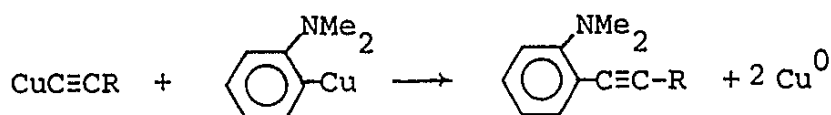


FACILE HIGH YIELD SYNTHESIS OF 1-METHYL-2-*p*-TOLYL-INDOLE
AND ITS 3-IODO DERIVATIVE

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Recently we found that the 1/1 reaction of a copper acetylide and 2-(dimethylamino)phenylcopper¹ in DMF results in the formation of *N,N*-dimethyl-2-(arylethynyl)benzenamines in 80-100% yield².



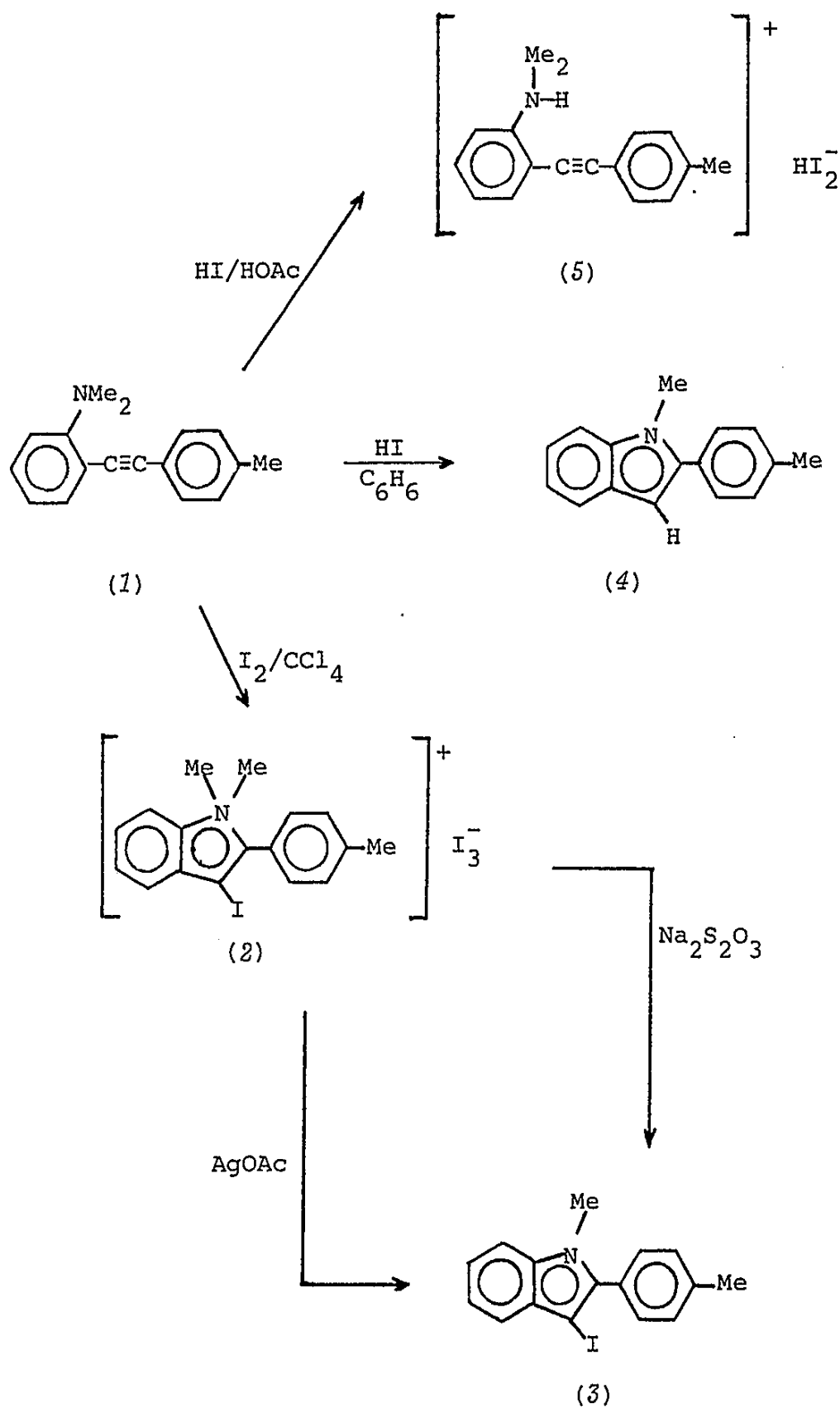
Ethynylbenzenamines can be used for the synthesis of indoles as reported by Reisch³ and Castro et al.⁴, but high temperatures and the use of a catalyst are required. We wish to report a new indole synthesis involving the interaction of *N,N*-dimethyl-2-(aryl-ethynyl)benzenamines with iodine or hydrogen iodide at room temperature. This reaction has been extensively studied for *N,N*-di-

methyl-2-(*p*-tolylethynyl)benzenamine (1) as the starting compound (see SCHEME).

