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LETTERS

Conversions of primary amines to azides by *n*-butyllithium and azidotris(diethylamino)phosphonium bromide

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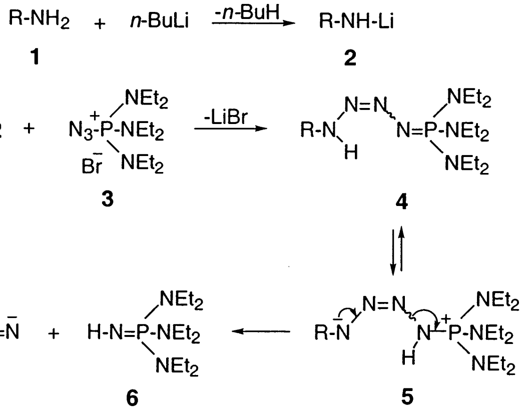
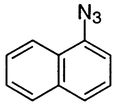
Abstract—Lithium derivatives of varied aromatic, heterocyclic, aliphatic, and alicyclic primary amines react efficiently with azidotris(diethylamino)phosphonium bromide in THF at low temperatures to give azides, lithium bromide, nitrogen, and tris(diethylamino)phosphorimine. © 2002 Elsevier Science Ltd. All rights reserved.

Organic azides (R-N_3) are important chemicals.[1] Of interest with respect to their synthesis is that aliphatic and alicyclic primary amines have been converted by excess *n*-BuLi or NaH and then tosyl azide (*p*-CH_3-C_6H_4-SO_2-N_3] to azides.[2a–f] More recently aliphatic and alicyclic primary amines have been found to give azides in greater yields by reactions with trifyl azide (CF_3-SO_2-N_3) as catalyzed by Cu^{++}, Ni^{++}, and Zn^{++} ions.[2g] Now reported is that aromatic, heterocyclic, aliphatic, and alicyclic primary amines (Scheme 1) in THF at −78°C react rapidly with *n*-BuLi and then azidotris(diethylamino)phosphonium bromide (**3**)[3] to give the corresponding azides (**7**) and tris(diethylamino)phosphorimine (**6**) efficiently, reliably, and safely. The method also has advantages in that sensitive azides can be prepared at low temperatures and separated from other reaction products simply. The overall methodologies, typical laboratory procedures, the gross reaction mechanism, and specific synthesis examples are discussed and illustrated as follows.



Scheme 1.

Treatment of 1-aminonaphthalene with *n*-BuLi (1.02 equiv.) and then **3** (1.20 equiv.) in THF at −78°C, simple workup after 0.5–1.0 h, rapid chromatography on silica gel, and elution with Et_2O give 1-azidonaphthalene (**8**, 88%).[4a,b] Similarly, 2-aminonaphthalene is converted to 2-azidonaphthalene (**9**, 81%).[4b,5a] Further, one-pot double diazo transfer on 1,5-diaminonaphthalene with *n*-BuLi (2.05 equiv.) and **3** (2.37 equiv.) in THF at −78°C yields 1,5-diazidonaphthalene (**10**, 85%)[5b] and 1,2-diazidobenzene (**11**)[5c] is conveniently prepared (84%) from 1,2-diaminobenzene, *n*-BuLi (2.43 equiv.), and **3** (2.44 equiv.) in THF at −78°C.



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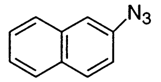

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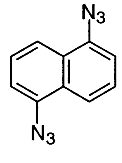

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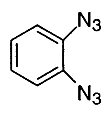

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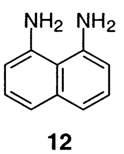
Diazo transfers on 1,8-diaminonaphthalene (**12**) to give 1,8-diazidonaphthalene (**13**)[5d] are more complicated than for 1,5-diaminonaphthalene to **10**. Additions of *n*-BuLi (1.71 equiv.) and then **3** (1.91 equiv.) to **12** in THF at −78°C yield 1-amino-8-azidonaphthalene (**14**, 74%).[5d,e] Similarly, **12**, *n*-BuLi (2.11 equiv.) and **3** (1.10 equiv.) in THF at −78°C (10 min) and then reaction with *n*-BuLi (1.07 equiv.) at −78°C give **14** (61%).[5e]



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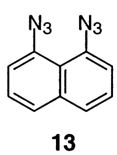

