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Novel *Tele* Nucleophilic Aromatic Substitutions in α-(Benzotriazol-1-yl)alkyl Aryl Ketones[1]

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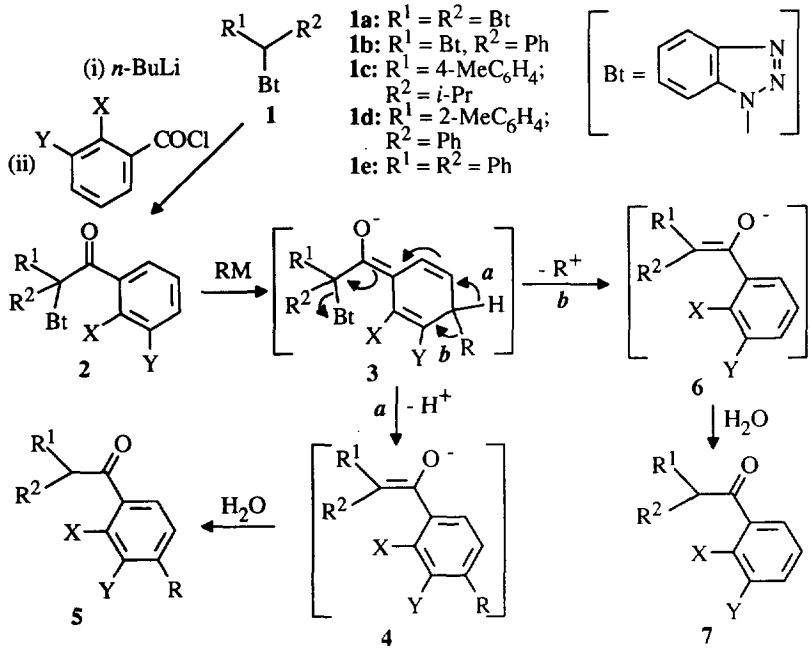
Abstract: Reactions of α-(benzotriazol-1-yl)alkyl aryl ketones **2** with alkyllithiums or Grignard reagents afforded *para*-alkylated products **5** *via* novel *tele* nucleophilic aromatic substitutions.

Nucleophilic aromatic substitutions enable valuable synthetic transformations and have attracted extensive studies.[2-4] In such processes, the incoming nucleophile normally replaces a leaving group attached to the same position. Well documented exceptions to this generalization include: 1) vicarious nucleophilic substitution of hydrogen (VNS),[5,6] in which the leaving group resided at the attacking atom of the nucleophile; 2) nucleophilic aromatic *cine* substitution,[2,3,7] in which the incoming nucleophile enters *ortho* with respect to the leaving group; and 3) nucleophilic aromatic *tele* substitution,[7-9] in which the incoming nucleophile ends up situated *para* or *meta* to the outgoing nucleofuge. Activation by a nitro substituent is usually a requisite to enter the VNS reaction,[10] and previously reported nucleophilic aromatic *tele* and *cine* substitutions are limited to the reactions of dinitroarenes (2,3-dinitrophenol or 2,3-dinitroaniline) with secondary amines.

Work from our laboratory has demonstrated that benzotriazole is an excellent synthetic auxiliary in many useful synthetic transformations.[11-14] Due to the good leaving ability and the size of benzotriazolyl group, tris(benzotriazol-1-yl)methane was recently shown to be an efficient reagent for the regiospecific *para*-bis(benzotriazolyl)methylation of nitroarenes *via* VNS, leading to the facile synthesis of various *p*-nitroarylaldehydes.[15] We now report a novel *tele* nucleophilic aromatic substitution in which treatment of α-(benzotriazol-1-yl)alkyl aryl ketones **2** with lithium or Grignard reagents furnished *para*-alkylated products **5** generally in moderate to good yields.

α-(Benzotriazol-1-yl)alkyl aryl ketones **2a-f** are readily prepared *via* the nucleophilic reaction of the lithio derivatives of the corresponding (benzotriazol-1-yl)methanes **1**[16] with an appropriate phenacyl chloride.[17] Treatments of **2** with 2 equivalents of a lithium or magnesium reagent in THF under argon from -78 °C to +20 °C results in the formation of *para*-alkylated products **5** (Scheme 1).[18] A plausible mechanism for the



Scheme 1

formation of **5** is outlined in Scheme 1. Since the carbonyl group in **2** is very well shielded by the neighboring bulky trisubstituted methyl group, carbanions attack the *para* position of the aryl group instead to give intermediates **3**.[19] With the assistance of the second equivalent of RM acting as a base, **3** undergo concurrent aromatization and departure of the benzotriazol-1-yl group to provide the observed products **5**. This transformation is analogous to vicarious nucleophilic substitution: while in VNS the leaving group is present at the attacking atom of the nucleophilic agent, in the present reaction the departing benzotriazol-1-yl group is located at the position α to the carbonyl group. As listed in Table 1, compounds **5a-f** and **5j** are isolated in yields of 34-78%. In the case of **5h**, an inseparable mixture of the *para* substituted product **5h** and the corresponding *ortho* substituted product in a ratio of 68:32 is obtained. Interestingly, in the cases of entries 7 and 9, in addition to the corresponding products **5g** and **5i**, we also isolated compounds **7g** and **7i** respectively, possibly *via* the competing departure of the *t*-butyl carbocation from intermediate **3** (Scheme 1, route *b*) due to its special stability.

In conclusion, a novel *tele* nucleophilic aromatic substitution occurs in the reactions of α-(benzotriazol-1-yl)alkyl aryl ketones **2** with alkyllithiums or Grignard reagents. A bulky trisubstituted methyl group attached to the carbonyl group is required in order to block it from nucleophilic attack.