Slow addition of solid iodine to a solution of 1 in carbon tetrachloride results in the rapid precipitation of 1,1-dimethyl-2-*p*-tolyl-3-iodoindolium triiodide (2). In order to obtain pure 2 an exact 1/2 molar ratio of 1 to iodine is required. The use of an excess of iodine results in the formation of 2 contaminated with iodine. In contrast, an excess of 1 lowers the yield of 2 considerably (see Experimental).

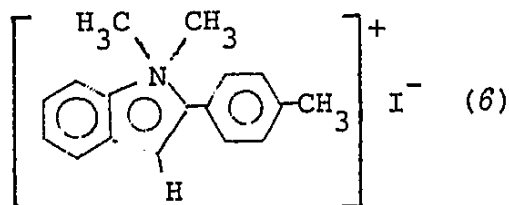
Interaction of 1 with HI in glacial acetic acid results in the formation of the quaternized product *N,N*-dimethyl-2-(*p*-tolylethynyl)benzenammonium diiodide (5), which has been isolated in 74% yield. Interestingly, the use of a water/benzene mixture instead of glacial acetic acid as a solvent, affords 1-methyl-2-*p*-tolylindole (4).

The fact that in 1 the dimethylamino group is favourably positioned with respect to the electrophilic site, which is generated upon attack of I^+ or H^+ on 1, accounts for the observed specificity of the formation of 2 and 4. Obviously, intramolecular nucleophilic attack by the dimethylamino group is favoured over the normally observed^{5,6} intermolecular attack by I^- . To our knowledge, these reactions provide the first examples of cyclization reactions of this type.



Obviously, the stability of 2 is a result of the large cation - large counterion stabilization effect⁷. Accordingly, the

precursor of 4, 1,1-dimethyl-2-*p*-tolylindolium iodide (6), is not stable and reacts spontaneously further to 4 and methyl iodide.



Furthermore, addition of silver acetate or thiosulfate, which both react with the triiodide anion of 2, results in the formation of the reductive elimination product 3.

EXPERIMENTAL

Elemental analyses were carried out under the supervision of Mr. W.J. Buis in the Analytical Department of this institute.

Melting points were measured on a Reichert melting point microscope and are uncorrected.

PMR spectra were recorded on a Varian Associates HA 100 NMR spectrometer. The values presented are given in ppm downfield to TMS.

Ultraviolet spectra were recorded on a Cary 15 spectrophotometer. GC/MS measurements were carried out on a Finnigan 3100 D gaschromatograph/mass spectrometer combination.

N,N-dimethyl-2-(*p*-tolylethynyl)benzenamine (1)

2-(dimethylamino)phenylcopper¹ (8.6 g; 46.8 mmol) and cuprous *p*-tolylacetylide⁴ (8.7 g; 48.7 mmol) were suspended in 500 ml of dimethylformamide under a dry nitrogen atmosphere. This mixture was heated for 2½ h at 130° C. Then 250 ml of ammonia (6 N) was added, followed by stirring for ½ h. The reaction mixture was filtered and extracted with ether. The ether fraction was washed with water, with HCl (0.4 N in water, 3 times 500 ml) and again with water. The ether fraction was dried on MgSO₄ and concentrated, yielding 8.5 g of an oily residu. Fractional distillation (0.15 mm, 158°) gave 5.3 g of pure 1¹. PMR (CCl₄): 2.3 (s, 3H, *p*-Me), 2.9 (s, 6H, NMe). PMR (pyridine-*d*₅): 2.18 (s, 3H, *p*-Me), 2.90 (s, 6H, NMe). Infrared (C₆D₆): νC≡C: 2208 cm⁻¹.

