3-butadienes, having branched alkoxyl group, especially isopropoxyl group, were obtained in good yields (Entry No. **1e—j**). Furthermore, 2-aza-1,3-butadienes derived from triethyl orthoacetate and triethyl orthopropionate were formed in considerable yields (Entry No. **1m** and **1n**). These results seemed to be attributed to the steric protection around the carbon–nitrogen double bond. Good results were obtained by use of excess amount of orthoesters in the cases of trimethyl orthoformate and triethyl orthoformate because of their low boiling points. When the reaction was carried out for a long time, polymeric substance was obtained.

Although this condensation reaction proceeded without catalyst, the presence of a small amount of PTS was favorable to afford good yields. For instance, the reaction of 2-methyl-1-phenyl-1-propanimine (**2**) with triethyl orthoacetate or triethyl orthopropionate in the presence of a small amount of PTS at 120 °C for 15 min gave the products **1m** and **1n** in 70 and 63% yields, respectively, while in the absence of PTS at 120 °C for 3h **1m** and **1n** were obtained in yields of 30 and 20%, respectively.

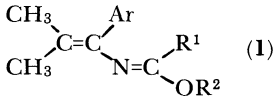
The 2-aza-1,3-butadiene (**3**), which is the dimer of **2**, was produced as a by-product in the reaction of **2** with orthoesters. Dimerization of ketimines has been



1

Scheme 1.

Table 1. 2-Aza-1,3-butadienes (**1**)

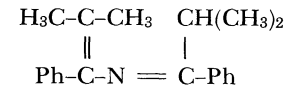


(**1**)

No.	Ar	R^1	R^2	Method[a]	Yield/%	Bp/°C/mmHg
a	5-Me-2-thienyl	H	Me	A	25	75—76/0.1
b	2-Me-C_6H_4	H	Et	C	53	75—76/0.2
c	3-Me-C_6H_4	H	Et	C	52	92—94/0.6
d	3-CF_3-C_6H_4	H	Et	B	49	73—75/0.3
e	C_6H_5	H	*i*-Pr	A	62	79—82/0.15
f	2-Me-C_6H_4	H	*i*-Pr	A	87	65—69/0.1
g	4-F-C_6H_4	H	*i*-Pr	A	71	69—70/0.1
h	2-Furyl	H	*i*-Pr	A	71	57—58/0.2
i	2-Thienyl	H	*i*-Pr	A	68	66/0.12
j	3-MeO-2-thienyl	H	*i*-Pr	A	69	94/0.1
k	C_6H_5	H	*s*-Bu	A	56	82—83/0.15
l	C_6H_5	Me	Me	C	40	73—75/0.35
m	C_6H_5	Me	Et	B	70	80—82/0.4
n	C_6H_5	Et	Et	B	63	82—83/0.25
o	C_6H_5	*n*-Pr	Me	B	55	84—86/0.5

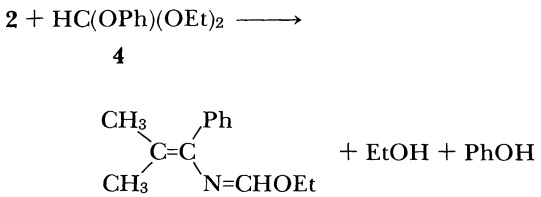
a) Method A: PTS catalyst at 150—160 °C for 10—15 min; Method B: PTS catalyst at 120—130 °C for 5—15 min; Method C: No catalyst at 110—120 °C for 2—8 h.

previously accomplished by refluxing a THF solution of ketimines in the presence of trifluoroacetic acid.[6] When **2** was heated at 150 °C in the presence or absence of PTS, **3** was obtained along with the evolution of ammonia.



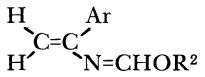
(**3**)

To synthesize 1-phenoxy-2-aza-1,3-butadiene (R^2= Ph), diethyl phenyl orthoformate (**4**) was allowed to react with **2**. However, this reaction was failed to give 2-ethoxy-2-aza-1,3-butadiene as shown in the following scheme because of higher ability of elimination of phenol.



