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## Synthetic Applications of Polystyrene-Supported 1,1,3,3-Tetramethylguanidine

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**Abstract:** Several applications of polystyrene-supported 1,1,3,3-tetramethylguanidine (PS-TMG) in synthetic organic chemistry have been explored. This study evidenced the effectiveness and versatility of this new member of the supported guanidine superbases as an attractive candidate to replace the bases usually employed in organic synthesis during the implementation of environmentally friendly preparative processes.

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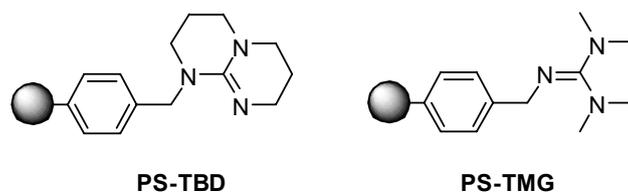
**Key words:** Supported reagents, TMG, base

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## Introduction

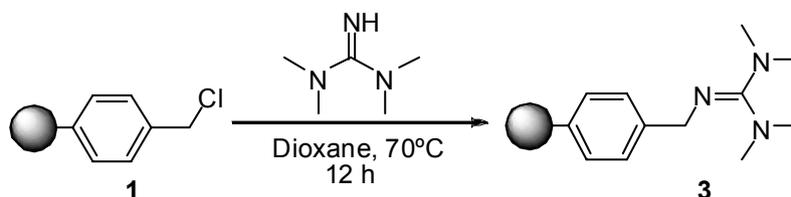
The quest for new drug molecules in the pharmaceutical industry is a long and expensive process that is undertaken in an increasingly competitive environment. Therefore, the development of novel synthetic strategies that allow efficient and rapid access to libraries of highly diverse small organic molecules remains a research topic of paramount interest for synthetic and medicinal chemists involved in drug discovery. Currently, combinatorial methods<sup>1</sup> that focus on the preparation of libraries<sup>2</sup> of organic molecules are mainly dominated by two strategies: solid-phase synthesis<sup>3</sup> and, with increasing importance, solution-phase parallel synthesis,<sup>4</sup> which involves the use of polymer-supported reagents and/or quenching reagents. The significant evolution and refinement of combinatorial methodologies during the last decade has highlighted the intrinsic advantages of the latter strategy over the well-established SPOS [i.e., allowing the use of the key features of SPOS (e.g., use of excess reactants to drive reactions to completion, simple reaction workup and purification) and avoiding the need for substrate linkage to a polymeric matrix]. Nevertheless, the enormous potential of polymer-assisted solution-phase synthesis is still limited by the relatively low abundance of commercially available supported reagents.

As part of a program aimed at the synthesis of azynone libraries,<sup>5</sup> we recently documented the use of different polymer-supported organic superbases as catalysts during the optimization of consecutive reactions.<sup>6</sup> These experiments demonstrated the superiority of polystyrene-supported 1,5,7-triazabicyclo[4,4,0]dec-5-ene (PS-TBD) in comparison to other commercially available supported bases (e.g., Si-TBD, PS-DIPEA, PS-N-methylpiperidine, PS-phosphazene). Despite the remarkable efficiency of PS-TBD, as well as the possibility of recovering and re-using supported bases, the cost of this material limited its extensive utilization for library production. In this context, the need to obtain a general purpose and readily available supported base to address the combinatorial exploitation of our methodologies became apparent. It was envisioned that a polymeric version of the former member of the guanidine superbases: polystyrene-supported 1,1,3,3-tetramethylguanidine (PS-TMG), although with a slightly weaker basicity than PS-TBD, could fulfill the desired profile. In this context, we decided to prepare and explore the synthetic scope of PS-TMG and the preliminary results obtained during this study are reported in this communication.



**Figure 1.** Structure of PS-TBD and PS-TMG

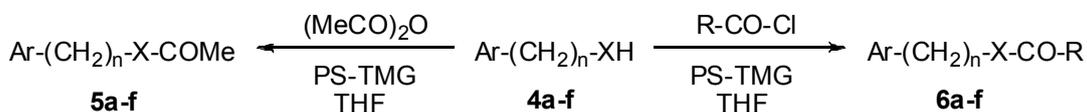
PS-TMG (**3**) was easily obtained by reaction of Merrifield's resin (**1**) with an excess of 1,1,3,3-tetramethylguanidine (**2**) according to a published protocol.<sup>7</sup> These general conditions were slightly modified in order to ensure quantitative substitution of the reactive chloro-substituents of the polymeric matrix, a detailed experimental procedure to prepare **3** is described.<sup>8,9</sup>



