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POLYMER SUPPORTED BASES IN SOLUTION-PHASE SYNTHESIS. 2. A CONVENIENT METHOD FOR N-ALKYLATION REACTIONS OF WEAKLY ACIDIC HETEROCYCLES

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Abstract: A convenient solution-phase method for N-alkylation reactions of weakly acidic heterocycles employing polymer supported super base PBEMP is described. By using this method, multiple-step and chemoselective N-alkylation sequences can be carried out in a one-pot process.

The high throughput synthesis of small molecules using combinatorial chemistry technologies has become an increasingly important approach for expediting the drug discovery process.[1] While earlier research activities reported in the literature focus in the area of solid-phase organic chemistry (SPOC), solution-phase methods have been developed that utilize polymer supported reagents and/or quenching agents,[2–6] thereby allowing the use of the key features of SPOC (use of excess reactants to drive reactions to completion, simple reaction workup and purification). This strategy for high throughput solution synthesis avoids the need for substrate linkage to a polymer support and long methodology development time. We have previously reported a solution-phase method for phenol O-alkylation reactions[7] with a polymer supported guanidine base PTBD (**1**)[8,9] that serves a dual purpose as a deprotonating reagent and as a quenching agent for excess starting phenol. In line with our continuing efforts in this area, we wish to report the use of polymer supported bases for the solution phase synthesis of N-alkyl heterocycles by the N-alkylation reaction of weakly acidic heterocycles. Using this methodology, multiple-step and chemoselective N-alkylation sequences can be carried out in a convenient one-pot process in high yield and chemical purity.

Aromatic heterocycles are important constituents in the structures of many pharmaceutically important chemical templates. Derivatization of heterocyclic pharmacophores represents a versatile approach to generate chemical diversity for lead identification and optimization. From a classical perspective, N-alkylation reactions of weakly acidic NH-containing aromatic heterocyclic compounds require the use of a strong base (sodium hydride, potassium *tert*-butoxide, lithium diisopropylamide, etc.) for deprotonation. With the inherent and obvious limitations of such systems in mind, we investigated a polymer-supported form of the non-ionic, organic super base, 2-*tert*-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine (BEMP, **2a**) as an effective reagent for heterocyclic N-alkylation reactions. BEMP is reported to be highly basic ($pK_{BH\oplus}$ = 27.5 in MeCN) with its basicity comparable to 5 M aq. KOH/Bu_4N^+/MeCN and higher than K_2CO_3/18-crown-6/MeCN.[10] Furthermore, reactions employing BEMP can be run under strictly

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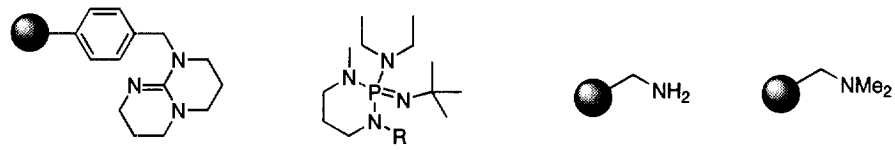
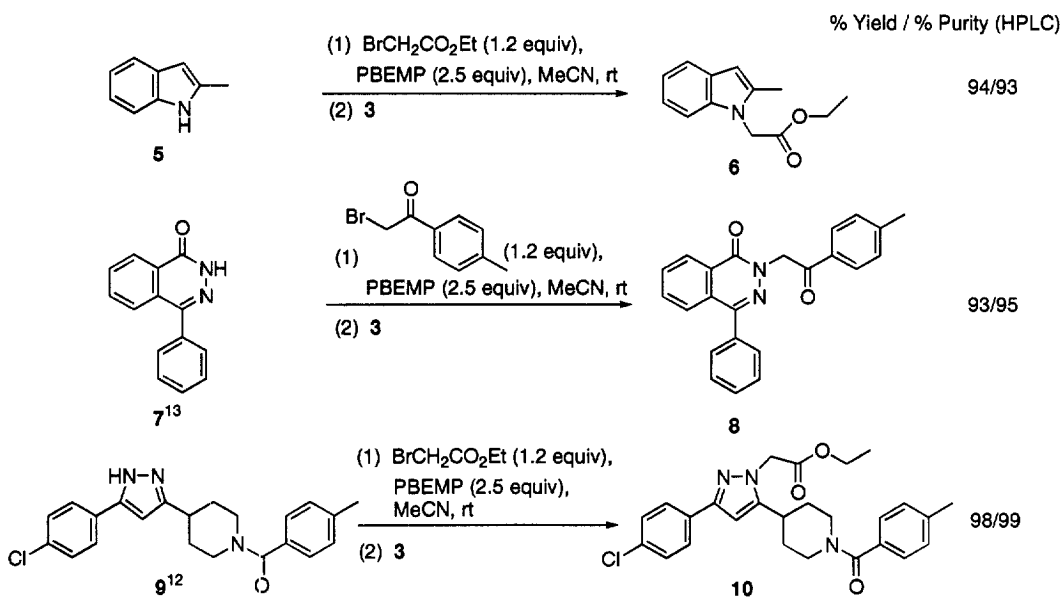
anhydrous conditions. We therefore proceeded to explore the synthetic application of the polystyrene supported BEMP (PBEMP, **2b**),[11] which is ether commercially available[9] or can be readily prepared from inexpensive starting materials.[10]



