

REGIOSELECTIVE ADDITIONS OF GRIGNARD AND LITHIUM REAGENTS TO
2-[(BENZYLIDENE)AMINO]BENZONITRILE AND
2-[(DIPHENYLMETHYLENE)AMINO]BENZONITRILE

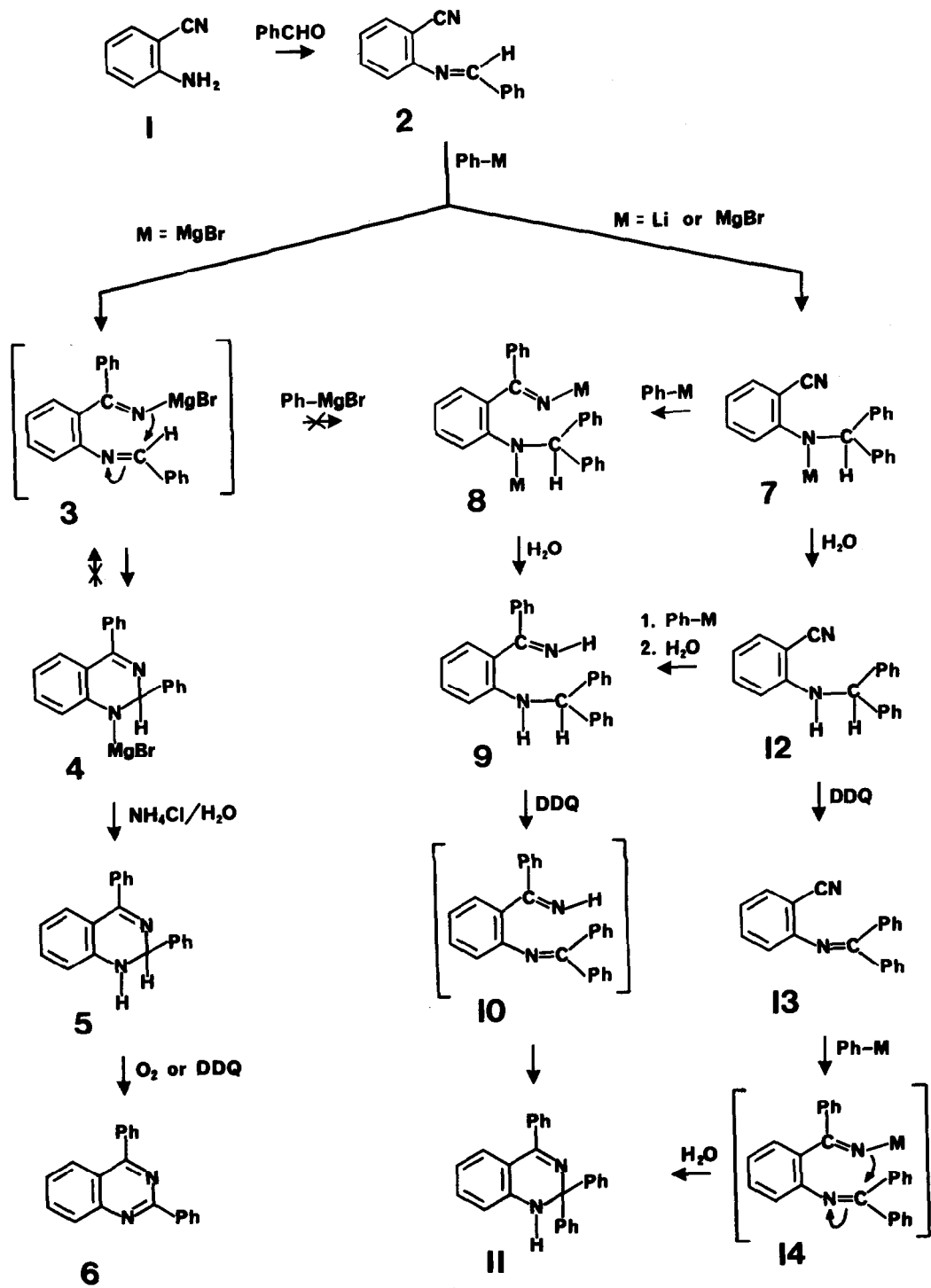
L. Strekowski,* M.T. Cegla, D.B. Harden, J.L. Mokrosz, and M.J. Mokrosz
Department of Chemistry, Georgia State University, Atlanta, Georgia 30303, U.S.A.

Abstract: Phenylmagnesium bromide and methylmagnesium bromide in tetrahydrofuran undergo a regioselective addition to the cyano group of the two title compounds. Phenyllithium and methyllithium add selectively to the azomethine portion of 2-[(benzylidene)amino]benzotrile, but to the cyano group of 2-[(diphenylmethylene)amino]benzotrile. These addition reactions are utilized in the synthesis of quinazoline derivatives.

