

N,N,N',N'-Tetramethylmethanediamine—A New Reagent for Aminomethylation of Acetylenes

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Abstract—A new procedure has been developed for aminomethylation of terminal acetylenes with *N,N,N',N'*-tetramethylmethanediamine in the presence of transition metals and lanthanide complexes and salts. The procedure ensures formation of the corresponding *N,N*-dimethylprop-2-yn-1-amines with high yield and selectivity.

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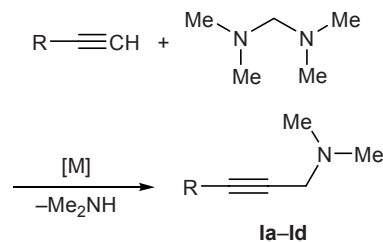
Prop-2-yn-1-amines attract interest as monomers in organic synthesis and as intermediate compounds for the preparation of biologically active substances [1–8]. A convenient method for the synthesis of prop-2-yn-1-amines remains so far classical aminomethylation of terminal alkynes according to Mannich [9] using secondary amines and aldehydes in the presence of copper(I) salts [10–15]. Kabalka et al. [16] recently proposed an improved procedure for aminomethylation of acetylenes by reaction of 1-alkynes with paraformaldehyde and secondary amines in the presence of CuI/Al₂O₃ under microwave irradiation in the absence of a solvent. Prior to our studies, there were no published data on catalytic aminomethylation of terminal alkynes with diamines as synthetic equivalents of formaldehyde and secondary amines.

Taking into account that the known methods for the synthesis of prop-2-yn-1-amines are not free from some disadvantages related to the necessity of using toxic solvents (such as dioxane, *N,N*-dimethylformamide, methylene chloride, acetonitrile, dimethyl sulfoxide, etc.) and considerable (up to stoichiometric) amounts of copper(I) salts, as well as to long reaction times (12–72 h), we now propose a new procedure for the preparation of aminomethyl-substituted acetylenes via reaction of *N,N,N',N'*-tetramethylmethanediamine with acetylene in the presence of a catalytic amount (up to 5 mol %) of *d*-metal and lanthanide salts and complexes. We tested a series of Cu, Nb, Pd, Co, Mn, Zr, Ti, Hf, Ni, V, Fe, and Sm salts and complexes, which are widely used as catalysts. The reactions were car-

ried out under solvent-free conditions. In addition, the effect of the solvent nature (ethanol, hexane, toluene, DMSO) on the yield and selectivity of the process was studied.

In the reaction of oct-1-yne with *N,N,N',N'*-tetramethylmethanediamine (hereinafter referred to as diamine) in the presence of CuCl as catalyst (molar ratio substrate–diamine–CuCl 1:3:0.05) under argon in 6 h afforded 81% of *N,N*-dimethylnon-2-yn-1-amine (**Ia**). Analogous reaction in toluene solution gave compound **Ia** in 95% yield (Scheme 1; Table 1, run nos. 1, 3). When the reaction was carried out in air, the product was hexadeca-7,9-diyne (**IIa**, yield 39%) which was formed via oxidative coupling of initial oct-1-yne. All copper(I) halides showed high catalytic activity and selectivity in toluene used as solvent. Copper(I) iodide favored formation of a considerable amount of dimerization product **IIa**: the yields of **Ia** and **IIa** were, respectively, 63 and 33% under argon and 30 and 66% in air (Table 1, run nos. 11, 12).

Scheme 1.



R = C₆H₁₃ (**a**), C₅H₁₁ (**b**), C₄H₉ (**c**), Ph (**d**).

Table 1. Aminomethylation of oct-1-yne with *N,N,N',N'*-tetramethylmethanediamine (molar ratio diamine–oct-1-yne–catalyst 3 : 1 : 0.05, 80°C, argon atmosphere for copper salts)

Run no.	Catalyst	Time, h (solvent)	Yield of Ia/IIa , %	Run no.	Catalyst	Time, h (solvent)	Yield of Ia/IIa , %
1	CuCl	4 (toluene)	95	13	CuBr	4	61/27
2	CuCl ^a	6	26/39	14	CuBr	4 (toluene)	94
3	CuCl	6	81	15	PdCl ₂	4 (toluene)	79
4	CuCl ₂	4 (toluene)	98	16	Fe(acac) ₃	6	3
5	CuCl ₂	6	98	17	CoCl ₂	4 (DMSO)	15/12
6	CuCl ₂ ^a	6	90/8	18	CoCl ₂	6	19
7	CuCl ₂	4 (EtOH)	14/6	19	CoCl ₂	4 (hexane)	46
8	CuCl ₂	4 (DMSO)	92/6	20	CoCl ₂	4 (EtOH)	52/1
9	CuCl ₂	4 (hexane)	53/48	21	Sm(NO ₃) ₂ ·5H ₂ O	4 (toluene)	82
10	CuI	4 (toluene)	96	22	Sm(NO ₃) ₂ ·5H ₂ O	4	21
11	CuI	6	63/33	23	VO(acac) ₂	6	23
12	CuI ^a	4	30/66	24	VO(acac) ₂	4 (toluene)	95

^a The reaction was carried out on exposure to air.

