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β-Nitrostyrenes as electrophiles in Parham cyclization chemistry: reaction with *o*-lithiobenzonitrile

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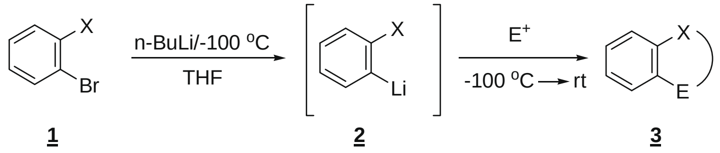
ABSTRACT

β-Nitrostyrenes react with *o*-lithiobenzonitrile, generated from the requisite aryl bromide at −100 °C by bromine–lithium exchange with *n*-butyllithium in THF, to afford 2-nitro-3-phenyl-3*H*-inden-1-ylamines resulting from 1,4-addition to the β-nitrostyrene followed by intramolecular capture of the resultant nitronate anion by the *ortho*-cyano functional group.

The construction of benzo-fused polycyclic carbocycles and heterocycles via low-temperature reaction of aryllithium reagents containing electrophilic ortho-substituted functional groups, a method known as the Parham cyclization, was developed three decades ago and has been widely accepted as a powerful tool for organic synthesis.[1] A sampling of electrophilic functional groups used in these reactions as external electrophiles includes ketones,[2] aldehydes,[3] nitriles,[4] imines,[5] isocyanates,[6] and anhydrides (Scheme 1).[7]

Reactions of β-nitrostyrenes and other nitroalkenes as Michael acceptors with a variety of organometallic reagents have been well documented.[8] More recently, the ability of β-nitrostyrenes and nitroalkenes to undergo conjugate additions with organolithium reagents has been utilized as a key carbon–carbon bond-forming step in the synthesis of a variety of cyclic ring systems.[9] Paulson and Stubbe described the first known reaction of a Parham-type substrate (the bromine–lithium-exchanged intermediate of **4**) with nitroalkene **5** as a Michael acceptor in the key step toward the construction of a ring system in the total synthesis of (+)-lycoricidine (**7**) (Scheme 2).[10]

We wish to report the first example of the reaction of an *ortho*-cyano-functionalized aryllithium reagent with a β-nitrostyrene and concomitant intramolecular capture of the resultant lithium nitronate to afford cyclized products, 2-nitro-3-phenyl-3*H*-inden-1-ylamines, in a single-pot procedure. The halogen–lithium exchange chemistry of the substrate chosen for this study, 2-bromobenzonitrile (**8**), has been well documented.[4] Thus, reaction of 2-bromobenzonitrile with *n*-butyllithium in THF under nitrogen at −95 to −100 °C generates the corresponding aryllithium which is then quenched with the β-nitrostyrene **9** followed by warming to room temperature (Scheme 3). Workup provides the 2-nitro-3-aryl-3*H*-inden-1-ylamines **11** in moderate-good yields (Table 1).[11] Using 2-methoxy-β-nitrostyrene as the electrophile in the reaction sequence resulted in the formation of **12d** as a minor by-product along with **11d**. A possible rationale for this observation may be related to the stability of the methoxy-chelated intermediate **10d** (Fig. 1). At any rate, the uncyclized Michael adduct **12** can be isolated as the major product upon low temperature quenching with CH_3OH.[12] The ^1H NMR spectra of inden-1-ylamines



Scheme 1.

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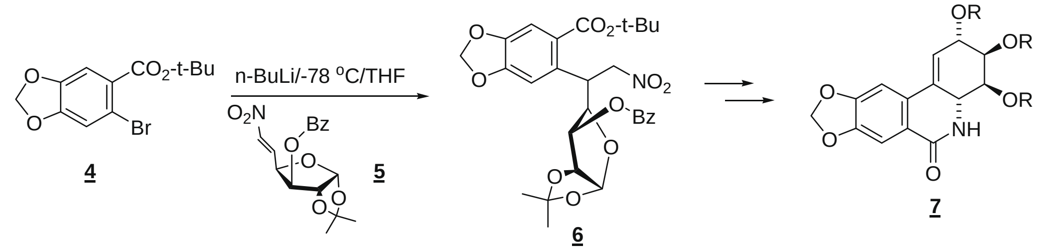
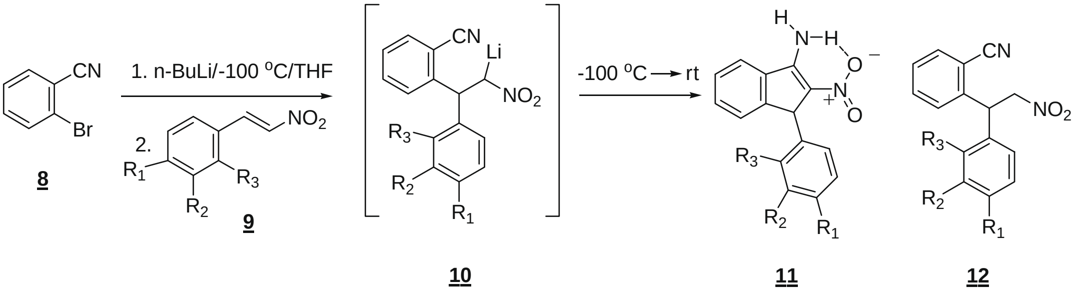
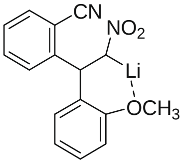


Scheme 2.