We carried out the reaction between 1-aryl-1-ethanimines and orthoesters. 1-Alkoxyl-2-aza-1,3-butadienes (**5a—d**) were obtained similarly as described in Table 2. The yield seemed to become higher with the increase of the steric protection around the carbon–nitrogen double bond to suggest the importance of the steric factor in these reactions. When 1-phenyl-1-pentanimine (**6**) was treated with triisopropyl orthoformate, a mixture of two isomers (**7a**:**7b**=2:1) were formed. The isomer ratio was determined by ^{1}H NMR.

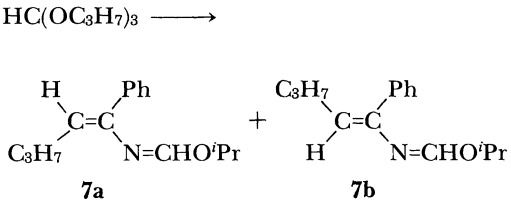
Table 2. 2-Aza-1,3-butadienes (**5**)[a]



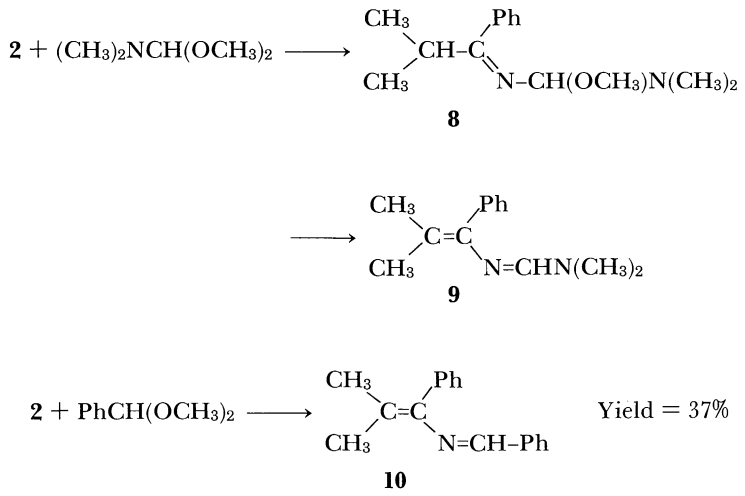
(**5**)

No.	Ar	R^2	Yield/%	Bp/°C/mmHg
a	C_6H_5	Et	11	65—66/0.15
b	2-Me-C_6H_4	Et	20	86—90/1.0
c	C_6H_5	*i*-Pr	28	76—78/0.15
d	2-Me-C_6H_4	*i*-Pr	55	74—75/0.1

a) Reaction was carried out in the presence of small amount of PTS at 140—160 °C for 5 min.



In the course of extention of 2-aza-1,3-butadiene synthesis using ketimines, we have investigated the reaction of ketimines with acetals instead of orthoesters. When *N*,*N*-dimethylformamide dimethylacetal was allowed to react with **2**,1-amino-2-aza-1,3-butadiene (**9**) was obtained as shown in Scheme 2. In this reaction, the formation of intermediate (**8**) proceeded smoothly. Subsequent reaction which involves removal of the methanol from **8** was slow. It was



Scheme 2.

difficult to separate these two compounds (**8** and **9**) by vacuum distillation. To make the reaction complete, longer reaction time at high temperature was required. It was also effective to carry out the reaction under a reduced pressure. R. Gompper and co-worker[7] have reported the synthesis of 4-amino-2-aza-1,3-butadienes by the reaction of *N*,*N*-dimethylformamide diethylacetal with azomethines. Moreover, the treatment of benzaldehyde dimethylacetal with **2** in a similar manner gave 1-phenyl-2-aza-1,3-butadiene (**10**). Since the condensation was rather slow in comparison with that of orthoesters, the competitive formation of **3** and **10** was observed. They could not be separated with each other by distillation under a reduced pressure. These results indicate that acetals, as well as orthoesters, react with ketimine to give 2-aza-1,3-butadienes. Although **10** was similarly prepared by the reaction of **2** with benzaldehyde, the yield was only 5% at 160 °C for 30 min.

