

2-(*N*-Methylanilino)-2-phenylthioacetonitrile: a Useful Reagent for Preparation of Conjugated α -Amino Alkenenitriles *via* Tandem Alkylation and Dehydrosulphenylation

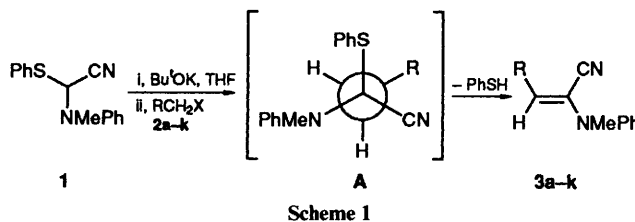
Jim-Min Fang* and Chih-Cheng Chen

Department of Chemistry, National Taiwan University, Taipei, Taiwan 10764, Republic of China

Alkylation of the anion of 2-(*N*-methylanilino)-2-phenylthioacetonitrile **1** with halogenoalkanes resulted in concurrent elimination of benzenethiol to give conjugated α -aminoalkenenitriles of *2E*-configuration. Counterattack by bromide and benzenethiolate ions was observed in the prolonged reactions of **1** with 1,4-dibromobut-2-ene and 3-bromo-1-(trimethylsilyl)prop-1-yne.

α -Aminonitrile alkenes and dienes have been extensively studied for both their special captodative effects¹ and general use in organic synthesis, where they can function as acceptors in Michael reactions,² substrates in Diels–Alder reactions,³ and radicophiles in intramolecular cyclisations.⁴ Previous methods for preparation of α -aminoalkenenitriles include (1) condensation of 2-aminoacetonitrile with an aldehyde or an α,β -unsaturated aldehyde by using the Peterson method or related procedures,⁵ (2) condensation of an α -chloroacetaldehyde or an α,β -unsaturated aldehyde with an amine and KCN (the Strecker procedure), followed by base-catalysed dehydrochlorination or double bond migration,^{3,6} and (3) treatment of an amide with phosgene followed by substitution with cyanide ion.⁷ Besides being tedious to carry out, these methods are limited to the availability of starting materials, and are hardly applicable to

compounds containing other sensitive functional groups. We herein describe an expeditious preparative method for various α -amino alkenenitriles by using the title reagent **1** and alkyl halides **2** (Scheme 1).



The title compound, 2-(*N*-methylanilino)-2-phenylthio-

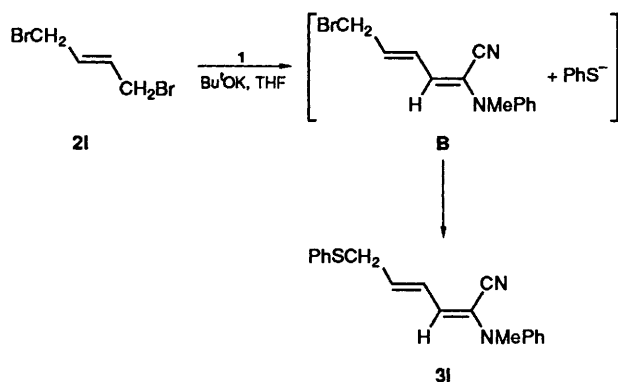
Table 1. Conjugated α -aminoalkenenitriles prepared from **1** and halides

Entry	Alkyl halide 2	Reaction temp. ($^{\circ}$ C)	Reaction time (h)	Product ^a (% yield)	R	Literature method ^d % yield (<i>E</i> : <i>Z</i>)
1	MeI	RT*	1	3a (83)	H	(1); ^e 83
2	EtI	RT	1.5	3b (82)	Me	
3	BuI	RT	12	3c (61)	Pr	(1); ^f 58 (mixture)
4	Br(CH ₂) ₃ I	60	24	3d (62)	Br(CH ₂) ₂	
5	I(CH ₂) ₅ I	RT	20	3e (50)	I(CH ₂) ₄	
6	ICH ₂ CO ₂ Et	60	24	3f (72)	CO ₂ Et	
7	PhCH ₂ Br	RT	1.5	3g (64)	Ph	(1); ^f 100 (mixture)
8	CH ₂ =CHCH ₂ Br	RT	20	3h (61)	CH ₂ =CH	(1); ^g 78 (2:1)
9	PhCH=CHCH ₂ Cl	60	1	3i (63)	PhCH=CH	(1); ^h 85 (1:1)
10	MeCH=CHCH ₂ Cl	60	24	3j (61) ^b	MeCH=CH	(1); ^h 84 (1:1)
11	BrCH=CHCH ₂ Br	RT	12	3k (72)	BrCH=CH	
12	BrCH ₂ CH=CHCH ₂ Br	RT	50	3l (60)	PhSCH ₂ CH=CH	
13	MeSi ₃ CCCH ₂ Br	RT	72	3m (55) ^c	PhSCH=CH	

