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Preparation of Polyfunctional Arylmagnesium Reagents Bearing a Triazene Moiety. A New Carbazole Synthesis

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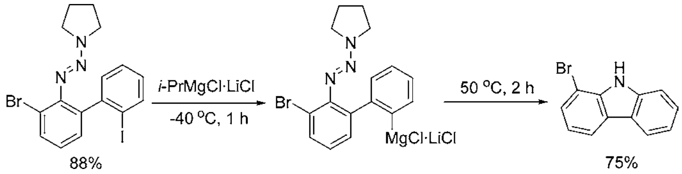
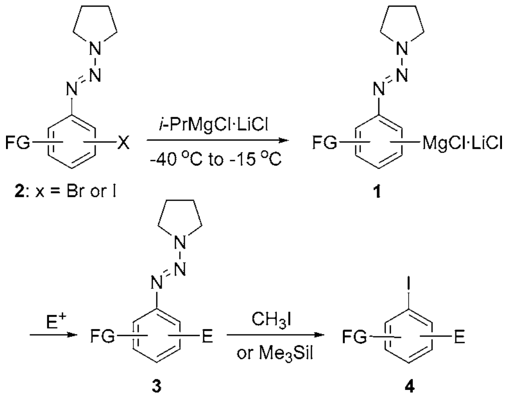
ABSTRACT



The reaction of iodo- or bromo-substituted aryltriazenes with *i*-PrMgCl·LiCl generates the corresponding magnesiated derivatives which react with various electrophiles (acid chlorides, 3-iodoenones, allylic halides, aldehydes) affording polyfunctional triazenes. They can be readily converted to the corresponding polyfunctional aryl iodides. This new synthetic strategy was applied to prepare functionalized carbazoles.

The triazene functionality (ArN═N−NR$_2$) is a convenient way to protect a diazonium salt and to carry this reactive functionality through several steps. It has also proved its utility as a linker in solid-phase combinatorial synthesis.[1] Of special synthetic interest is its conversion to an iodide function under mild conditions.[2] Recently, we have developed a general halogen−magnesium exchange reaction using the mixed Mg/Li reagent *i*-PrMgCl·LiCl.[3] Both aryl iodides and bromides undergo a halogen−magnesium exchange under mild conditions. Since this exchange reaction tolerates many functional groups, we have examined the compatibility of an I/Mg exchange

Scheme 1



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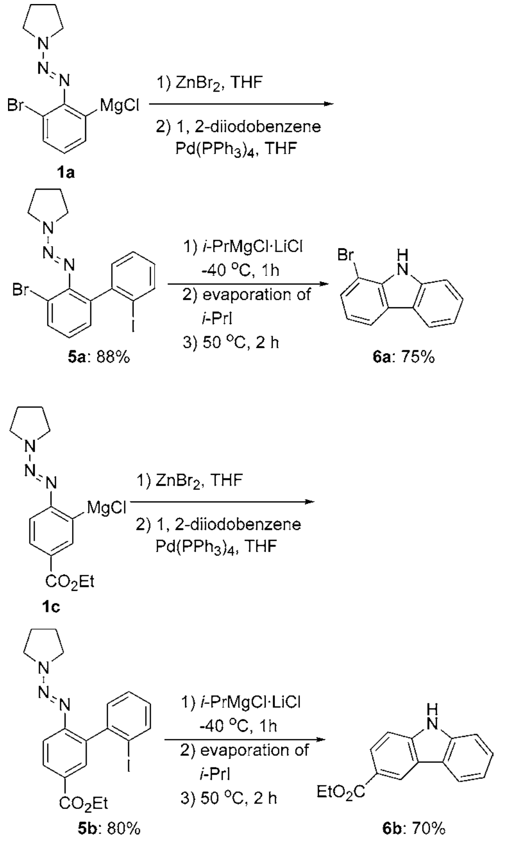
[1] For reviews, see: (a) Kimball, D. B.; Haley, M. M. *Angew. Chem., Int. Ed.* **2002**, *41*, 3338. (b) Moore, J. S. *Acc. Chem. Res.* **1997**, *30*, 402. (c) Bräse, S. *Acc. Chem. Res.* **2004**, *37*, 805. See also: (d) Nicolaou, K. C.; Li, H.; Boddy, C. N. C.; Ramanjulu, J. M.; Yue, T. Y.; Natarajan, S.; Chu, X. J.; Bräse, S.; Rübsam, F. *Chem. Eur. J.* **1999**, *5*, 2584. (e) Enders, D.; Rijksen, C.; Bremus-Köbberling, E.; Gillner, A.; Köbberling, J. *Tetrahedron Lett.* **2004**, *45*, 2839. (f) Lormann, M. E. P.; Dahmen, S.; Avemaria, F.; Lauterwasser, F.; Bräse, S. *Synlett* **2002**, 915. (g) Kimball, D. B.; Herges, R.; Haley, M. M. *J. Am. Chem. Soc.* **2002**, *124*, 1572. (h) Kimball, D. B.; Weakley, T. J. R.; Haley, M. M. *J. Org. Chem.* **2002**, *67*, 6395. (i) Gross, M. L.; Blank, D. H.; Welch, W. M. *J. Org. Chem.* **1993**, *58*, 2104.