In conclusion, the present reaction affords a facile and useful preparative method for 2-aza-1,3-butadienes bearing an alkoxyl or an amino group at the end position. At present, we are trying to prepare biologically active compounds by use of thus obtained 2-aza-1,3-butadienes.

Experimental

The IR spectra were measured with a Hitachi I-2000 spectrometer. The ^{1}H NMR spectra were measured in a $CDCl_3$ solution with a Hitachi R-1500 spectrometer using tetramethylsilane as an internal standard. The mass spectra were obtained on a Hitachi M-80 spectrometer. Elemental analysis data (C, H, and N) agreed within ±0.3% for the calculated values.

Materials. Most of the orthoesters and acetals were commercially available. Triisopropyl orthoformate and tri-*s*-butyl orthoformate were prepared by the transesterification of trimethyl orthoformate and triethyl orthoformate with 2-propanol and 2-butanol, respectively.

Synthesis of Ketimines.[8] Some compounds were prepared by the reaction of benzonitrile with methyllithium or *n*-butyllithium, followed by the addition of ice at low temperature. Some compounds were synthesized by the reaction of aryllithium with isobutyronitrile. The other compounds were prepared by the reaction of aryl Grignard reagent with isobutyronitrile or isopropyl Grignard reagent with arylnitrile.

Synthesis of 2-Aza-1,3-butadienes (1). Method A: A typical procedure is as follows. To a 100 ml flask equipped with distillation head were added 1-(3-methoxy-2-thienyl)-2-methyl-1-propanimine (6.11 g, 33 mmol), triisopropyl orthoformate (6.98 g, 36 mmol) and a small amount of PTS. The mixture was heated in an oil bath (160 °C) for about 20 min until 2-propanol, which was formed during the reaction, was distilled out. The resulting mixture afforded a yellow liquid (5.82 g, 69%) of 1-isopropoxy-3-(3-methoxy-2-thienyl)-4,4-dimethyl-2-aza-1,3-butadiene which boiled at 94 °C/0.1 mmHg (1 mmHg=133.322 Pa) (Table 1, **1j**). ^{1}H NMR ($CDCl_3$) δ=1.28 (6H, d, J=6 Hz, CH_3×2), 1.68 (3H, s, CH_3), 2.00 (3H, s, CH_3), 3.74 (3H, s, OCH_3), 5.10 (1H, quint., J=6 Hz, OCH), 6.76 (1H, d, J=5 Hz, thienyl H), 7.12 (1H, d, J=5 Hz, thienyl H), 7.27 (1H, s, N=CHO); IR(KBr) 1630 cm^{-1} (N=CHO); MS m/z 253 (M^+), 210 ([$M-C_3H_7$]$^+$). Found: C, 61.73; H, 7.53; N, 5.49%. Calcd for $C_{13}H_{19}NO_2S$: C, 61.63; H, 7.56; N, 5.53%.

Method B: A typical procedure is as follows. To a 100 ml flask equipped with distillation head were added 1-phenyl-2-methyl-1-propanimine (10.44 g, 71 mmol), triethyl orthoacetate (15.90 g, 98 mmol) and a small amount of PTS. The mixture was heated in an oil bath (120 °C) for about 15 min until ethanol, which was formed during the reaction, was distilled out. The resulting mixture afforded a pale yellow liquid (10.84 g, 70%) of 1-ethoxy-1,4,4-trimethyl-3-phenyl-2-aza-1,3-butadiene which boiled at 80—82 °C/0.4 mmHg (Table 1, **1m**). ^{1}H NMR ($CDCl_3$) δ=1.25 (3H t, J=7 Hz, CH_3), 1.63 (3H, s, CH_3), 1.73 (6H, s, CH_3×2), 4.13 (2H, q, J=7 Hz, OCH_2), 7.12 (5H, s, aromatic H); IR(KBr) 1670 cm^{-1} (N=CMeO); MS m/z 217 (M^+), 188 ([$M-C_2H_5$]$^+$). Found: C, 77.59; H, 8.66; N, 6.34%. Calcd for $C_{14}H_{19}NO$: C, 77.37; H,

8.81; N, 6.45%.