Table 1. Preparation of 4-Substituted Aryl Ketones **5a-j**

entry	substrate	R^1	R^2	X,Y	RM	product	yield (%)
1	**2a**	Bt	Bt	H,H	*n*-BuLi	**5a**	78
2	**2a**	Bt	Bt	H,H	*s*-BuLi	**5b**	62
3	**2a**	Bt	Bt	H,H	*t*-BuLi	**5c**	49
4	**2b**	Bt	Bt	C_4H_4 [a]	*n*-BuLi	**5d**	76
5	**2c**	Bt	Ph	H,H	*t*-BuLi	**5e**	62
6	**2d**	4-MeC_6H_4	*i*-Pr	H,H	*t*-BuLi	**5f**	46
7	**2e**	2-MeC_6H_4	Ph	H,H	*t*-BuLi	**5g**	72 [b]
8	**2f**	Ph	Ph	H,H	*s*-BuLi	**5h**	69 [c]
9	**2f**	Ph	Ph	H,H	*t*-BuLi	**5i**	48 [d]
10	**2f**	Ph	Ph	H,H	PhMgBr	**5j**	34

[a] 1-Naphthyl. [b] Total yield of **5g** and **7g** in a ratio of 36:59. [c] Total yield of **5h** and *ortho* substituted product in a ratio of 68:32 . [d] Total yield of **5i** and **7i** in a ratio of 85:13.

REFERENCES AND NOTES

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16. **Preparation of (Benzotriazol-1-yl)methanes 1a-e:** Tris(benzotriazol-1-yl)methane (**1a**) (see: Katritzky, A. R.; Yang, Z.; Lam, J. N. *Synthesis* **1990**, 666) and 1-(diphenylmethyl)benzotriazole (**1e**) (see: Katritzky, A. R.; Perumal, S.; Fan, W.-Q. *J. Chem. Soc., Perkin Trans. 2* **1990**, 2059) were prepared according to the literature procedures quoted. Compounds **1b** and **1d** were prepared by the following general procedure: phenyldichloromethane (for **1b**) or (2-methylphenyl)phenylmethanol (for **1d**) (30 mmol) with benzotriazole (40 mmol) in the presence of *p*-toluenesulfonic acid (0.3 g) in toluene (50 mL) was refluxed for 40 h. The mixture was washed with NaOH (aq. 2 *N*, 40 mL) and the organic layer was extracted with HCl (conc. 30 mL). The acid solution was neutralized with NaOH (aq. 4 *N*) to give a precipitate, which was washed with water (3 × 30 mL) and dried under vacuum to give the pure product (**1b**: 62%; **1d**: 68%). New compounds **1b** and **1d** were characterized by NMR and CHN analyses. Compound **1c** was prepared by the following procedure: to (4-methylbenzyl)benzotriazole (2.2 g, 10 mmol) (for its preparation, see Katritzky, A. R.; Xie, L.; Toader, D.; Serdyuk, L. *J. Am. Chem. Soc.* **1995**, *117*, 12015) in THF (100 mL) at -78 °C under argon was added *n*-BuLi (2.0 *M* in cyclohexane, 5.5 mL, 11 mmol). After 1 h, 2-bromopropane (1.2 g, 10 mmol) in THF (10 mL) was added. The mixture was stirred at -78 °C for an additional 6 h. The mixture without work-up was used directly for the preparation of **2d**.[17]

17. **Preparation of α-(Benzotriazol-1-yl)alkyl Aryl Ketones 2a-f. General Procedure.** To the corresponding (benzotriazol-1-yl)methane **1** (10 mmol) in dry THF (100 mL) was added *n*-BuLi (2.5 *M* in cyclohexane, 4.4 mL, 11 mmol) at - 78 °C under argon. After 1 h, the appropriate phenacyl chloride (11 mmol) in THF (10 mL) was added. The mixture was stirred at -78 °C for 3 h, and then gradually warmed to rt overnight. Water (50 mL) and chloroform (50 mL) were added and the organic layer separated. The aqueous layers were extracted with $CHCl_3$ (3×25 mL). The combined organic layer was washed with H_2O (30 mL) and dried over $MgSO_4$. After the solvent was removed, the crude product was purified by recrystalization from Et_2O and hexanes (**2a-c**, **2e** and **2f**) to give pure **2** (**2a**:92%; **2b**:56%; **2c**:82%; **2e**:86%; **2f**:86%). Crude **2d** was used directly for the next step reaction. Products **2b,c,e,f** were all previously unknown and were fully characterized by ^1H and ^{13}C NMR spectroscopy and elemental analyses. Physical data for **2a** (NMR, mp 265-267 °C) are consistent with the reported data (see: Katritzky, A. R.; Yang, Z.; Lam, J. N. *Synthesis* **1990**, 666).

18. **Preparation of 4-Substituted Aryl Ketones 5a-j and 4-Unsubstituted Aryl Ketones 7g and 7i. General Procedure.** To a solution of an appropriate **2** (2 mmol) in THF (50 mL) was added the corresponding lithium or magnesium reagent (4 mmol) at - 78 °C under argon. The mixture was gradually warmed to rt overnight. Water (50 mL) and EtOAc (50 mL) were added to the mixture and the organic layer was separated. The aqueous layer was extracted with EtOAc (3×25 mL). The combined organic layer was washed with H_2O (30 mL) and dried over $MgSO_4$. After the solvent was removed, the crude product was purified by column chromatography (silica gel, hexane:EtOAc = 5:1 for **5a-e** and hexane:EtOAc =25:1 for **5f-j**, **7g** and **7i**) to give pure **5a-f**, **5j** and mixtures of **5h** with *ortho* product, **5g** with **7g**, and **5i** with **7i**. All products were fully characterized by ^1H and ^{13}C NMR spectroscopy and elemental analyses/HRMS.

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