Direct and Selective *N*-Monoalkynylation and *N*-Monoalkenylation of Anilines with Alky(e)nyl Methanesulfonates Using Methylmagnesium Bromide as a Base

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Several anilines were directly *N*-monoalkynylated and *N*-monoalkenylated with alkynyl methanesulfonates and alkenyl methanesulfonates, respectively, using methylmagnesium bromide as a base in good yields with high selectivities.

Many methods have been developed for the *N*-monoalkylation of anilines.[1] These include direct *N*-monoalkylation using alkyl halides,[2] methyl sulfites,[3] trifluoromethanesulfonates,[4] and phosphonium salts,[5] which are simple and straightforward, however, liable to cause a serious problem of accompanying *N*,*N*-dialkylation. To circumvent this defect, indirect methods through partially protecting anilines have been frequently employed. Another direct and effective method utilizes the reductive *N*-monoalkylation using anilines and ketones (or aldehydes).[6]

Meanwhile, *N*-alkynyl and *N*-alkenyl anilines are recognized as useful precursors for preparing various amino arenes and nitrogen-containing heterocycles.[1] However, most of the direct procedures for the *N*-monoalkylation could hardly be applied to *N*-monalky(e)nylations due to the following reasons: (a) the tendency of dialky(e)nylation is higher than that of the simple *N*-dialkylation due to stereo- and electronic reasons; and (b) the reductive *N*-monoalkylation is liable to suffer from undesirable hydrogenation of the multiple bonds.[1] Monoalky(e)nylations of the active methylene compounds meet with such a similar problem.[7] One of the successful methods worth noting is the *C*-monopropargylation of dialkyl 3-oxopentanedioates using magnesium alkoxides as the bases, wherein the dimeric magnesium enolate complex fairly circumvents the undesirable dipropargylation.[8]

In connection with our studies on the effective silylations[9] and sulfonylations[10] of alcohols, we planned to make good use of alky(e)nyl methanesulfonates (mesylates). We report here a direct and practical method for the *N*-monolky(e)nylation using alky(e)nyl mesylates and magnesium salts of the anilines.

First, we examined the *N*-alkynylation of magnesium amide of aniline **(1a)** (prepared from aniline and MeMgBr) with 1-bromo-2-propyne (propargyl bromide), but this reaction proceeded with moderate selectivity; for example, *N*-monopropargylated aniline **4a** (55% conversion yield analyzed by GC) and the *N*,*N*-dipropargylated aniline (15% as such) were obtained under the standard conditions (*vide supra*). Taking into account this result and also the explosive nature of 2-alkynyl halides,[10,11] we replaced them with 2-alkynyl mesylates **2** which are easy to handle and more reactive. These reactions were found to proceed not only more smoothly but also much more selectively to give *N*-monoalkynylated anilines **4** (Scheme 1). Table 1 lists these results.