Method C: A typical procedure is as follows. To a 100 ml flask equipped with distillation head were added 1-(3-methylphenyl)-2-methyl-1-propanimine (10.10 g, 63 mmol) and triethyl orthoformate (10.34 g, 70 mmol). The mixture was heated in an oil bath (110 °C) for about 3 h until ethanol, which was formed during the reaction, was distilled out. The resulting mixture afforded a pale yellow liquid (7.10 g, 52%) of 1-ethoxy-4,4-dimethyl-3-(3-methylphenyl)-2-aza-1,3-butadiene which boiled at 92—94 °C/0.6 mmHg (Table 1, **1c**). ^{1}H NMR ($CDCl_3$) δ=1.28 (3H, t, J=7 Hz, CH_3), 1.59 (3H, s, CH_3), 1.96 (3H, s, CH_3), 2.30 (3H, s, CH_3), 4.20 (2H, q, J=7 Hz, OCH_2), 6.80—7.33 (5H, m, N=CHO and aromatic H); IR(KBr) 1625 cm^{-1} (N=CHO); MS m/z 217 (M^+), 188 ([M−C_2H_5). Found: C, 77.25; H, 8.78; N, 6.50%. Calcd for $C_{14}H_{19}NO$: C, 77.37; H, 8.81; N, 6.45%.

Synthesis of 3. To a 100 ml flask were added **2** (5.06 g, 34 mmol) and a small amount of PTS. The mixture was heated in an oil bath (150 °C) for about 20 min. The resulting mixture afforded a yellow viscous liquid (1.65 g, 35%) of 1-isopropyl-4,4-dimethyl-1,3-diphenyl-2-aza-1,3-butadiene which boiled at 123 °C/0.3 mmHg. ^{1}H NMR ($CDCl_3$) δ=1.18 (6H, d, J=6 Hz, CH_3×2), 1.59 (3H, s, CH_3), 1.65 (3H, s, CH_3), 2.85 (1H, quint., J=6 Hz, OCH), 6.80—7.80 (10H, m, aromatic H); IR(KBr) 1632 cm^{-1} (N=C); MS m/z 277 (M^+).

Synthesis of 5d. To a 100 ml flask equipped with distillation head were added 1-(2-methylphenyl)-1-ethanimine (4.55 g, 39 mmol), triisopropyl orthoformate (8.25 g, 43 mmol) and a small amount of PTS. The mixture was heated in an oil bath (140—150 °C) for about 5 min until 2-propanol was distilled out. The resulting mixture afforded a pale yellow liquid (4.33 g, 55%) of 1-isopropoxy-3-(2-methylphenyl)-2-aza-1,3-butadiene which boiled at 74—75 °C/0.1 mmHg (Table 2, **5d**). ^{1}H NMR ($CDCl_3$) δ=1.27 (6H, d, J=6 Hz, CH_3×2), 2.32 (3H, s, CH_3), 4.56 (1H, s, =CH), 4.92 (1H, s, =CH), 5.10 (1H, quint., J=6 Hz, OCH), 7.19 (4H, m, aromatic H), 7.43 (1H, s, N=CHO); IR(KBr) 1622 cm^{-1} (N=CHO); MS m/z 203 (M^+). Found: C, 76.55; H, 8.32; N, 7.04%. Calcd for $C_{13}H_{17}NO$: C, 76.81; H, 8.43; N, 6.89%.

Synthesis of 7. To a 100 ml flask equipped with distillation head were added **6** (4.93 g, 31 mmol), triisopropyl orthoformate (7.89 g, 41 mmol) and a small amount of PTS. The mixture was heated in an oil bath (160 °C) for about 5 min until 2-propanol was distilled out. The resulting mixture afforded a yellow liquid (3.03 g, 42%) of 1-isopropoxy-4-propyl-3-phenyl-2-aza-1,3-butadiene which boiled at 92 °C/0.15 mmHg. ^{1}H NMR ($CDCl_3$) δ=0.94 (t, J=7 Hz, CH_3), 1.25 (d, J=6 Hz, CH_3×2), 1.35 (d, J=6 Hz, CH_3×2), 1.40—1.70 (m, CH_2), 1.90—2.30 (m, CH_2), 5.11 (quint., J=6 Hz, OCH), 5.24 (t, J=7 Hz, C=CH), 5.45 (t, J=7 Hz, C=CH), 7.10—7.50 (m, N=CHO and aromatic H); IR(KBr) 1648 cm^{-1} (N=CHO); MS m/z 231 (M^+). From the NMR spectrum and GC of the mixture, it was assigned as being a 2:1 mixture of **7a** and **7b**.