The N-alkylation reactions of a number of representative aromatic N-heterocycles with alkyl halides in the presence of PBEMP have been studied and the results are shown in Scheme 1. In a typical protocol, alkyl halide (0.12 mmol) and N-heterocyclic substrate (0.10 mmol) were added to the reaction vessel containing the PBEMP (0.25 mmol) in 0.8 mL of acetonitrile. The reaction mixture was vortexed at room temperature until the N-heterocyclic substrate was completely consumed, as determined by HPLC analysis. Then aminomethyl polystyrene (**3**, 0.10 mmol) was then added to sequester the remaining excess alkyl halide. After quenching the reaction for 16 h, the product was collected after filtration and solvent evaporation. The products were all analyzed by reversed-phase HPLC and ^{1}H NMR. As shown in Scheme 1, the N-alkylation products obtained by this method exhibit high purity (93–99%) and high chemical yields (93–98%). Using the PBEMP base, the N-alkylation of 2-methylindole (**5**) where the N-1 position is sterically hindered, product **6** is obtained in 94% yield. The alkylation of 5-(4-chlorophenyl)-3-(piperidin-4-yl) disubstituted pyrazole **9**[12] occurred exclusively at the N-2 position of pyrazole ring to give product **10**. The regiochemistry of the substituents in **10** was

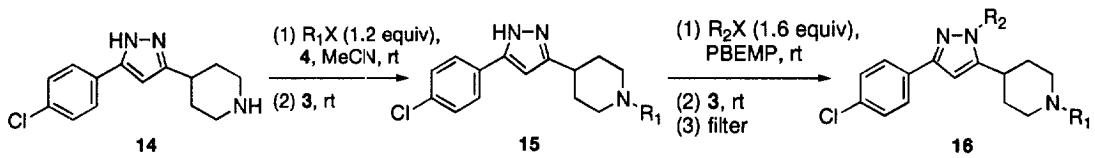


Scheme 1. Examples of N-alkylation of aromatic heterocycles employing polymer supported bases as deprotonating reagent and quenching agent

confirmed by a NOESY experiment that shows a clear NOE between the ester α-proton and the piperdinyl C-4' proton.

In a comparison study between PBEMP and other weakly basic resins, we found that PBEMP is superior to other commonly used basic resins in the heterocyclic N-alkylation reaction. For example, the alkylations of **5**, **7**, and **9** did not take place, to any measurable extent, when dimethylaminomethyl polystyrene **4** was used as a base under identical reaction conditions to those outlined with PBEMP resin. In addition, substrates **5**, **7**, or **9** proceeded to only 15–25% conversion when the moderately basic PTBD resin **1** was employed.

Our interests in developing simple yet practical processes for creating diverse chemical libraries via laboratory automation led us to explore the concept of one-pot synthetic process for multiple-step reaction sequences.[14] In an extension of the methodology described above, we chose to examine the tandem acylation and/or alkylation on 5-(4-chlorophenyl)-3-(piperidin-4-yl)pyrazole (**14**) as a 'proof of concept' experiment.



14 15 16

Scheme 2. A two-step reaction sequence in one-pot (R_1X = alkyl bromides or acid chloride; R_2X = alkyl bromides)

The pyrazole **14**[12] contains two distinct amino functionality with widely different acidities that should facilitate the combinatorial elaboration of this well known pharmacophore. Therefore, pyrazole **14** represents an interesting template for library production since it possess two unique sites for introducing diversity through tandem N-alkylation and/or acylation reactions. To demonstrate the potential of this methodology, pyrazole **14** was therefore acylated or alkylated, in the presence of tertiary base resin **4**, selectively at the piperdinyl-N by using excess of R^1X (acid halides or alkyl halides) to generate intermediate **15** (Scheme 2). Aminomethyl resin **3** was added to sequester the excess R_1X in the first step of the sequence and alkylation reaction of **15** with excess R_2X in presence of super base resin PBEMP (**2b**) afforded the product. Aminomethyl resin **3** was again added to sequester the excess R_2X used in the second alkylation step and the acid by-products from both alkylation steps were scavenged by polymer bases **4** and **2b** during the reaction sequences. Finally, product **16** was obtained by a simple filtration and concentration. Representative products obtained from this two-step/one-pot protocol,[15] along with the chemical yield and purity are shown in Table 1. These results demonstrate that regioselective di-alkylation/acylation products from tandem N-alkylation reactions and tandem acylation/alkylation sequences can proceed in high chemical yield and purity after simple filtration and solvent evaporation.

Table 1. Representative Alkylation Products From the Two-Step One-Pot Protocol

Compound	16a	16b	16c	16d
R_1	4-CN-PhCH$_2$-	PhCH$_2$-	4-Me-PhCO-	4-Cl-PhCH$_2$-
R_2	-CH$_2$CO$_2$Et	-CH$_2$CO$_2$Et	-CH$_2$CO$_2$Et	4-CN-PhCH$_2$-
Yield[a]	97%	99%	96%	95%
Purity[b]	96%	92%	95%	86%

[a] Based on mass recovery of product. [b] Determined by HPLC (at λ = 254 nm).