10.1021/ol0505454 CCC: $30.25

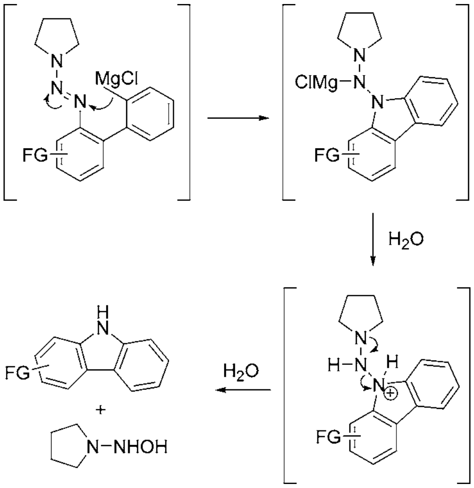
Scheme 2. Synthesis of Functionalized Carbazoles **6a** and **6b**



with a triazene moiety. We have found that in the case of the reaction of iodotriazene with *i*-PrMgCl the triazene group reacted, and no arylmagnesium reagent was formed. However, by using the more reactive exchange reagent *i*-PrMgCl•LiCl, this exchange reaction proceeds smoothly. Herein, we wish to report the preparation of polyfunctional arylmagnesium reagents bearing a triazene functionality of type **1** starting from the aromatic halides of type **2** (X = I or Br) and leading to polyfunctional triazenes such as **3** which can be converted to the polyfunctional iodides **4**, allowing an effective functionalization of aromatic derivatives (Scheme 1).

Thus, 1-(2,6-dibromophenylazo)pyrrolidine (**2a**) obtained from 2,6-dibromoaniline in 95% yield (see the Supporting Information) reacts with *i*-PrMgCl•LiCl (1.05 equiv, −40 to −15 °C, 3.5 h) affording the expected arylmagnesium derivative **1a** (see entries 1−4 of Table 1). After a transmetalation with CuCN•2LiCl,[4] the resulting copper reagent is readily allylated giving the triazene **3a** (78%; entry 1 of Table 1). Acylation of the copper derivatives of **1a** or **1b** with acyl, heteroaryl or aliphatic acid chlorides furnishes the expected ketones **3b** (82%; entry 2), **3c** (85%; entry 3) or **3e** (82%; entry 5). An addition−elimination reaction with 3-iodo-2-cyclohexen-1-one leads to the triazene **3d** in 80% yield (entry 4). Starting with 1-(2-iodo-4-carbo ethoxyphenylazo)-pyrrolidine (**2c**), the reaction with *i*-PrMgCl•LiCl is complete within 40 min at −40 °C leading