Synthesis of 9. To a 100 ml flask were added **2** (4.05 g, 28 mmol), *N*,*N*-dimethylformamide dimethylacetal (3.77 g, 32 mmol) and a small amount of PTS. The mixture was heated in an oil bath (130—150 °C) for about 1h until methanol was distilled out. The resulting mixture afforded a yellow liquid (3.10 g, 56%) of 4,4-dimethyl-1-dimethylamino-3-phenyl-2-aza-1,3-butadiene which boiled at 88 °C/0.15 mmHg. ^{1}H NMR ($CDCl_3$) δ=1.53 (3H, s, CH_3), 2.02

Table 3. ^{1}H NMR Data of 2-Aza-1,3-butadienes

Compound	^{1}H NMR ($CDCl_3$, δ)
1a	1.77 (3H, s, CH_3), 1.94 (3H, s, CH_3), 2.43 (3H, s, CH_3), 3.79 (3H, s, OCH_3), 6.61 (2H, s, thienyl H), 7.42 (1H, s, N=CHO)
1b	1.26 (3H, t, J=7 Hz, CH_3), 1.45 (3H, s, CH_3), 2.01 (3H, s, CH_3), 2.09 (3H, s, CH_3), 4.18 (2H, q, J=7 Hz, OCH_2), 6.90—7.05 (2H, m, aromatic H), 7.08 (2H, s, aromatic H), 7.14 (1H, s, N=CHO)
1d	1.30 (3H, t, J=7 Hz, CH_3), 1.59 (3H, s, CH_3), 1.96 (3H, s, CH_3), 4.25 (2H, q, J=7 Hz, OCH_2), 7.16 (1H, s, N=CHO), 7.43 (4H, brs, aromatic H)
1e	1.25 (6H, d, J=6 Hz, CH_3×2), 1.57 (3H, s, CH_3), 1.96 (3H, s, CH_3), 5.08 (1H, quint., J=6 Hz, OCH), 7.00—7.40 (6H, m, N=CHO and aromatic H)
1f	1.26 (6H, d, J=6 Hz, CH_3×2), 1.47 (3H, s, CH_3), 2.03 (3H, s, CH_3), 2.29 (3H, s, CH_3), 5.07 (1H, quint., J=6 Hz, OCH), 6.95 (1H, s, N=CHO), 7.15 (4H, brs, aromatic H)
1g	1.28 (6H, d, J=6 Hz, CH_3×2), 1.58 (3H, s, CH_3), 1.96 (3H, s, CH_3), 5.10 (1H, quint., J=6 Hz, OCH), 7.01 (2H, s, aromatic H), 7.13 (3H, s, N=CHO and aromatic H)
1h	1.30 (6H, d, J=6 Hz, CH_3×2), 1.87 (6H, s, CH_3×2), 5.16 (1H, quint., J=6 Hz, OCH), 6.17 (1H, d, J=3 Hz, furyl H), 6.34 (1H, t, J=3 Hz, furyl H), 7.35 (2H, s, N=CHO and furyl H)
1i	1.29 (6H, d, J=6 Hz, CH_3×2), 1.76 (3H, s, CH_3), 1.92 (3H, s, CH_3), 5.11 (1H, quint., J=6 Hz, OCH), 6.80—7.25 (3H, m, thienyl H), 7.30 (1H, s, N=CHO)
1k	0.90 (3H, t, J=7 Hz, CH_3), 1.25 (3H, d, J=6 Hz, CH_3), 1.35—1.80 (2H, m, CH_2), 1.58 (3H, s, CH_3), 1.95 (3H, s, CH_3), 4.89 (1H, q, J=6 Hz, CH), 7.00—7.42 (6H, m, N=CHO and aromatic H)
1l	1.62 (3H, s, CH_3), 1.69 (3H, s, CH_3), 1.74 (3H, s, CH_3), 3.64 (3H, s, OCH_3), 7.12 (5H, s, aromatic H)
1n	0.90 (3H, t, J=7 Hz, CH_3), 1.25 (3H, t, J=7 Hz, CH_3), 1.64 (3H, s, CH_3), 1.75 (3H, s, CH_3), 2.09 (2H, q, J=7 Hz, CH_2), 4.14 (2H, q, J=7 Hz, OCH_2), 7.13 (5H s, aromatic H)
1o	0.73 (3H, t, J=6 Hz, CH_3), 1.10—1.60 (2H, m, CH_2), 1.63 (3H, s, CH_3), 1.75 (3H, s, CH_3), 1.90—2.25 (2H, m, CH_2), 3.67 (3H, s, OCH_3), 7.12 (5H, s, aromatic H)
5a	1.36 (3H, t, J=7 Hz, CH_3), 4.32 (2H, q, J=7 Hz, OCH_2), 4.54 (1H, s, =CH), 4.95 (1H, s, =CH), 7.20—7.80 (6H, m, N=CHO and aromatic H)
5b	1.29 (3H, t, J=7 Hz, CH_3), 2.34 (3H, s, CH_3), 4.23 (2H, q, J=7 Hz, OCH_2), 4.58 (1H, s, =CH), 4.94 (1H, s, =CH), 7.19 (4H, s, aromatic H), 7.47 (1H, s, N=CHO)
5c	1.35 (6H, d, J=6 Hz, CH_3×2), 4.53 (1H, s, =CH), 4.94 (1H, s, =CH), 5.18 (1H, quint., J=6 Hz, OCH), 7.20—7.70 (6H, m, N=CHO and aromatic H)