1,1-Dimethyl-2-(*p*-tolyl)-3-iodoindolium triiodide (2)

Solid iodine (1.5 g; 5.91 mmol) was added to a solution of 1 (1 g; 4.25 mmol) in 100 ml of CCl₄, affording a light brown solid. The reaction mixture was stirred for 2 h. The precipitate was filtered off and washed with pentane. Recrystallization from an acetone/methanol/water mixture yielded gold-brown, plate-like crystals of 2 (1.7 g, 77% yield based on iodine). Dec. pnt. 116° C. Anal. C: 27.94, H: 2.54, N: 1.87, I: 67.74. Calcd. for C₁₇H₁₇NI₄: C: 27.48, H: 2.31, N: 1.89, I: 68.32%. PMR (acetone-*d*₆): 2.49 (s,

3H, *p*-Me), 3.84 (s, 6H, NMe). Ultraviolet spectra (EtOH):

$\lambda_{\max}(\epsilon_{\max})$: 358 (13.000), 288 (27.000) at a concentration of 6.14×10^{-5} mol/liter. ϵ_{\max} is concentration dependent. (2) in acetonitrile: λ_{\max} : 361, 290. $\text{Me}_4\text{N}^+\text{I}_3^-$ in acetonitrile⁹: $\lambda_{\max}(\epsilon_{\max})$: 360 (25.500), 291 (48.800)).

1-Methyl-2(*p*-tolyl)-3-iodoindole (3)

(i) By the reaction of 2 with sodium thiosulfate

A solution of sodium thiosulfate (1 g; 6.32 mmol) in water (100 ml) was added to a suspension of 2 (1 g; 1.35 mmol) in 100 ml of ether. The precipitate dissolved upon addition of acetone (100 ml). The resulting reaction mixture was stirred for three hours. Extraction of this mixture with ether, followed by drying and concentration resulted in the isolation of a colourless oily residu (± 450 mg). The oil was dissolved in an ethanol/pentane mixture, which on cooling afforded 3 as white crystalline solid. M.p. 67-69^o C. Anal.: C: 56.27, H: 4.72, N: 4.05. I: 34.80.

Calcd. for $\text{C}_{16}\text{H}_{15}\text{NI}$: C: 55.35, H: 4.06, N: 4.03, I: 36.55%. PMR (CCl_4): 2.38 (s, 3H, *p*-Me), 3.54 (s, 3H, NMe).

(ii) By the reaction of 2 with silver acetate

A suspension of 2 (200 mg; 0.27 mmol) and silver acetate (160 mg; 0.96 mmol) in acetone (20 ml) was stirred for 6 h. The precipitate (AgI) was filtered off and the filtrate was extracted

with ether. The ether fraction was washed with water, dried on MgSO_4 and concentrated, yielding **3** according to NMR spectroscopy. Mass spectral values of **3**: m/e : 347 (parent ion, base peak), 219 (23.81%), 218 (26.85%), 217 (10.05%), 205 (39.12%), 204 (53.31%), 190 (8.02%), 178 (12.15%), 173 (10.36%), 126 (10.13%).

1-Methyl-2-(*p*-tolyl)-indole (4)

Hydroiodic acid (10 ml, 5.7% in water) was added to a solution of **1** (450 mg, 1.91 mmol) in 50 ml of benzene. The resulting heterogeneous mixture was stirred at room temperature for four days. Extraction of this mixture with ether resulted in the isolation of an oily residue (400 mg), containing **4** (according to NMR). This residue solidified on standing. Recrystallization from petroleum ether (60-80) resulted in the isolation of white crystalline **4** (47% yield). M.p. 96-98° C. Anal.: C: 85.82, H: 6.82, N: 6.34. Calcd. for $\text{C}_{16}\text{H}_{15}\text{N}$: C: 86.84, H: 6.83, N: 6.33%. PMR (CDCl_3): 2.39 (s, 3H, *p*-Me), 3.68 (s, 3H, NMe), 6.51 (s, 1H, H_3). (Lit.¹⁰ for 1-methyl-2-phenylindol (CDCl_3): 3.53 (s, 3H, NMe), 6.51 (s, 1H, H_3)).

N,N-dimethyl-2-(*p*-tolylethynyl)benzenammonium diiodide (5)

Hydroiodic acid (1 g, 57% solution in water) dissolved in 10 ml of glacial acetic acid was added to a solution of **1** (350 mg; 1.48 mmol) in 10 ml of glacial acetic acid. Violet crystals were

formed on standing for two days, which were filtered off and washed with pentane and ether. Yield 540 mg (74%). Dec.pnt. 108° C.

Anal.: C: 41.79, H: 4.07, N: 2.83, I: 48.87. Calcd. for $C_{17}H_{19}NI_2$:
C: 41.49, H: 4.10, N: 2.85, I: 51.57%.

Treatment of **5** with base in acetone afforded **1**. PMR spectroscopy revealed that **5** dissociates when dissolved in pyridine into **1** [δ : 2.18 (s, 3H, *p*-Me), 2.90 (s, 6H, NMe)] and hydrogen iodide.

ACKNOWLEDGEMENT

This investigation was supported (in part) by the Netherlands Foundation for Chemical Research (SON) with financial aid from the Netherlands Organization for the Advancement of Pure Research (ZWO) (to R.W.M.t.H.).

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Received: November 1, 1976