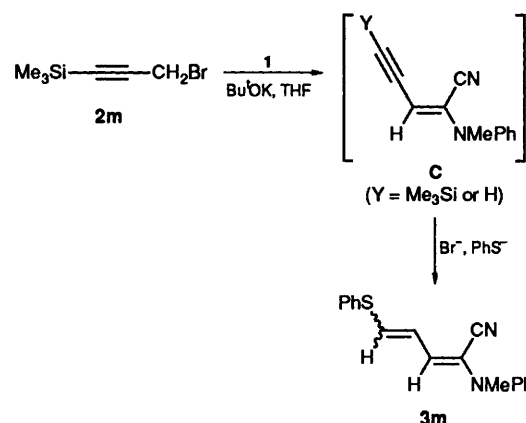
RT = room temp. ^a All new products are characterised by spectral methods (IR, MS, ¹H and ¹³C NMR) and combustion analyses. ^b The prepared α -aminoalkenenitriles **3** are exclusively of the *2E*-form, except for **3j** which consists of *2E*- and *2Z*-isomers (2:1). ^c The product mixture is composed of the *2E,4E*- and *2E,4Z*-dienenitriles in a ratio of 3:2. ^d Refer to the previous method (1) described in the text. ^e By addition of α -aminoacetonitrile with formaldehyde according to the Peterson method, see ref. 2. ^f By the Peterson method, see ref. 5 (K. Takahashi *et al.*). ^g The allylic alcohol obtained by addition of 2-aminoacetonitrile to acrolein was activated as the acetate and subjected to base-catalysed elimination, see ref. 5 (C. C. Lin). ^h By the Peterson method, see ref. 3 (J. M. Fang *et al.*).

acetonitrile⁸ was prepared in 91% yield from 2-(*N*-methyl-anilino)acetonitrile by deprotonation with lithium di-isopropylamide and subsequent treatment with diphenyl disulphide in THF solution. Compound **1** is a colourless solid, m.p. 61–61.5 $^{\circ}$ C (from hexane). It is stable, and no apparent decomposition occurs after storage for months under a nitrogen atmosphere at room temperature. To prepare α -aminoalkenenitriles **3a–f** (Table 1), compound **1** was simply treated with equimolar amounts of Bu^tOK and iodoalkanes in THF solution either at room temperature or with mild heating. These reactions are selective in giving the monosubstitution products **3d** and **3e** with retention of other halogen atoms (entries 4 and 5). If allylic bromides or allylic chlorides were used instead of iodoalkanes, the α -amino dienenitriles were then obtained in modest yields (entries 8–12).

The nature of intermediate **A** was characterised by NMR spectral analyses when iodomethane or allyl bromide was used as the alkylating agent.⁹ The facile elimination of the benzenethiol molecule, occurring either under the alkaline reaction conditions or during the SiO₂ chromatographic work-up, is presumably promoted by the electron-donating α -amino group.¹⁰ The conjugated alkenenitriles **3** of *2E*-configuration were exclusively obtained as the consequence of *anti* elimination of benzenethiol and the thermodynamic stability of products. Counterattack of the benzenethiolate ion on the intermediate **B** is shown for the reaction product **3l** (Scheme 2). The diene-



nitrile **3m** is conceivably derived from desilylation of the intermediate **C** followed by addition of benzenethiol to the enyne intermediate (*Y* = H, Scheme 3).¹¹



In summary, utilisation of the title reagent to prepare conjugated α -aminonitrile alkenes and dienes has several advantages: (1) The starting reagent **1** is stable and easily prepared on a large scale. (2) The reactions of **1** are simply brought about under mild conditions with the many readily available alkyl halides which may incorporate other functional groups. (3) The current method is stereoselective to afford *2E*-alkenenitriles that cannot be realised in pure isomeric form by earlier methods.^{2–4} Besides a number of well-documented applications,^{2–4} the described α -anilinoalkenenitriles **3a–m** may be further transformed by photochemical cyclisation into a variety of 2-cyanoindoles compounds of importance for alkaloid synthesis.¹²