**Scheme 1.** Synthesis of PS-TMG

Having established a simple and effective protocol to prepare **3**, we proceeded to evaluate its effectiveness as a base in a set of very common organic transformations (schemes 2–8). Initially, the acylation of compounds incorporating an XH residue (e.g., amines **4a–c**, phenols **4d–e** or alcohols **4f**) was studied by treatment with acetic anhydride or acyl chlorides (scheme 2, table 1). As expected, regardless of the nature of the acylating agent [ $R-COCl$  or  $(CH_3CO)_2O$ ] and the reactivity differences between the nucleophiles (**4**), PS-TMG proved to be an extremely effective additive for this kind of transformation. Amidation proceeded almost quantitatively under mild conditions (room temperature, 4–10 h) on employing catalytic amounts (0.1 equiv.) of **3** in different solvents (e.g., acetonitrile, dioxane, tetrahydrofuran). In a similar fashion, the presence of **3** markedly accelerated the esterification of hydroxyl groups (scheme 2, table 1 entries 4–6, 9–10 and 12). The different reactivity profiles of alcohols and phenols are clearly reflected in the amount of base required to accelerate ester formation. Thus, for simple alcohols (table 1, entry 10) the use of PS-TMG in a catalytic manner (0.2 equiv.) produced the expected esters in almost quantitative yields, while phenols required the

use of stoichiometric amounts of the supported base (**3**) and proved to be less effective (or failed) when acyl chlorides were employed. In most cases the desired compounds were isolated in pure form after the appropriate workup (e.g., filtration and washing of the resin and then evaporation of the solvents).

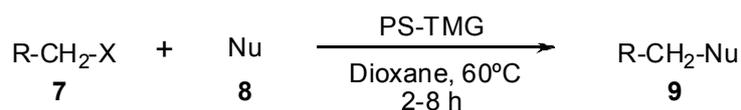


**Scheme 2.** Synthesis of esters and amides employing PS-TMG as basic catalysts

**Table 1.** Synthesis of esters and amides employing PS-TMG as a basic catalyst

Entry	Compd	Ar	n	X	R	Yield (%)
1	5a	Ph	0	NH	-	97
2	5b	4-F-Ph	0	NH	-	99
3	5c	Ph	1	NH	-	84
4	5d	Ph	0	O	-	88
5	5e	4-F-Ph	0	O	-	92
6	5f	Ph	1	O	-	96
7	6a	Ph	0	NH	Me	78
8	6b	Ph	1	NH	Me	89
9	6c	Ph	0	O	Me	67
10	6d	Ph	1	O	Me	91
11	6e	Ph	0	NH	CH <sub>2</sub> -Cl	93
12	6f	Ph	0	O	CH <sub>2</sub> -Cl	53

The effectiveness of **3** in accelerating nucleophilic substitutions on different substrates (**7**) was investigated (scheme 3, table 2). Replacement of the leaving group (Cl or Br) on **7**, when using amines or phenols as nucleophiles (**8**), required the utilisation of stoichiometric amounts of PS-TMG and proceeded smoothly, giving high yields of the expected substitution products **9** (scheme 3, table 2).

