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

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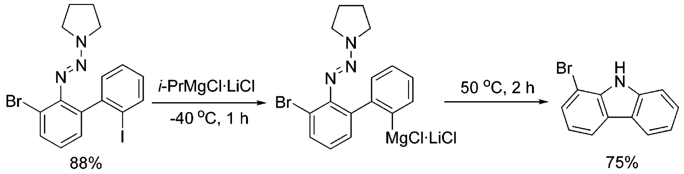
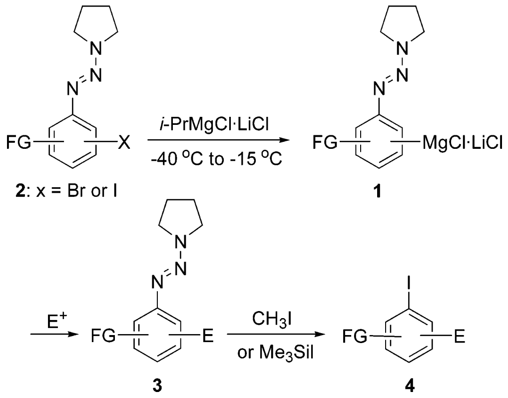
ABSTRACT



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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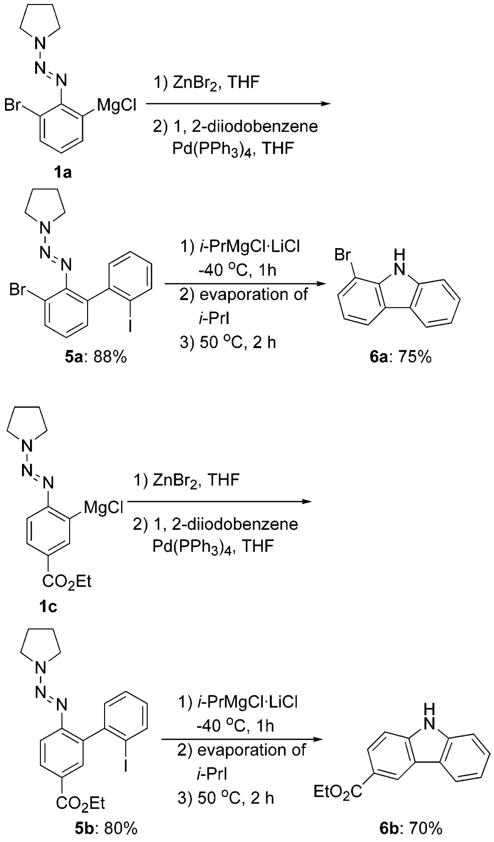
[1] For reviews, see: (a) Kimball, D. B.; Haley, M. M. *Angew. Chem., Int. Ed.* **2002**, *41*, 3338. (b) Moore, J. S. *Acc. Chem. Res.* **1997**, *30*, 402. (c) Bräse, S. *Acc. Chem. Res.* **2004**, *37*, 805. See also: (d) Nicolaou, K. C.; Li, H.; Boddy, C. N. C.; Ramanjulu, J. M.; Yue, T. Y.; Natarajan, 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

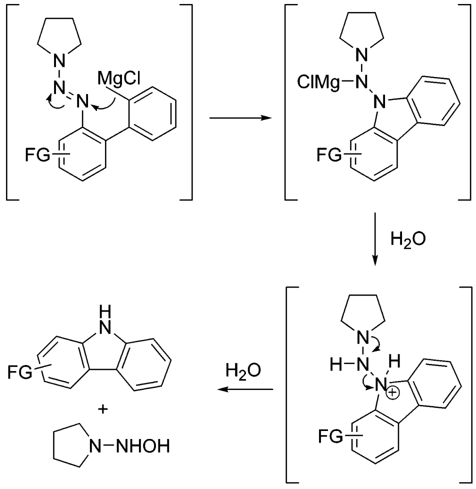
Scheme 2. Synthesis of Functionalized Carbazoles **6a** and **6b**



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 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).