It has been reported recently¹ that the reaction of phenylmagnesium bromide with 2-[(benzylidene)amino]benzotrile (**2**) is regioselective resulting in the addition to the nitrile moiety of **2**. The adduct **3** thus formed undergoes cyclization to a dihydroquinazoline derivative **4**. Quenching of the reaction mixture with diluted hydrochloric acid has produced a hydrochloride of 1,2-dihydro-2,4-diphenylquinazoline (**5**) in a high yield. A triphenyl derivative **9** has also been isolated as a minor product (<5%). The formation of **9** has been explained in terms of an equilibrium between **4** and **3**, and the addition of phenylmagnesium bromide to the benzylideneamine moiety of **3** to give the adduct **8** (M=MgBr).

In sharp contrast to the published results,¹ in our hands the treatment of **2** with an excess of phenylmagnesium bromide in an ether/toluene solvent (under the reported conditions) gave the adduct **9** in a quantitative yield.³ The same result was always obtained regardless of the source and purity of the Grignard reagent. Neither the reagent prepared from high purity magnesium metal nor transition metal catalysts added especially to the reaction mixtures affected the course of our numerous experiments.⁴ Compound **9** was also the sole product for the reaction conducted in pure ethyl ether. However, the reaction conducted in tetrahydrofuran produced the dihydroquinazoline **5** and the adduct **9** in a 3:1 ratio.⁵ Again the purity of the Grignard reagent and transition metal additives did not affect this ratio within the experimental error. The same ratio of products was also obtained for the reaction conducted in the presence of a large excess of the Grignard reagent regardless of the reaction time. Moreover, the treatment of pure dihydroquinazoline **5** under the same conditions did not produce **9**. These results demonstrate that a magnesium derivative **4** does not undergo ring opening to form **3**. Since **3** is not a precursor for **8**, the latter derivative must be formed from **7** (M=MgBr), the addition product of phenylmagnesium bromide to the azomethine bond in Schiff's base **2**. In fact, the corresponding amine **12** was isolated in a low yield upon treatment of **2** with less than one equivalent of the Grignard reagent. The regioselective addition to the azomethine bond in **2** was observed upon treatment of **2** with one equivalent of phenyllithium to give product **12** in a high yield.⁶ Treatment of **12** with either phenylmagnesium bromide or phenyllithium produced the adduct **9**.

We have, thus, shown that dihydroquinazoline **5** and a triphenyl adduct **9** are formed from two different intermediates resulting from the addition of an organometallic reagent to the cyano and azomethine moieties, respectively, in **2**. Phenylmagnesium bromide adds preferentially to the cyano group if tetrahydrofuran is chosen as a reaction medium. The resultant adduct **3** undergoes a spontaneous cyclization to give a stable dihydroquinazoline **4**. In ethyl ether the same reagent adds to the azomethine portion of **2** first to produce

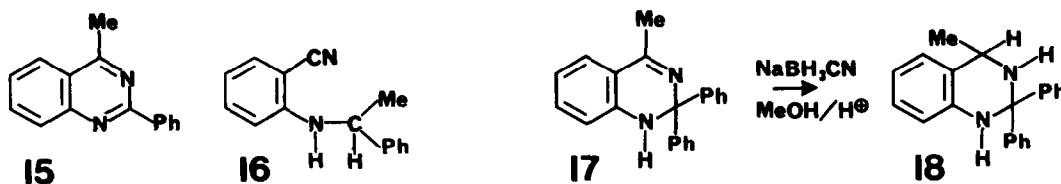


7($M=MgBr$), which is followed by the second addition to form the adduct 8 ($M=MgBr$), even if only one equivalent of the Grignard reagent is used. In contrast, the addition of one equivalent of phenyllithium to 2 gives rise to the adduct 7 ($M=Li$) as the major product.

These regioselective additions can be utilized in the synthesis of quinazoline derivatives. Dihydroquinazoline 5 is easily oxidized with molecular oxygen¹ or DDQ⁷ to give 2,4-diphenylquinazoline (6) in a quantitative yield. The dehydrogenation of 9 with DDQ⁷ gives an intermediate Schiff's base 10 which undergoes a spontaneous cyclization to produce 2,2,4-triphenyl-1,2-dihydroquinazoline (11).⁸ A similar oxidation of 12 gave 2-[(diphenylmethylene)amino]benzonitrile (13).⁹ In agreement with our other results a regioselective addition of phenylmagnesium bromide to the cyano group in 13 was observed in tetrahydrofuran. The intermediate adduct 14 ($M=MgBr$) undergoes cyclization to form a 1,2-dihydroquinazoline system. Quenching of the reaction mixture with water gave compound 11 in a 77% yield. To our astonishment, however, a quantitative yield of 11 was obtained upon treatment of the Schiff's base 13 with phenyllithium, indicating the complete regioselective addition of the lithium reagent to the cyano group of 13. This result is unexpected because phenyllithium adds to the azomethine moiety of the analog 2. However, the opposite regioselectivities of the two addition reactions can be understood in terms of the strikingly different stereochemistries of molecules 2 and 13.