Experimental

Typical Procedure.—To a solution of Bu^tOK (113 mg, 1 mmol) in THF (8 ml) was added a solution of 2-(*N*-methyl-anilino)-2-phenylthioacetonitrile (254 mg, 1 mmol) in THF (2 ml) at room temperature. After 20 min, the resulting

pale yellow solution was treated with 1,3-dibromopropene (1.1 mmol, 0.11 ml). The brownish yellow turbid mixture was stirred at room temperature for 12 h and then quenched with saturated aqueous NH_4Cl . After removal of THF under reduced pressure the residue was extracted with EtOAc. The combined extracts were concentrated and passed through a column of silica gel to give the desired product 5-bromo-2-(*N*-methylanilino)penta-2,4-dienenitrile **3k** (189 mg, 72%).

Acknowledgements

We are grateful to the National Science Council for financial support of this work.

References and Footnotes

- 1 H. G. Viehe, Z. Janousek, R. Merenyi and L. Stella, *Acc. Chem. Res.*, 1985, **18**, 148.
- 2 H. Ahlbrecht and K. Pfaff, *Synthesis*, 1978, 897; 1985, 421; J. M. Fang and H. T. Chang, *J. Chem. Soc., Perkin Trans. 1*, 1988, 1945.
- 3 J. L. Boucher and L. Stella, *Tetrahedron*, 1985, **41**, 875; J. M. Fang, C. C. Yang and Y. W. Wang, *J. Org. Chem.*, 1989, **54**, 477.
- 4 J. M. Fang, H. T. Chang and C. C. Lin, *J. Chem. Soc., Chem. Commun.*, 1988, 1385.
- 5 B. Costisella and H. Gross, *Tetrahedron*, 1982, **38**, 139; K. Takahashi, K. Shibasaki, K. Ogura and H. Iida, *J. Org. Chem.*, 1983, **48**, 3566; J. M. Fang and C. C. Yang, *J. Chem. Soc., Chem. Commun.*, 1985, 1356; C. C. Lin, M.S. Thesis, National Taiwan University, 1989.
- 6 D. Dopp and M. Pies, *J. Chem. Soc., Chem. Commun.*, 1987, 1734.
- 7 J. Toye and L. Ghosez, *J. Am. Chem. Soc.*, 1975, **97**, 2276; B. Lesur, J. Toye, M. Chantrenne and L. Ghosez, *Tetrahedron Lett.*, 1979, 2835.
- 8 Compound **1**: ν_{max} (KBr) 2237 cm^{-1} (CN); m/z 254 [$\text{M}]^+$, 145 (base peak); δ_{H} (CDCl_3) 3.05 (s, NCH_3), 5.8 (s, 1 H) and 6.8–7.6 (m, 10 H); δ_{C} (CDCl_3) 35.5 (NCH_3), 61.7 (C-2), 116.5 (CN), 121.5, 129.5, 129.6, 129.9, 135.7 and 146.7. The analogous compound 2-dimethylamino-2-methylthioacetonitrile has been reported as liquid (S. A. Okecha and F. Stansfield, *J. Chem. Soc., Perkin Trans. 1*, 1977, 1811).
- 9 The intermediate **A** (R = Me) showed two singlets at δ_{H} 1.6 and 3.15 attributable to the 2-Me and *N*-Me groups, while the one with R = $\text{CH}_2=\text{CHCH}_2$ displayed proton resonances at δ 2.6 (m, 1 H), 2.9 (m, 1 H), 3.15 (s, 3 H), 5.0–5.2 (m, 2 H), 5.7–6.0 (m, 1 H) and 7.0–7.4 (m, 10 H).
- 10 A. Padwa, W. Dent, H. Nimmesgern, M. K. Venkatramanan and G. S. K. Wong, *Chem. Ber.*, 1986, **119**, 813.
- 11 J. R. Hwu and B. A. Gilbert, *Tetrahedron*, 1989, **45**, 1233.
- 12 H. T. Chang, M.S. Thesis, National Taiwan University, 1987.

Paper 0/042601

Received 31st July 1990

Accepted 20th September 1990