In summary, we have demonstrated a convenient solution-phase methodology for N-alkylation reactions of weakly acidic heterocycles utilizing the polymer supported superbase PBEMP. In addition, one-pot solution phase, multiple-step reaction sequences proceed in high chemical yield and purity with the complete control of chemoselectivity by employing appropriate polymer supported reagents with different chemical properties. This solution-phase approach is easily adaptable for parallel and automated chemical synthesis. Further studies on the application of PBEMP and other polymer supported bases are in progress and will be reported in due course.

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REFERENCES AND NOTES

1. For recent reviews see (a) Balkenhohl, F.; von dem Bussche-Hunnefeld, C.; Lansky, A.; Zechel, C. *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 2288. (b) Bristol, J. A. *Tetrahedron*, **1997**, *53*, 6573.
2. (a) Kaldor, S. W.; Siegel, M. G.; Fritz, J. E.; Dressman, B. A.; Hahn, P. J. *Tetrahedron Lett.* **1996**, *37*, 7193. (b) Kaldor, S. W.; Siegel, M. G. *Curr. Opin. Chem. Biol.* **1997**, *1*, 101.
3. Gayo, L. M.; Suto, M. J. *Tetrahedron Lett.* **1997**, *38*, 513.
4. Flynn, D.L.; Crich, J. Z.; Devraj, R. V.; Hockerman, S. L.; Parlow, J. J.; South, M. S.; Woodard, S. J. C. *J. Am. Chem. Soc.* **1997**, *119*, 4874.
5. Booth, R. J.; Hodges, J. C. *J. Am. Chem. Soc.* **1997**, *119*, 4882.
6. Parlow, J. J.; Naing, W.; South, M. S.; Flynn, D. L. *Tetrahedron Lett.* **1997**, *38*, 7959.
7. Xu, W.; Mohan, R.; Morrissey, M. M. *Tetrahedron Lett.* **1997**, *38*, 7337.
8. Iijima, K.; Fukuda, W.; Tomoi, M. *J. Macromol. Sci. Pure Appl. Chem.* **1992**, *A29*, 249.
9. The polymer supported bases, PTBD and PBEMP used in this work were purchased from Fluka/Aldrich.
10. Schwesinger, R. *Nachr. Chem. Tech. Lab.* **1990**, *38*, 1214. Schwesinger, R. *Chimia*, **1985**, *39*, 269.
11. To our knowledge, there was no prior report on the synthetic application of PBEMP, although monomeric BEMP had been employed as a base for elimination and alkylation reactions.[10]
12. For the synthesis and biological activities of 5-phenyl-3-piperidinylpyrazoles, see Rowley, M.; Broughton, H. B.; Collins, I.; Baker, R.; Emms, F.; Marwood, R.; Patel, S.; Ragan, C. I.; Freedman, S. B.; Leeson, P. D. *J. Med. Chem.* **1996**, *39*, 1943.
13. For the synthesis and antiasthmatic activities of phthalazinones, see Yamaguchi, M.; Kamei, K.; Koga, T.; Akima, M.; Kuroki, T.; Ohi, N. *J. Med. Chem.* **1993**, *36*, 4052 and 4061.
14. For earlier examples of simultaneous multi-step synthesis using polymeric reagents, see Parlow, J. J. *Tetrahedron Lett.* **1995**, *36*, 1395.
15. Typical reaction procedure: a mixture of **14** (0.10 mmol), α-bromo-*p*-tolunitrile (0.12 mmol) and **4** (0.15 mmol) in 1.0 ml MeCN was vortexed at rt for 24 h. **3** (0.06 mmol) was added and the reaction mixture was vortexed at rt for 16 h. Ethyl bromoacetate (0.16 mmol) and **2b** (0.35 mmol) were added and the mixture was vortexed for another 24 h at rt. Additional **3** (0.06 mmol) was added and the mixture was vortexed at rt for 16 h. After filtration of the reaction mixture and evaporation of solvent in vacuo, **16a** (45 mg; 97% yield) was obtained as a solid in 96% purity, determined by HPLC (column: Dynamax-60A C18, 20 cm; solvent: MeCN-H_2O; flow rate: 1 mL/min; UV detection: 254 nm): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.28 (t, J = 7.2 Hz, 3H), 1.78-1.92 (m, 4H), 2.11 (dt, J= 11.1 and 2.7 Hz, 2H), 2.47 (m, 1H), 2.95 (d, J = 11.1 Hz, 2H), 3.58 (s, 2H), 4.25 (q, J = 7.2 Hz, 2H), 4.90 (s, 2H), 6.39 (s, 1H), 7.34 (d, J = 8.7 Hz, 2H), 7.47 (d, J = 8.4 Hz, 2H), 7.63 (d, J = 8.4 Hz, 2H), 7.69 (d, J = 8.7 Hz, 2H).