Scheme 3. Plausible Mechanism of the Cabazole Formation



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$_2$Cl$_2$ 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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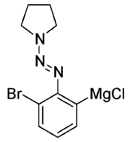
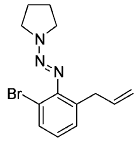
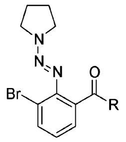
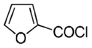
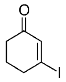
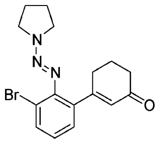
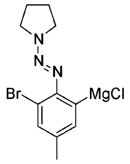
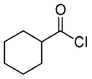
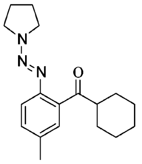
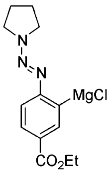
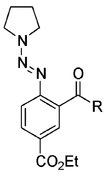
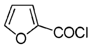
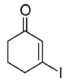
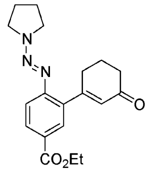
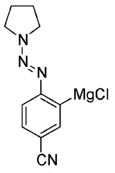
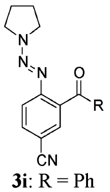
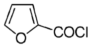
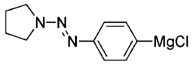
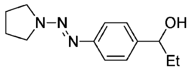
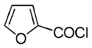
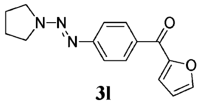
(2) (a) Moore, J. S.; Weinstein, E. J.; Wu, Z. *Tetrahedron Lett.* **1991**, *32*, 2465. (b) Wu, Z.; Moore, J. S. *Tetrahedron Lett.* **1994**, *35*, 5539. (c) Ku, H.; Barrio, J. R. *J. Org. Chem.* **1981**, *46*, 5239. (d) Wan, W. B.; Chiechi, R. C.; Weakley, T. J. R.; Haley, M. M. *Eur. J. Org. Chem.* **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**	electro-phile	product of type **3**	yield (%)[a]
1	 **1a**	allyl-bromide	 **3a**	78
2	**1a**	PhCOCl	 **3b**: R = Ph	82
3	**1a**		**3c**: R = 2-furyl	85
4	**1a**		 **3d**	80
5	 **1b**		 **3e**	82
6	 **1c**	PhCOCl	 **3f**: R = Ph	78
7	**1c**		**3g**: R = 2-furyl	86
8	**1c**		 **3h**	80
9	 **1d**	PhCOCl	 **3i**: R = Ph	86
10	**1d**		**3j**: R = 2-furyl	85
11	 **1e**	EtCHO	 **3k**	90
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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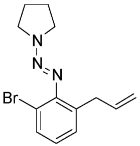
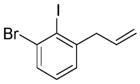
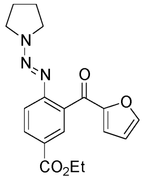
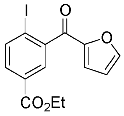
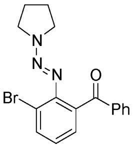
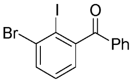
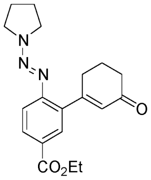
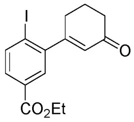
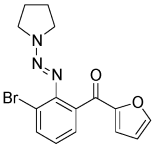
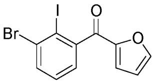
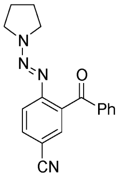
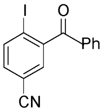
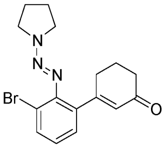
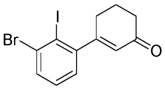
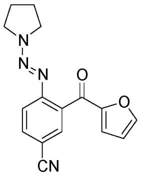
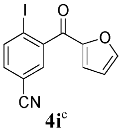
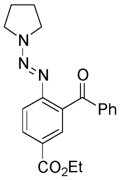
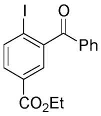
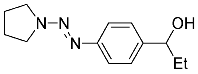
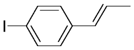
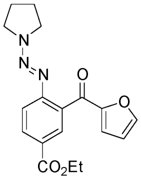
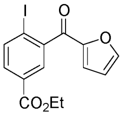
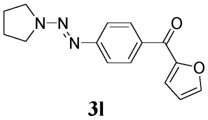
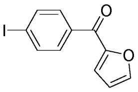
(6) (a) Green, L.; Chauder, B.; Snieckus, V. *J. Heterocycl. Chem.* **1999**, *36*, 1453. (b) Negishi, E.; Valente, L. F.; Kobayashi, M. *J. Am. Chem. Soc.* **1980**, *102*, 3298. (c) Kobayashi, M.; Negishi, E. *J. Org. Chem.* **1980**, *45*, 5223. (d) Negishi, E. *Acc. Chem. Res.* **1982**, *15*, 340. (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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