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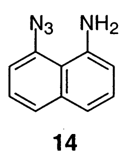

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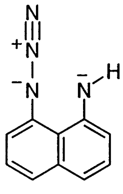
Pure **14** is converted however by **3** (1.13 equiv.) and *n*-BuLi (1.02 equiv.) in THF at −78°C to **13** (52%) after a 2.5 h reaction period and allowing the mixture to warm to room temperature. Further, stirring diamine **12** with *n*-BuLi (2.06 equiv.) and **3** (2.42 equiv.) in THF for 1 h at −78°C, adding additional *n*-BuLi (1.03 equiv.) and **3** (1.15 equiv.) at −78°C for 30 min, and allowing the reactions to proceed for 4 h at 20–25°C yield diazide **13** (74%). The slowness of double diazo transfer of **12** at −78°C may be due to difficulty in deprotonation of **14** by *n*-BuLi to give the 8-azido-1-naphthylamide ion (**15**) and/or interactions of the azide and the amide groups in **15** yielding **16** and/or **17**. Detailed studies of the behaviors of **15**–**17** are to be made.



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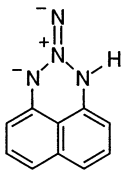

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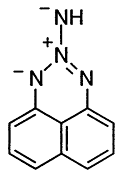

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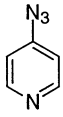
Heteroaromatic azides are also easily prepared from lithium derivatives of primary heteroaromatic amines and **3**. Thus 4-azidopyridine (**18**, 85%)[5f] and 2-azidopyridine (**19**, 80%)[5g] are readily obtained from their respective aminopyridines, *n*-BuLi, and **3** by procedures essentially identical to that for **8** and **9**. The IR absorptions of the azido group in **19** are weak and thus indicative of the major equilibrative presence of its ring-closure isomer, tetrazolo[1,5-*a*]pyridine (**20**).[5g]



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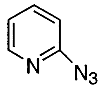

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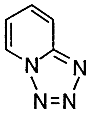

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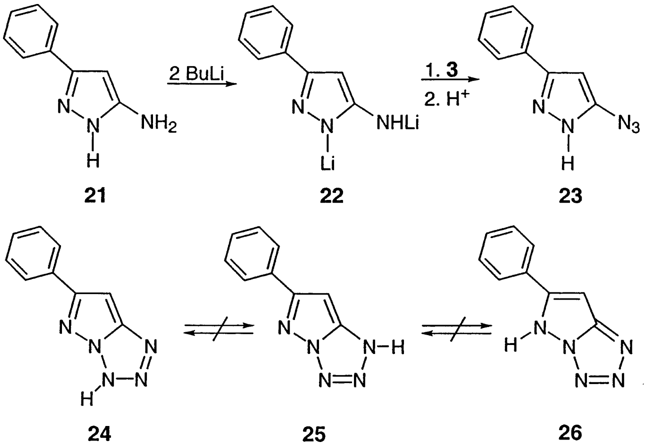
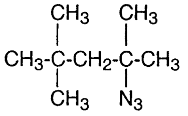
The present diazo transfer methodology (Scheme 1) is also usable for preparing 5-membered ring hetaryl azides. Thus, 5-azido-3-phenylpyrazole (**23**)[5h] is obtained from 5-amino-3-phenylpyrazole (**21**), *n*-BuLi (1.91 equiv.), and **3** (1.12 equiv.) at −78°C to ~25°C for 3 h. The synthesis is of interest in that **23** is apparently formed by directed diazo transfer to the dilithio derivative (**22**) of **21** and protonation (Scheme 2). The spectra of **23** reveal ^{1}H NMR absorptions for N–H and C–H in its pyrazole ring and a very strong IR band for its azide group. These spectra indicate that azidopyrazole **23** does not undergo extensive heterocyclization and tautomerism (Scheme 2) to triazolopyrazole isomers **24** and **25**.[5h]



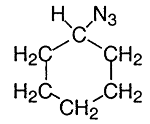
Scheme 2.