Scheme 3. Plausible Mechanism of the Cabazole Formation



to the polyfunctional magnesiated triazene (**1c**; entries 6−8) which reacts with electrophiles leading to the ester-substituted triazenes **3f**, **3g**, and **3h** in 78−86%. A similar transformation is also achieved for a cyano-substituted iodoaryltriazene (**2d**) providing the Grignard reagent (**1d**) and the acylated products **3i** (86%; entry 9) and **3j** (85%; entry 10). Finally, not only triazenes bearing a halogen in the ortho-position undergo a halogen/magnesium exchange smoothly, but also 1-(4-iodophenylazo)pyrrolidine (**2e**) reacts with *i*-PrMgCl•LiCl (−40 °C, 40 min) affording the corresponding magnesiated triazene **1e**. Its direct reaction with EtCHO provides the benzylic alcohol **3k** (90%; entry 11). A copper-catalyzed acylation leads to the ketone **3l** (88%; entry12).

The triazenes of type **3** are readily converted to the corresponding aryl iodides using either a reaction in a sealed-tube with MeI[2a,b,d] (15 equiv, 120 °C, 24−48 h; method A) or in refluxing CH_2Cl_2 with TMSI (2 equiv, 4−6 h; method B) in 70−90% yield; see Table 2. Various functional groups such as ketones, enones or an ester are tolerated. In the case of a benzylic alcohol such as **3k**, a dehydration is observed leading to the iodostyrene **3j** in 85% yield (entry 10).

Using our method, we have developed a new carbazole synthesis.[5] Starting from the Grignard reagents **1a** and **1c**, we performed a Negishi cross-coupling[6] with 1,2-diiodobenzene leading to the derived polyfunctional

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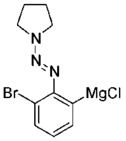
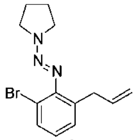
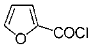
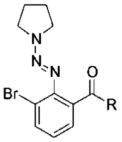
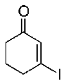
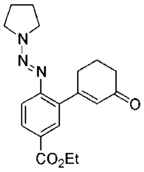
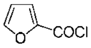
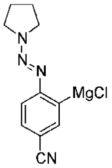
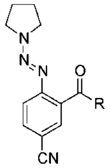
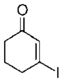
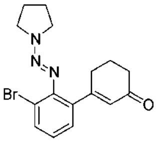
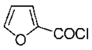
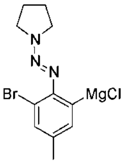
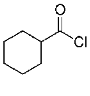
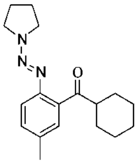
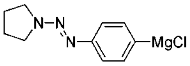
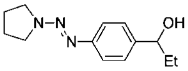
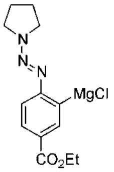
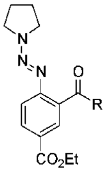
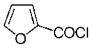
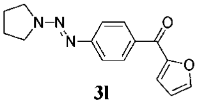
(2) (a) Moore, J. S.; Weinstein, E. J.; Wu, Z. *Tetrahedron Lett.* **1991**, *32*, 2465. (b) Wu, Z.; Moore, J. S. *Tetrahedron Lett.* **1994**, *35*, 5539. (c) Ku, H.; Barrio, J. R. *J. Org. Chem.* **1981**, *46*, 5239. (d) Wan, W. B.; Chiechi, R. C.; Weakley, T. J. R.; Haley, M. M. *Eur. J. Org. Chem.* **2001**, 3485.

(3) (a) Krasovskiy, A.; Knochel, P. *Angew. Chem., Int. Ed* **2004**, *43*, 3333. (b) Kopp, F.; Krasovskiy, A.; Knochel, P. *Chem. Commum.* **2004**, 2288. (c) Ren, H.; Krasovskiy, A.; Knochel, P. *Org. Lett.* **2004**, *6*, 4215. See also: (d) Knochel, P.; Dohle, W.; Gommermann, N.; Kneisel, F. F.; Kopp, F.; Korn, T.; Sapountzis, I.; Vu, V. A. *Angew. Chem., Int. Ed.* **2003**, *42*, 4302.

(4) Knochel, P.; Yeh, M. C. P.; Berk, S. C.; Talbert, J. *J. Org. Chem.* **1988**, *53*, 2390.