The MM-2 analysis of 2 shows that the molecule exists in an equilibrium conformation with a negligible deviation from co-planarity of the two aromatic rings and the imine linkage. In contrast, the MM-2 analysis for 13 revealed an extensively twisted conformation with the central imino group sterically hindered by the two phenyl substituents and the benzonitrile moiety.¹⁰ The cyano group in this low-energy conformation of 13 is not sterically hindered and, as such, is an easy target for a nucleophilic attack.

The addition reactions of methylmagnesium bromide and methyllithium to either 2 or 13 follow the patterns discussed above. Thus, the reaction of the Grignard reagent with 2, followed by quenching the mixture with water and the treatment with DDQ produced 4-methyl-2-phenylquinazoline (15).¹¹ A regioselective addition of methyllithium to the azomethine bond in 2 takes place to give the adduct 16 if only one equivalent of the lithium reagent is used.¹² Unfortunately, 16 resisted all dehydrogenation attempts to give a corresponding Schiff's base. On the other hand, methyllithium adds smoothly to the cyano group of 13 to produce 4-methyl-2,2-diphenyl-1,2-dihydroquinazoline (17),¹³ as expected. It should be noted that 11 and 17 thus obtained are the first examples of this previously unknown class of compounds. In order to obtain an additional support for the given structures, compound 17 was reduced to 4-methyl-2,2-diphenyl-1,2,3,4-tetrahydroquinazoline (18). The latter derivative was extensively characterized by spectral methods.^{14,15}