The above azidation methodology has been extended to 2-amino-2,4,4-trimethylpentane, cyclohexylamine, and 1-hexylamine. Thus 2-azido-2,4,4-trimethylpentane (**27**, 45%),[5i] azidocyclohexane (**28**, 41%),[5j] and 1-azidohexane (**29**, 47%) are obtained conveniently from their corresponding amines, *n*-BuLi, and **3** by procedures similar to that for preparing the prior aromatic and pyridyl azides using *n*-BuLi and **3** at −78°C.



$$CH_3\text{-}C(CH_3)_2\text{-}CH_2\text{-}C(CH_3)_2\text{-}N_3$$

27



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$CH_3\text{-}(CH_2)_5\text{-}N_3$

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No efforts were made to improve the yields of the above aliphatic and alicyclic azides other than to find that the conversion of 2-amino-2,4,4-trimethylpentane to **27** is increased by successive sequential additions of *n*-BuLi and **3**. Thus, reactions of 2-amino-2,4,4-trimethylpentane with *n*-BuLi (1.0 equiv.) and **3** (1.12 equiv.) at −78°C followed by further addition of *n*-BuLi (1.04 equiv.) and **3** (1.14 equiv.) at −78°C give **27** (>59%).[5i]

Further uses of **3** for diazo transfer and as an oxidizing agent will be reported.

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3. (a) Azidophosphonium bromide **3**, an excellent diazo transfer reagent for stabilized carbanions, is prepared by (1) bromination of tris(diethylamino)phosphine [$(Et_2N)_3P$)] obtained from Et_2NH and PCl_3 and (2) reaction of the resulting bromotris(diethylamino)phosphonium bromide [$(Et_2N)_3P^+BrBr^-$] with NaN_3[3b]; (b) McGuiness, M.; Shechter, H. *Tetrahedron Lett.* **1990**, *31*, 1990; (c) We should like to thank M. McGuiness for his counsel in the present investigation.
4. (a) A typical procedure for monoaziridination of the amines of the present study is described for preparation of **8** as follows. 1-Aminonaphthalene (0.3687 g, 2.58 mmol) in dry THF (10 mL) at −78°C was deprotonated with n-BuLi (1.05 mL, 2.50 M, 2.62 mmol in hexane, 1.02 equiv.). Azidophosphonium bromide **3** (1.1410 g, 3.09 mmol, 1.20 equiv.) in dry THF (20 mL) was added. After being stirred for ~45 min at −78°C, the reaction mixture was washed with aqueous 0.25 M NH_4Cl and with CH_2Cl_2. The organic layer was concentrated at reduced pressure. Rapid chromatography on silica gel, elution with Et_2O, and solvent removal gave **8** (0.3838 g, 2.27 mmol, 88%), a red liquid. TLC of the product gave only one spot: FTIR (thin film) 2111.8 (-N=$^+$N=$^-$N) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.27 (d, $J = 7.37$ Hz, 1H), 7.42–7.70 (m, 4H), 7.86–7.91 (m, 1H), 8.18–8.23 (m, 1H). The ^{1}H NMR and FTIR spectra of **8** match literature values[4b]; (b) Boshev, G.; Dyall, L. K.; Sadler, P. R. *Aust. J. Chem.* **1972**, *25*, 599.
5. The ^{1}H NMR and FTIR spectra and/or other physical constants of the additional azides presently reported and as designated by number agree with literature values: (a) **9a**: Ref 4b; (b) **10**: Smith, P. A. S.; Brown, B. B. *J. Am. Chem. Soc.* **1951**, *73*, 2438; (c) **11**: Hall, J. H.; Patterson, E. *J. Am. Chem. Soc.* **1965**, *8*, 1147; (d) **13**: Reese, C. W.; Storr, R. C.; Bradbury, S. *J. Chem. Soc.*, *Perkin 1* **1972**, 68; (e) **14**: Ref. 5d; (f) **18**: El'tsov, A. V.; Khanchmann, A.; Rtishchov, N. I. *Zh. Org. Khim.* **1977**, *13*, 465; (g) **19**: Wentrup, C.; Winter, H.-W. *J. Am. Chem. Soc.* **1980**, *102*, 6159; (h) **23**: deMendoza, J.; Elguero, J. *J. Heterocycl. Chem.* **1974**, *11*, 921; (i) **27**: Ref. 5h; (j) **28**: Steinheimer, T. R.; Wulfman, D. S.; McCullagh, L. N. *Synthesis* **1971**, 325; (k) **29**: Ref. 2b.