(5) Knölker, H. S.; Reddy, K. R. *Chem. Rev.* **2002**, *102*, 4303.

Table 1. Polyfunctional Aryl Triazenes of Type **3** Obtained by the Reaction of the Grignard Reagents **1** with Electrophiles

entry	Grignard reagent of type **1**	electrophile	product of type **3**	yield (%)[a]	entry	Grignard reagent of type **1**	electrophile	product of type **3**	yield (%)[a]
1	 **1a**	allyl-bromide	 **3a**	78	7	**1c**		**3g**: R = 2-furyl	86
2	**1a**	PhCOCl	 **3b**: R = Ph	82	8	**1c**		 **3h**	80
3	**1a**		**3c**: R = 2-furyl	85	9	 **1d**	PhCOCl	 **3i**: R = Ph	86
4	**1a**		 **3d**	80	10	**1d**		**3j**: R = 2-furyl	85
5	 **1b**		 **3e**	82	11	 **1e**	EtCHO	 **3k**	90
6	 **1c**	PhCOCl	 **3f**: R = Ph	78	12	**1e**		 **3l**	88

[a] Isolated yield of analytically pure product.

biphenyls **5a** (88%) and **5b** (80%). The reaction of compound type **5** with *i*-PrMgCl·LiCl (1.1 equiv, −40 °C, 1 h) provides the functionalized carbazoles **6a** (75%) and **6b** (70%). The evaporation of *i*-PrI resulting from the I/Mg-exchange is important before heating (50 °C, 2 h). Otherwise, unwanted cross-coupling products with *i*-PrI are observed (Scheme 2). A tentative mechanism of the cyclization involving the formation of a hydroxylamine derivative as side-product is described in Scheme 3.

In summary, we have shown that the reaction of iodo- or bromo-substituted aryltriazenes with *i*-PrMgCl·LiCl generates magnesiated derivatives which react with various electrophiles (acid chlorides, 3-iodoenones, allylic halides, and aldehydes) to afford polyfunctional triazenes which can be readily converted to the corresponding polyfunctional aryl iodides. As an application of the versatility of these prod-

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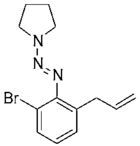
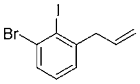
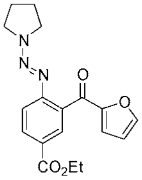
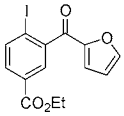
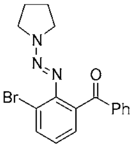
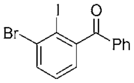
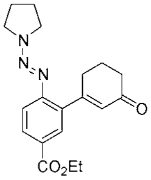
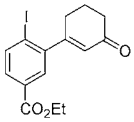
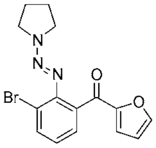
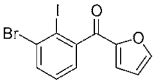
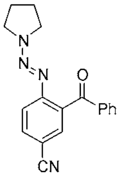
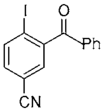
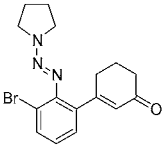
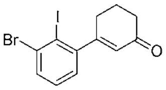
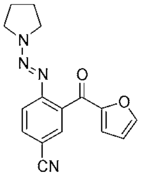
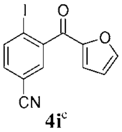
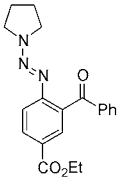
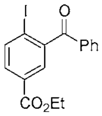
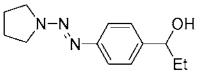
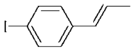
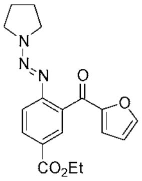
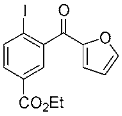
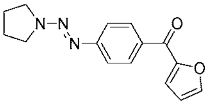
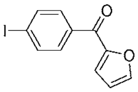
(6) (a) Green, L.; Chauder, B.; Snieckus, V. *J. Heterocycl. Chem.* **1999**, *36*, 1453. (b) Negishi, E.; Valente, L. F.; Kobayashi, M. *J. Am. Chem. Soc.* **1980**, *102*, 3298. (c) Kobayashi, M.; Negishi, E. *J. Org. Chem.* **1980**, *45*, 5223. (d) Negishi, E. *Acc. Chem. Res.* **1982**, *15*, 340. (e) Tamaru, Y.; Ochiai, H.; Nakamura, T.; Yishida, Z. *Tetrahedron Lett* **1986**, *27*, 955. (f) Klement, I.; Rottländer, M.; Tucker, C. E.; Majid, T. N.; Knochel, P.; Venegas, P.; Cahiez, G. *Tetrahedron* **1996**, *52*, 7201.