In the aminomethylation of oct-1-yne under argon in the presence of CuCl₂ (molar ratio 1-octyne–diamine–CuCl₂ 1 : 3 : 0.05; 80°C, 6 h), the yield of **Ia** increased to 98%. When the reaction was carried out on exposure to air, the yield of **Ia** was 90%, and up to 8% of **IIa** was obtained (Table 1, run no. 6).

The use of toluene as solvent almost did not change the reaction direction, and compound **Ia** was obtained in 98% yield in 4 h. In DMSO, the yield of amine **Ia** was 92%, and the reaction was accompanied by formation of dimeric product **IIa** (6%). The reaction in diethyl ether was characterized by reduced conversion of the initial acetylene (20%), the yield of amine **Ia** was as poor as 14%, and 6% of by-product **IIa** was formed (Table 1, run nos. 7, 8). The complexes Cu(acac)₂, NbCl₅, SnCl₂, SnCl₄, MnCl₂, ZrCl₄, Hf(acac)₄, Pd(acac)₂–PPh₃, Ni(acac)₂–PPh₃, Cp₂ZrCl₂, Cp₂TiCl₂, and Fe(acac)₃ showed no appreciable catalytic activity. No aminomethylation occurred in the absence of catalyst.

Our further study revealed high catalytic activity and selectivity in the aminomethylation of oct-1-yne in the presence of VO(acac)₂ and Sm(NO₃)₂·5H₂O. These catalysts (5 mol %) ensured formation of the aminomethylation product in 95 and 82%, respectively, in toluene at 80°C in 4 h (Table 1, run nos. 21, 24). Under the optimal conditions, we performed aminomethylation of hept-1-yne and hex-1-yne with *N,N,N',N'*-tetramethylmethanediamine in the presence of the most catalytically active Cu, V, and Sm com-

pounds and isolated the corresponding prop-2-yn-amines in more than 90% yield. Aminomethylation of phenylacetylene gave *N,N*-dimethyl-3-phenylprop-2-yn-1-amine (**Id**) whose yield reached ~98% in the presence of VO(acac)₂ and Sm(NO₃)₂·5H₂O as catalyst. Copper(II) chloride showed a lower catalytic activity in the aminomethylation of phenylacetylene: the

Table 2. Aminomethylation of phenylacetylene with *N,N,N',N'*-tetramethylmethanediamine (molar ratio diamine–phenylacetylene–catalyst 3 : 1 : 0.05, 80°C, argon atmosphere for copper salts, 4 h)

Run no.	Catalyst	Solvent	Yield of Id/IIId , %
1	VO(acac) ₂	Toluene	98
2	Sm(NO ₃) ₂ ·5H ₂ O	None	98
3	VO(acac) ₂	None	82
4	CuCl ₂	None	82/10
5	Cp ₂ ZrCl ₂	None	72
6	Cp ₂ TiCl ₂	None	61
7	CoCl ₂	Toluene	51
8	MnCl ₃	Toluene	38
9	SnCl ₂	Toluene	17
10	NbCl ₅	Toluene	12
11	ZrCl ₄	Toluene	5
12	Cu(acac) ₂	Toluene	–
13	PdCl ₂	Toluene	–
14	Fe(acac) ₃	Toluene	–

Table 3. Aminomethylation of hepta-1,6-diyne with *N,N,N',N'*-tetramethylmethanediamine (molar ratio diamine–phenylacetylene–catalyst 3:1:0.05, 80°C, argon atmosphere for copper salts, 4 h)

Run no.	Catalyst	Solvent	Yield of IIIa/IVa , %
1	Sm(NO ₃) ₂ ·5H ₂ O	Toluene	98
2	VO(acac) ₂	Toluene	96
3	VO(acac) ₂	None	88
4	CuCl ₂	None	77
5	Sm(NO ₃) ₂ ·5H ₂ O	None	41
6	CuCl ₂	EtOH	20/15
7	CuCl ₂	Hexane	8/70

yield of **Id** was only 82% in 6 h, and ~10% of 1,4-diphenylbut-2-yne (**IId**) was formed (Table 2, run no. 5). Apart from the above catalysts, Cp₂ZrCl₂ and Cp₂TiCl₂ turned out to be fairly active in the aminomethylation of phenylacetylene (Table 2, run nos. 5, 6).