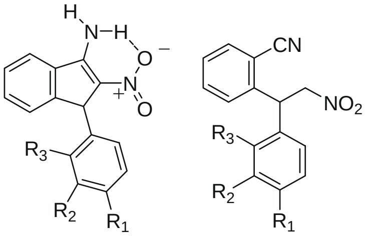
Scheme 3.



10d

Figure 1.

Table 1



11 **12**

Compound	R$_1$	R$_2$	R$_3$	Yield (%) **11**	Yield (%) **12**
9a	H	H	H	61	
9b	OCH$_3$	H	H	52	
9c	H	OCH$_3$	H	52	
9d	H	H	OCH$_3$	39	19
9e	H	H	CH$_3$	56	
9f	H	C$_2$H$_5$	H	54	
9e	H	H	CH$_3$		46
9d	H	H	OCH$_3$		41

11a–d reveal two –NH protons which are non-equivalent, presumably due to intramolecular hydrogen bonding of the enamino protons with the adjacent nitro group.[13] Future work will address the scope and limitations of Michael addition chemistry of β-nitrostyrenes with other Parham substrates and applications to total synthesis.

Acknowledgments

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11. *General procedure illustrated by the preparation of* **11a**: To a solution of 2-bromobenzonitrile (1.00 g; 5.49 mmol) in dry THF (25 mL) under N$_2$ at −100 °C, 1.1 equiv of *n*-butyllithium (3.92 mL; 1.4 M in hexane; 5.49 mmol) was added at such a rate that a strong exotherm was not produced. After stirring for 30 min at −95 to −100 °C, a solution of the nitrostyrene **9a** (.819 g; 5.49 mmol in 5 mL THF) was added in the same fashion. Upon completion of the addition, the reaction was maintained at −100 °C for 30 min, then allowed to warm to room temperature and stirred overnight. The mixture was then poured into water and extracted with CH$_2$Cl$_2$ (3 × 35 mL). The combined organics were dried (MgSO$_4$), filtered, and concentrated. The crude product was purified by recrystallization from EtOAc to afford 2-nitro-1-phenyl-1*H*-inden-3-amine (**11a**) as a pale yellow amorphous solid, yield = 0.840 mg (61%); mp 211–215 °C (dec); IR: 3360, 3128, 1649, 1459, 1376 cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz): δ 5.18 s, 1, benzylic C*H*), 7.19–7.34 m, 6, ArH), 7.49–7.54 (m, 2, ArH), 8.10–8.11 (m, 1, ArH), 8.44 (br s, 1, N*H*), 8.72 (br s, 1, N*H*); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 51.00, 122.18, 125.34, 126.91, 127.56, 127.90, 128.58, 132.06, 140.03, 205.44. Anal. Calcd for $C_{15}H_{12}N_2O_2$ 1:8 H_2O:C, 70.80; H, 4.82; N, 11.01. Found: C, 70.72; H, 4.58; N, 10.64.

12. *General procedure illustrated by the preparation of* **12d**: To a solution of 2-bromobenzonitrile (1.00 g; 5.49 mmol) in dry THF (25 mL) under N_2 at −100 °C, 1.1 equiv of *n*-butyllithium (3.92 mL; 1.4 M in hexane; 5.49 mmol) was added at such a rate that a strong exotherm was not produced. After stirring for 30 min at −95 to −100 °C, a solution of the nitrostyrene **9c** (.819 g; 5.49 mmol in 5 mL THF) was added in the same fashion. Upon completion of the addition, the reaction was maintained at −100 °C for 15 min, then poured into CH_3OH (35 mL) and stirred overnight. The mixture was diluted with water and extracted with CH_2Cl_2 (3 × 35 mL). The combined organics were dried ($MgSO_4$), filtered, and concentrated, and the crude product was purified by flash chromatography on silica gel (1:1 hexanes/EtOAc) to afford 2-(1-(2-methoxyphenyl)-2-nitroethyl)benzonitrile (**12d**) as a fluffy off-white solid, yield = 0.635 mg (41%); mp 121–121.3 °C; IR: 2226, 1490, 1377 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz): δ 3.86 s, 3, OC*H*$_3$), 5.34 dd, 2, diastereotopic C*H*$_2$), 5.67 (t, 1, benzylic C*H*), 6.95–7.03 (m, 2, Ar*H*), 7.27–7.32 (m, 2, Ar*H*), 7.45–7.48 (m, 1, Ar*H*); 7.66–7.78 (m, 3, Ar*H*); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 41.26, 55.12, 76.66, 111.34, 113.64, 117.37, 120.75, 126.43, 127.84, 128.04, 128.49, 129.32, 133.10, 133.51, 143.00, 157.19 Anal. Calcd for $C_{16}H_{14}N_2O_3$ 1/8 H_2O: C,67.55; H, 4.93; N, 9.85. Found: C, 67.36; H, 4.71; N, 9.73.
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