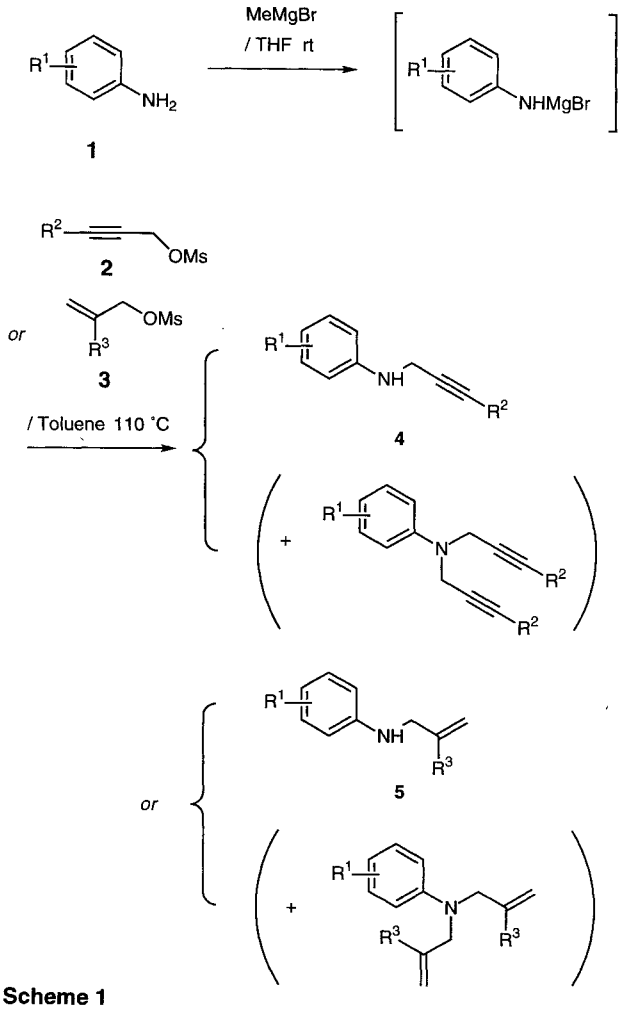
We next applied the similar procedure to a selective *N*-monoalkenylation of anilines **1**, whose results are shown in Table 2. As expected, these reactions as well as the *N*-monoalkynylations proceeded in good yields and with good selectivities. As solvent, toluene was found to be much better than CH_2Cl_2, THF, MeCN, and DMF. The use of toluene should be practical and desirable in view of the environmental standpoints. It should be noted that the removal of the solvent THF which was contained in MeMgBr reagent during these reactions significantly accelerated the conversion of **3**. We suppose that THF tightly coordinates the magnesium amides to form a stable complex for the alky(e)nylation. Use of other bases such as BuMgCl and *t*-BuMgCl did not give significantly better results than MeMgBr.

The higher selectivity of the present *N*-alky(e)nylations would be accounted for by a similar effect in the afore-

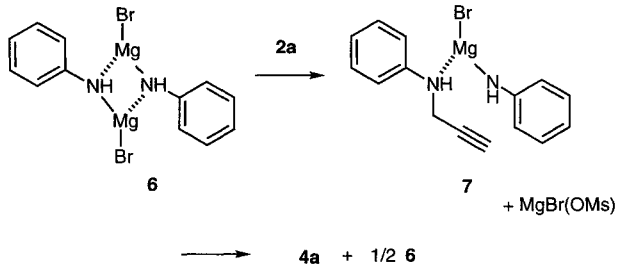
Table 1. Monoalkynylation of Anilines **1** Using Alkynyl Mesylates **2**

Aniline	R^1	Alkynyl Mesylate	R^2	Product	Ratio[a] mono **4**/di	Yield (%)
1a	H	**2a**	H	**4a**	93:7	76
		2b	Me	**4b**	96:4	78
		2c	Ph	**4c**	95:5	70
1b	4-Me	**2a**	H	**4d**	96:4	83
1c	4-MeO	**2a**	H	**4e**	95:5	80
1d	2-Cl	**2a**	H	**4f**	99:trace	76
1e	3-CF_3	**2a**	H	**4g**	92:8	73
1a	H	**2a**	H	**4a**	68:32	58[b]
1e	3-CF_3	**2a**	H	**4g**	53:47	42[b]

[a] The ratio of mono- and dialkynylated products was determined by GC.
[b] The reaction was carried out using K_2CO_3 as a base in the place of MeMgBr (DMF solvent and at r.t. for 10 h).



Scheme 1



Scheme 2

mentioned case of the *C*-monopropargylation of dialkyl 3-oxopentanedioates. Following is a plausible reaction mechanism exemplified by the *N*-monopropargylation (Scheme 2). The initially formed magnesium anilide is transformed into a binuclear structure-complex **6**, which in turn undergoes the propargylation with 2-propynyl mesylate **2a** to give the intermediate **7**. Then, the relatively unstable intermediate **7** is immediately rearranged to give (reform) a half molar amount of complex **6** yielding the desired product **4a**.

For comparison, we carried out the reaction of anilines **1a** or **1e** with **2a**, using K_2CO_3, KOH, NaH, and KH as the inorganic bases, and **1a** and **1e** themselves as the amine bases, under several conditions: temperature: from room temperature to 100 °C; solvent: toluene, THF, DMF. All these experiments resulted in the substantial formation of the *N*,*N*-dipropargyl anilines (minimum 15–20 %) when more than 80 % consumption of **1a** and **1e**. These results suggest the preferential formation of bimolecular like complex **6** which contributes to the selective *N*-monoalky(e)nylation.