With a view to extend the scope of the developed procedure, we examined aminomethylation of terminal diacetylenic compounds with *N,N,N',N'*-tetramethylmethanediamine. The reaction of hepta-1,6-diyne with *N,N,N',N'*-tetramethylmethanediamine at a ratio of 1:3 in toluene in the presence of 5 mol % of VO(acac)₂ or Sm(NO₃)₂·5H₂O involved both terminal C–H bonds in the substrate and resulted in selective formation of *N,N,N',N'*-tetramethylnona-2,7-diyne-1,9-diamine (**IIIa**) in 96 and 98% yield, respectively (Scheme 2; Table 3, run nos. 1, 2). Likewise, octa-1,7-diyne and deca-1,9-diyne gave rise to the corresponding bisaminomethyl derivatives in more than 95% yield. Copper halides were less active as catalysts in these reactions. For example, in the presence of 5 mol % of CuCl₂ under solvent-free conditions, the yield of **IIIa** was 77%, and it decreased to 20 and 8% in going to ethanol and hexane as solvent, respectively; in addition, the reaction was accompanied by formation of the

corresponding oxidative coupling product (Table 3, run nos. 6, 7).

Thus we have developed a new procedure for the aminomethylation of terminal acetylenes with *N,N,N',N'*-tetramethylmethanediamine using transition *d*-metal and lanthanide salts and complexes as catalysts, which ensures preparation of the target *N,N*-dimethylprop-2-ynamines with high yield (>95%) and selectivity (~100%).

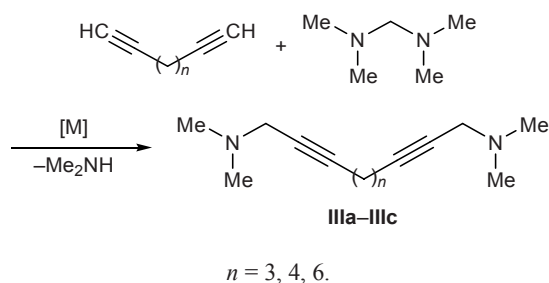
EXPERIMENTAL

The purity of the products was checked by TLC on Silufol plates using acetone–methanol [9:(2–3)], acetone–chloroform (9:1), and acetone–ethanol (9:1) as eluents. Initial terminal acetylenes were commercially available products, and solvents of chemically pure grade were used. The mass spectra were recorded on a VG-Trio instrument. The ¹H and ¹³C NMR spectra were measured on a Jeol FX-90Q spectrometer at 22.5 MHz for ¹³C and 90 MHz for ¹H; CDCl₃ was used as solvent, and tetramethylsilane, as internal reference. The IR spectra were obtained in KBr on a Specord 75IR spectrometer. The elemental compositions were determined on a Carlo Erba 1106 analyzer. The UV spectra were recorded on a Specord M40 spectrophotometer. GLC analysis was performed on a Khrom-5 chromatograph equipped with a flame ionization detector and a 2000×3-mm column (stationary phase SE-30); oven temperature programming from 50 to 280°C at 8 deg/min; injector temperature 300°C, detector temperature 250°C.

General procedure for aminomethylation of terminal acetylenes with *N,N,N',N'*-tetramethylmethanediamine. A glass reactor equipped with a magnetic stirrer was filled with argon and charged with 0.1 mmol of the corresponding terminal acetylene, 0.3 mmol of *N,N,N',N'*-tetramethylmethanediamine, and 0.001–0.005 mmol of the catalyst, and the mixture was stirred for 6 h at 80°C under argon. Dimers **IIa**, **IId**, and **IVa** formed as by-products from initial acetylenes were identified by comparing with samples synthesized according to the procedure described in [17].

***N,N*-Dimethylnon-2-yn-1-amine (Ia).** bp 75–76°C (3 mm). IR spectrum: ν 1255 cm⁻¹. ¹H NMR spectrum, δ , ppm: 0.89 t (3H, *J* = 6.09 Hz), 1.2–1.97 m (8H), 1.98 t (2H, *J* = 6.69 Hz), 2.19 s (6H), 3.21 s (2H). ¹³C NMR spectrum, δ _C, ppm: 13.70, 18.84, 22.26, 28.25, 28.38, 31.09, 43.72, 48.18, 75.66, 84.90. Mass spectrum, *m/z* (*I*_{rel}, %): [*M*]⁺ 167 (26.47), 166 (100), 152 (14.7), 138 (11.76), 110 (35.8), 108 (14.6), 96

Scheme 2.