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REFERENCES AND NOTES

- Bergman, J.; Brynolf, A.; Elman, B.; Vuorinen, E. *Tetrahedron* 1986, 42, 3697.
- For pyridine-catalyzed preparation of 2, see: Bergman, J.; Brynolf, A.; Vuorinen, E. *Tetrahedron* 1986, 42, 3689. Compound 2 was obtained in an acid-catalyzed reaction in this work: A solution of 1 (2.36 g, 20 mmol), benzaldehyde (2.1 mL, 21 mmol), and p-toluenesulfonic acid (50 mg, 0.3 mmol) in benzene (60 mL) was heated under reflux for 2 h with azeotropic removal of water. The solution was concentrated and cooled, and the precipitated material was crystallized from hexanes to give 3.95 g (96%) of 2; m.p. 109-111°C.
- TLC analysis (silica gel, hexanes/Et₃N/EtOH, 7:2:1) revealed that 2 was consumed after 2 h and only one product was formed. Quenching of the mixture with an aqueous solution of NH₄Cl was followed by drying of the organic layer with Na₂SO₄. Evaporation of the solvent *in vacuo* furnished 100% of 9. The ¹H-NMR spectrum of 9 was identical with that published.¹ See also footnote 5.
- The same results were obtained with phenylmagnesium bromide solution (i) obtained from Aldrich and Fluka, (ii) prepared from distilled bromobenzene and "Grignard grade" magnesium (98%, Fisher, Aldrich) or high-purity magnesium (99.95+%, Aldrich), and (iii) in the presence of cuprous chloride or dichloro-1,3-bis(diphenylphosphino)propane/nickel(II). The nickel complex was prepared as described: Van Hecke, G.R.; Horrocks, W.D. *Inorg. Chem.* 1966, 5, 1968.
- Although we failed to demonstrate what caused the dramatic differences between Bergman's¹ and our results, we showed that compound 5 can be prepared in a good yield if tetrahydrofuran is used as the reaction medium. Phenylmagnesium bromide was prepared in tetrahydrofuran for these particular experiments. The ¹H-NMR spectrum of 5 was identical with that published.¹ The same results were obtained after heating the mixture for 2 h and 24 h.
- A solution of 2 (0.824 g, 4.0 mmol) in ethyl ether (50 mL) was treated dropwise with phenyllithium (4.1 mmol) at 0°C. The resultant mixture was stirred at 0°C for 1 h and quenched with water, and the organic layer was dried (Na₂SO₄) and concentrated. Crystallization from hexanes afforded 0.910 g (80%) of 12; m.p. 115-117°C; ¹H-NMR (400 MHz, CDCl₃) δ: 5.10 (d, J=4 Hz, 1H, exchangeable with D₂O), 5.61 (d, J=4 Hz, 1H), 6.48 (d, J=8 Hz, 1H), 6.71 (t, J=8 Hz, 1H), 7.22-7.41 (m, 11 H), 7.46 (d, J=8 Hz, 1H); IR (nujol): 2210, 3360 cm⁻¹; MS (EI; m/z, %): 167 (100), 284 (13, M⁺).
- One equivalent of DDQ. The mixture in toluene was heated at 100°C for 10 min, cooled, and extracted with a 5% solution of NaOH. The toluene was dried (Na₂SO₄) and evaporated.
- Yield 97%; m.p. 149-150°C (from hexanes); ¹H-NMR (400 MHz, CDCl₃) δ: 4.67 (broad s, 1H), 6.62 (t, J=8 Hz, 1H), 6.77 (d, J=8 Hz, 1H), 7.05 (d, J=8 Hz, 1H), 7.27 (m, 7H), 7.42 (m, 3H), 7.51 (m, 4H), 7.58 (m, 2H); IR (nujol): 3365 cm⁻¹; MS (EI; m/z, %): 283 (100), 359 (8), 360 (6, M⁺); MS (CI with isobutane; m/z, %): 283 (100), 361 (57, M⁺+1).
- Yield 70%; m.p. 118-119°C (from hexanes/toluene); ¹H-NMR (400 MHz, DMSO-d₆) δ: 6.91 (d, J=8 Hz, 1H), 7.06 (t, J=8 Hz, 1H), 7.19 (m, 2H), 7.36 (m, 3H), 7.46 (t, J=8 Hz, 1H), 7.52 (m, 2H), 7.60 (m, 1H), 7.64 (d, J=8 Hz, 1H), 7.72 (m, 2H); IR (nujol): 2220 cm⁻¹. Compound 13 cannot be prepared from 2-aminobenzonitrile and benzophenone using standard conditions of acid or base catalysis.² Our synthesis route is suitable for the preparation of other diaryl- and aryl-heteroaryl-substituted derivatives, analogues of 13 (work in progress).
- The following torsion angles were obtained relative to the plane of the central N=C bond: 1° and 5° for PhCN and Ph, respectively, in 2; 61° for PhCN, 13° for (E)-Ph, and 23° for (Z)-Ph in 13.
- Yield 42%; m.p. 88-90°C (reported m.p. 89-90°C: Anderson, R.K.; Carter, S.D.; Cheesman, G.W.H. *Tetrahedron* 1979, 35, 2463). Compound 15 was the only low molecular product.
- Yield 80%; m.p. 89-91°C (from hexanes); ¹H-NMR (60 MHz, CDCl₃) δ: 1.53 (d, J=6 Hz, 3H), 4.50 (q, J=6 Hz, 1H), 4.97 (d, J=6 Hz, 1H, exchangeable with D₂O), 6.40 (d, J=8 Hz, 1H), 6.54 (t, J=8 Hz, 1H), 7.00-7.50 (m, 7H); IR (nujol): 2212, 3370 cm⁻¹.
- Yield 67%; m.p. 136-138°C (from hexanes); ¹H-NMR (60 MHz, CDCl₃) δ: 2.39 (s, 3H), 4.48 (broad s, 1H, exchangeable with D₂O), 6.56 (t, J=8 Hz, 1H), 6.60 (d, J=8 Hz, 1H), 7.00-7.50 (m, 12H); IR (nujol): 1606, 1628, 3397 cm⁻¹.
- A solution of 17, NaBH₃CN and a catalytic amount of HCl in MeOH was refluxed for 10 h. Product 18 was obtained by chromatography on silica gel (hexanes/Et₃N, 9:1); yield 43%. ¹H-NMR (400 MHz, CDCl₃) δ: 1.44 (d, J=6.4 Hz, CH₃), 3.76 (q, J=6.4 Hz, C4-H), 4.74 (s, N1-H), 6.61 (d of d, J=7.6 Hz, J=1.2 Hz, C8-H), 6.65 (t of d, J=7.6 Hz, J=1.2 Hz, C6-H), 6.85 (d of d, J=7.6 Hz, J=1.6 Hz, C5-H), 7.05 (t of d, J=7.6 Hz, J=1.6 Hz, C7-H), 7.18 (s, N3-H), 7.20-7.36 (m, Ph), these chemical shift assignments were obtained using proton decoupling and NOE experiments; IR (nujol): 1609, 3297, 3430 cm⁻¹.
- Satisfactory elemental analyses were obtained for all new compounds: C, ±0.2; H, ±0.1; N, ±0.1%. All given yields correspond to the analytically pure compounds.

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