Melting points were determined using a hot-stage apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a JEOL EX-90 (90 MHz) spectrometer using TMS as an internal standard in $CDCl_3$. IR spectra were recorded on a Hitachi 270–30 spectrophotometer. MS spectra were recorded on JMS-AutoMass 50 KTR-3. Analytical GC were performed on a Shimadzu GC-7A with a DB-1701 widebore column (15 m × 0.545 mm). Alkynyl and alkenyl mesylates were prepared by the reported method.[10] Reagents were of commercial grade and were used without further purification. The solvents were purified by standard methods. Column chromatography was performed using Merck (Art. 7734 and/or 9385) silica gel.

N-(Prop-2-ynyl)aniline (4a); Typical Procedure:

MeMgBr (1 M THF solution; 24.0 mL, 24.0 mmol) was added to a stirred solution of aniline (**1a**; 1.86 g, 20.0 mmol) in THF (20.0 mL) maintained at 20–30 °C with the help of a water bath, and the mixture was stirred at that temperature for 1 h. The color of the mixture changed from light yellow to dark brown. Then, prop-2-ynyl mesylate (**2a**; 3.22 g, 24.0 mmol) in toluene (40.0 mL) was added to the mixture at 25–30 °C. The mixture was gradually heated to 100 °C during 1 h with evaporation of THF and it was kept at 110 °C for 20 h. Then, precipitates gradually appeared and the GC analysis indicated >90 % consumption of aniline **1a**. The mixture was poured onto ice sat NH_4Cl solution and extracted with Et_2O. The organic phase was washed with H_2O and brine, dried (Na_2SO_4) and concentrated. The crude oil obtained was purified by silica gel column chromatography (hexane/EtOAc, 14:1) to give 1.93 g (74 %) of **4a**[12] as a light brown oil and 0.22 g (6 %) of *N*,*N*-bis(prop-2-ynyl)aniline as a light brown oil.

IR (neat): ν = 3402, 2185, 1604 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 2.30 (1 H, t J = 2.0 Hz), 4.19 (2 H, d, J = 2.0 Hz), 6.68–7.50 (6 H, m).

MS (70 eV): *m*/*z* (rel intensity) = 131 (55), 130 (100), 77 (34).

Table 2. Monoalkynylation of Anilines **1** Using Alkynyl Mesylates **3**

Aniline	R^1	Alkynyl Mesylate	R^3	Product	Ratio[a] mono **5**/di	Yield (%)
1a	H	**3a**	H	**5a**	91:9	74
		3b	Me	**5b**	98:2	84
1b	4-Me	**3a**	H	**5c**	95:5	75
1c	4-MeO	**3a**	H	**5d**	95:5	80
1d	2-Cl	**3a**	H	**5e**	99:trace	83
1e	3-CF_3	**3a**	H	**5f**	93:7	82

[a] The ratio of mono- and dialkenylated products was determined by GC.

N-(But-2-ynyl)benzenamine **(4b)**:[12] light brown oil.

IR (neat): ν = 3405, 1605 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 1.81 (3 H, t, J = 2.0 Hz, 3.87 (2 H, q, J = 2.0 Hz), 6.58–7.42 (6 H, m).

MS (70 eV): m/z (rel intensity) = 145 (100), 144 (92), 130 (19).

N-(3-Phenylprop-2-ynyl)benzenamine **(4c)**:[13] brown oil.

IR (neat): ν = 3407, 1603 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 4.18 (2 H, s), 6.63–7.60 (11 H, m).

MS (70 eV): m/z (rel intensity) = 207 (90), 206 (84), 115 (100).

4-Methyl-N-(prop-2-ynyl)benzenamine **(4d)**:[14] light brown needles, mp 44.0–44.5 °C.

IR (KBr): ν = 3393, 2105, 1615 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 2.18 (1 H, t, J = 2.0 Hz), 2.26 (3 H, s), 3.89 (2 H, d, J = 2.0 Hz), 6.59–6.68 (2 H, d, J = 10.0 Hz), 6.99–7.10 (3 H, m).