(35.29), 94 (41.18), 82 (91.18), 58 (32.35). Found, %: C 78.90; H 12.78; N 7.46. $C_{11}H_{21}N$. Calculated, %: C 79.04; H 12.57; N 8.39.

N,N-Dimethyloct-2-yn-1-amine (Ib). bp 61–62°C (3 mm). 1H NMR spectrum, δ , ppm: 0.95–1.4 m (6H), 2.12 t (2H, $J = 6.87$ Hz), 2.20 s (6H), 3.14 s (2H). ^{13}C NMR spectrum, δ_C , ppm: 13.82, 18.35, 22.38, 28.21, 31.08, 43.71, 48.02, 75.10, 84.90. Found, %: C 77.02; H 12.19; N 9.41. $C_{10}H_{19}N$. Calculated, %: C 78.43; H 12.42; N 9.15.

N,N-Dimethylhept-2-yn-1-amine (Ic). bp 49–50°C (3 mm). UV spectrum: λ_{max} 289 nm. IR spectrum: ν 1255 cm^{-1} . 1H NMR spectrum, δ , ppm: 0.88 (3H, $J = 6.2$ Hz), 1.3–1.7 m (4H), 2.06–2.12 t (2H, $J = 6.68$ Hz), 2.20 s (6H), 3.19 s (2H). ^{13}C NMR spectrum, δ_C , ppm: 13.00, 17.80, 20.96, 30.21, 42.9, 47.14, 74.14, 83.93. Found, %: C 76.91; H 12.01; N 9.81. Calculated, %: C 77.70; H 12.23; N 10.07.

N,N-Dimethyl-3-phenylprop-2-yn-1-amine (Id). bp 86–87°C (3 mm). UV spectrum: λ_{max} 279 nm. IR spectrum, ν , cm^{-1} : 2240 (C \equiv C), 1250 (N–C), 1590 (C–C $_{arom}$). 1H NMR spectrum, δ , ppm: 2.06 s (6H), 3.17 s (2H), 7.21–7.28 m (5H, H_{arom}). ^{13}C NMR spectrum, δ_C , ppm: 43.53, 48.02, 84.32, 84.88, 123.04, 128.18, 128.57, 131.67. Mass spectrum, m/z (I_{rel} , %): $[M]^+$ 159 (52.5), 158 (100), 143 (20.6), 144 (6.25), 129 (3.12), 115 (100), 89 (28.0), 82 (53.0), 63 (18.6). Found, %: C 81.84; H 8.43; N 8.54. $C_{11}H_{13}N$. Calculated, %: C 83.02; H 8.18; N 8.80.

N,N,N',N'-Tetramethylnona-2,7-diyne-1,9-diamine (IIIa). bp 79–80°C (3 mm). 1H NMR spectrum, δ , ppm: 1.52–1.81 m (2H), 2.10 t (4H, $J = 6.77$ Hz), 2.19 s (12H), 3.23 s (4H). ^{13}C NMR spectrum, δ_C , ppm: 18.28, 23.36, 43.75, 48.42, 75.71, 84.42. Found, %: C 74.78; H 10.10; N 13.98. $C_{13}H_{22}N_2$. Calculated, %: C 75.73; H 10.68; N 13.59.

N,N,N',N'-Tetramethyldeca-2,8-diyne-1,10-diamine (IIIb). bp 91°C (3 mm). IR spectrum: ν 1270 cm^{-1} . 1H NMR spectrum, δ , ppm: 1.47 t (4H, $J = 6.87$ Hz), 2.19 s (12H), 2.2–2.5 m (4H), 3.11 s (4H). ^{13}C NMR spectrum, δ_C , ppm: 18.65, 27.89, 43.80, 48.12, 75.66, 84.71. Found, %: C 75.9; H 11.30; N 11.92. $C_{14}H_{24}N_2$. Calculated, %: C 76.36; H 10.92; N 12.72.

N,N,N',N'-Tetramethyldodeca-2,10-diyne-1,12-diamine (IIIc). bp 103–105°C (3 mm). 1H NMR spec-

trum, δ , ppm: 1.07–1.67 m (8H), 2.02 t (4H, $J = 6.68$ Hz), 2.18 s (12H), 2.96 s (4H). ^{13}C NMR spectrum, δ_C , ppm: 18.58, 28.10, 28.36, 42.75, 48.65, 75.67, 84.35. Found, %: C 76.98; H 11.31; N 10.95. $C_{16}H_{28}N_2$. Calculated, %: C 77.44; H 11.27; N 11.29.

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