(7) **Typical Procedure 1: Preparation of 3f.** To a solution of triazene **2c** (187 mg, 0.5 mmol) in THF (0.5 mL) was slowly added *i*-PrMgCl·LiCl (0.26 mL, 0.53 mmol, 2.05 M in THF) at −40 °C. The reaction mixture was continuously stirred at −40 °C for 40 min. A complete conversion to the Grignard reagent (**1c**) was observed as indicated by GC analysis of hydrolyzed reaction aliquots. CuCN·2LiCl (0.5 mmol, 0.5 mL, 1.0 M in THF) was added dropwise at −40 °C, and then the reaction mixture was slowly warmed to −30 °C over 30 min. Benzoyl chloride (0.75 mmol) in THF (0.1 mL) was added, and the mixture was stirred at −30 °C for 1 h and then warmed to rt and stirred again for 1 h before the addition of aq NH_3 (2 mL). The aqueous phase was extracted with diethyl ether (2 × 10 mL). The organic fractions were washed with brine (10 mL), dried ($MgSO_4$), and concentrated in vacuo. Purification by flash chromatography (pentane/ether = 2:1) yielded the pure product **3f** (137 mg, 78%) as yellow crystals.

(8) **Typical Procedure 2: Preparation of 6a.** To a solution of compound **5a** (228 mg, 0.5 mmol) in THF (0.25 mL) was slowly added *i*-PrMgCl·LiCl (0.26 mL, 0.53 mmol, 2.0 M in THF) at −40 °C. The reaction mixture was continuously stirred at −40 °C. After 1 h, isopropyl iodide resulting from the I/Mg exchange was evaporated in vacuo (evaporation was done twice, 1 h for each time). Then the mixture was heated to 55 °C for 2 h after addition of fresh THF (1.5 mL). The mixture was cooled to rt and quenched as usual. The aqueous phase was extracted with ether (2 × 5 mL). The organic fractions were washed with brine (5 mL), dried ($MgSO_4$), and concentrated in vacuo. Purification by flash chromatography (pentane/ether = 32:1) yielded the pure product **6a** (92 mg, 75%) as a white solid.

Table 2. Polyfunctional Aryl Iodides Obtained by the Iodolysis of Triazenes of Type **3** with CH_3I (Method A) or TMSI (Method B)

entry	triazenes of type **3**	aryl iodide of type **4**	yield (%)[a]	entry	triazenes of type **3**	aryl iodide of type **4**	yield (%)[a]
1	 **3a**	 **4a**[b]	83	6	 **3g**	 **4f**[c]	78
2	 **3b**	 **4b**[c]	88	7	 **3h**	 **4g**[b]	76
3	 **3c**	 **4c**[c]	78	8	 **3i**	 **4h**[c]	70
4	 **3d**	 **4d**[b]	87	9	 **3j**	 **4i**[c]	82
5	 **3f**	 **4e**[c]	72	10	 **3k**	 **4j**[b]	85
6	 **3g**	 **4f**[c]	78	11	 **3l**	 **4k**[b]	90

[a] Isolated yield of analytically pure product. [b] Prepared according to Method A: CH_3I, 120 °C, 24−48 h. [c] Prepared according to Method B: $(CH_3)_3SiI$, CH_2Cl_2, reflux, 4−6 h.

ucts,we also have developed a new synthesis of functionalized carbazoles.

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Supporting Information Available: Experimental procedures and full characterization of all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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