MS (70 eV): m/z (rel intensity) = 145 (100), 144 (95), 130 (55).

4-Methoxy-N-(prop-2-ynyl)benzenamine **(4e)**:[15] brown oil.

IR (neat): ν = 3378, 2160, 1514 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 2.11 (1 H, t, J = 2.0 Hz), 3.71 (3 H, s), 3.91 (2 H, d, J = 2.0 Hz), 6.60–6.98 (5 H, m).

MS (70 eV): m/z (rel intensity) = 161 (100), 146 (57), 122 (94).

2-Chloro-N-(prop-2-ynyl)benzenamine **(4f)**: brown oil.

IR (neat): ν = 3416, 2115, 1599 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 2.24 (1 H, t, J = 2.0 Hz), 4.02 (2 H, d, J = 2.0 Hz), 6.60–7.48 (5 H, m).

MS (70 eV): m/z (rel intensity) = 165 (81), 164 (67), 130 (100).

N-(Prop-2-ynyl)-3-(trifluoromethyl)benzenamine **(4g)**:[16] brown oil.

IR (neat): ν = 3416, 2190, 1616 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 2.24 (1 H, t, J = 2.0 Hz), 3.94 (2 H, d, J = 2.0 Hz), 6.75–7.44 (5 H, m).

MS (70 eV): m/z (rel intensity) = 199 (92), 198 (100), 130 (33).

N-Allylbenzenamine **(5a)**:[17] light brown oil.

IR (neat): ν = 3414, 1602, 920 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 3.78 (2 H, d, J = 5.0 Hz), 5.08–5.42 (2 H, m), 5.77–6.21 (1 H, m), 6.52–7.37 (6 H, m).

MS (70 eV): m/z (rel intensity) = 133 (84), 132 (72). 106 (100).

N-(2-Methylprop-2-enyl)benzenamine **(5b)**:[18] light brown oil.

IR (neat): ν = 3420, 1605, 895 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 1.80 (3 H, br s), 3.71 (2 H, br s), 4.81–5.03 (2 H, m), 6.50–6.81 (3 H, m), 7.01–7.30 (3 H, m).

MS (70 eV): m/z (rel intensity) = 147 (43), 132 (72), 106 (100).

N-Allyl-4-methylbenzenamine **(5c)**:[19] light brown oil.

IR (neat): ν = 3412, 1618, 918 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 2.22 (3 H, s), 3.75 (2 H, d, J = 5.5 Hz), 5.05–5.42 (2 H, m), 5.73–6.22 (1 H, m), 6.51–6.61 (2 H, d, J = 10.0 Hz), 6.95–7.02 (2 H, d, J = 10.0 Hz).

MS (70 eV): m/z (rel intensity) = 147 (100), 146 (46), 120 (91).

N-Allyl-4-methoxybenzenamine **(5d)**:[20] light brown oil.

IR (neat): ν = 3395, 1620, 920 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 3.72 (2 H, d, J = 5.0 Hz), 3.75 (3 H, s), 5.08–5.42 (2 H, m), 5.77–6.22 (1 H, m), 6.51–6.97 (5 H, m).

MS (70 eV): m/z (rel intensity) = 163 (100), 148 (49), 122 (64).

N-Allyl-2-chlorobenzenamine **(5e)**:[21] light brown oil.

IR (neat): ν = 3424, 1599, 922 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 3.82 (2 H, d, J = 4.0 Hz), 5.10–5.45 (2 H, m), 5.86–6.20 (1 H, m), 6.51–6.80 (2 H, m), 7.01–7.38 (3 H, m).

MS (70 eV): m/z (rel intensity) = 167 (100), 166 (36), 132 (92).

N-Allyl-3-(trifluoromethyl)benzenamine **(5f)**:[22] light yellow oil.

IR (neat): ν = 3430, 1615, 922 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 3.79 (2 H, d, J = 5.0 Hz), 5.09–5.45 (2 H, m), 5.73–6.21 (1 H, m), 6.68–7.42 (5 H, m).

MS (70 eV): m/z (rel intensity) = 201 (97), 200 (54), 174 (100).

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