(3H, s, CH_3), 2.84 (6H, s, $CH_3 \times 2$), 6.90 (1H, s, N=CHN), 7.00—7.50 (5H, m, aromatic H); IR(KBr) 1626 cm^{-1} (N=C); MS *m/z* 222(M^+).

Synthesis of 10. To a 100 ml flask were added **2** (4.27 g, 29 mmol), benzaldehyde dimethylacetal (4.68 g, 31 mmol) and a small amount of PTS. The mixture was heated in an oil bath (160 °C) for about 30 min until methanol was distilled out. The resulting mixture afforded a yellow viscous liquid (3.60 g) of 4,4-dimethyl-1,3-diphenyl-2-aza-1,3-butadiene which boiled at 120—125 °C/0.15 mmHg. The obtained liquid contained 70% of **10** and 30% of **3**, which was confirmed by GC. The other 2-aza-1,3-butadienes were prepared by the methods described above. Their ^1H NMR data are summarized in Table 3.

References

1) K. Dietliker and H. Heimgartner, *Helv. Chim. Acta*, **66**, 262 (1983); A. Dehnel, J. P. Finet, and G. Lavielle, *Synthesis*, **1977**, 474; J. Baum, D. Scholz, F. Tataruch, and H. G. Viehe, *Chimia*, **29**, 514 (1975) and references cited therein.

2) T. Saegusa, I. Murase, and Y. Ito, *J. Org. Chem.*, **36**, 2876 (1971).

3) D. H. Aue and D. Thomas, *J. Org. Chem.*, **40**, 1349 (1975).

4) D. J. Brown and K. Ienega, *J. Chem. Soc., Perkin Trans. 1*, **1974**, 372.

5) L. A. Pavlova, Yu. A. Davidovich, and S. V. Rogozhin, *Usp. Khim.*, **55**, 1803 (1986); R. S. Hosmane, *Tetrahedron Lett.*, **25**, 363 (1984).

6) J. Barluenga, J. Joglar, S. Fustero, V. Gotor, C. Krueger, and M. J. Romao, *Chem. Ber.*, **118**, 3652 (1985).

7) R. Gompper and U. Heinemann, *Angew. Chem., Int. Ed. Engl.*, **20**, 296 (1981).

8) P. L. Pickard and D. J. Vaughan, *J. Am. Chem. Soc.*, **72**, 876 (1950); I. Pattison, K. Wade, and B. K. Wyatt, *J. Chem. Soc. A*, **1967**, 837.