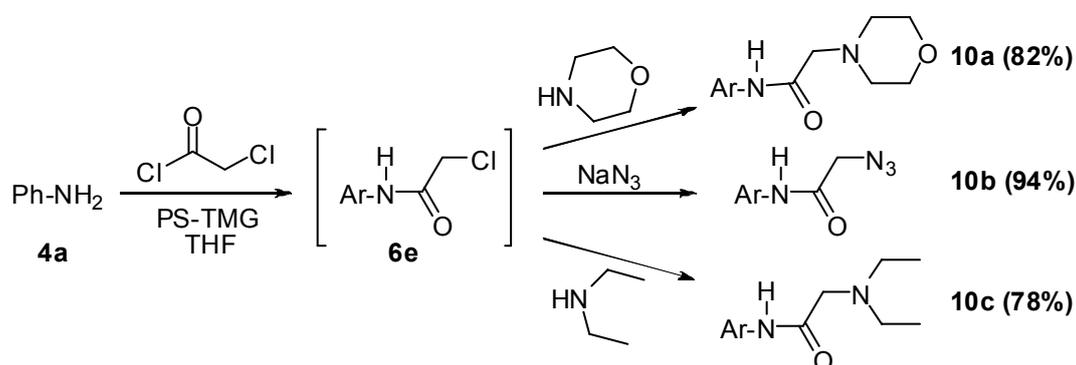


**Scheme 3.** PS-TMG-catalyzed nucleophilic replacement

**Table 2.** Synthesis of amines and ethers employing PS-TMG as a catalyst

Entry	R-CH <sub>2</sub> -X	Nu	Yield (%)
1	Ph-CH <sub>2</sub> -Cl	HN(Et) <sub>2</sub>	89
2	Ph-CH <sub>2</sub> -Cl	HN(Et) <sub>2</sub> O	93
3	Ph-CH <sub>2</sub> -Cl	Ph-NH <sub>2</sub>	84
4	Ph-CH <sub>2</sub> -Cl	Ph-OH	91
5	Ph-CO-CH <sub>2</sub> -Br	HN(Et) <sub>2</sub>	97
6	Ph-CO-CH <sub>2</sub> -Br	HN(Et) <sub>2</sub> O	96

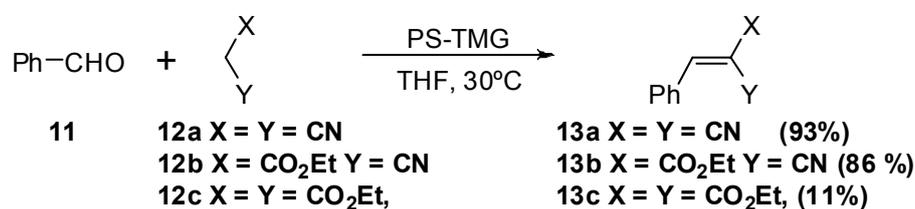
Having confirmed the feasibility of using PS-TMG to catalyze the transformations outlined in schemes 2 and 3, the ability of **3** to assemble more complex structures (e.g., lidocaine analogues **10a** and **10c**) was explored by adopting a consecutive sequence. Thus, the in situ generated  $\alpha$ -chloroacetanilide **6e** was treated with a second nucleophile (scheme 4). It was found that the use of PS-TMG strongly facilitated the synthesis of the  $\alpha$ -aminoacetanilides **10**, which can be obtained in a one-pot reaction in which PS-TMG catalyzes both process. The use of this approach also simplifies the work-up and isolation of the desired compounds (**10**).



**Scheme 4.** PS-TMG as a base in consecutive reactions

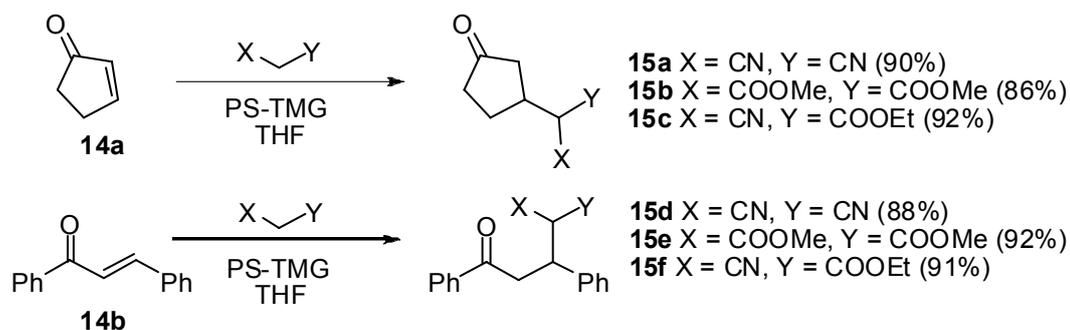
The availability of PS-TMG to catalyze carbon-carbon bond formation was also evaluated by exploring its effectiveness in two powerful classical synthetic reactions: the Knoevenagel condensation (scheme 5) and the Michael addition (scheme 6). In order

to explore the scope of PS-TMG as a base for the Knoevenagel reaction, benzaldehyde (**11**) was reacted with three malonic acid derivatives (**12**) in the presence of 25% of PS-TMG as a catalyst (scheme 5). All experiments were performed at 35 °C using either acetonitrile or tetrahydrofuran as solvents. It was found (scheme 5) that Ps-TMG was a highly efficient catalyst for the Knoevenagel reaction, with the only exception being the reaction in which ethyl malonate was used as the reactive partner (**13c**, scheme 5). Condensation reactions were generally complete in 1–3 h, affording the benzylidene derivatives (**13**) in excellent yields. All attempts to improve the yields of **13c** by raising the reaction temperature (50 °C or 60 °C) or performing the experiments under solvent free conditions<sup>10, 11</sup> did not lead to a significant improvement in yields.



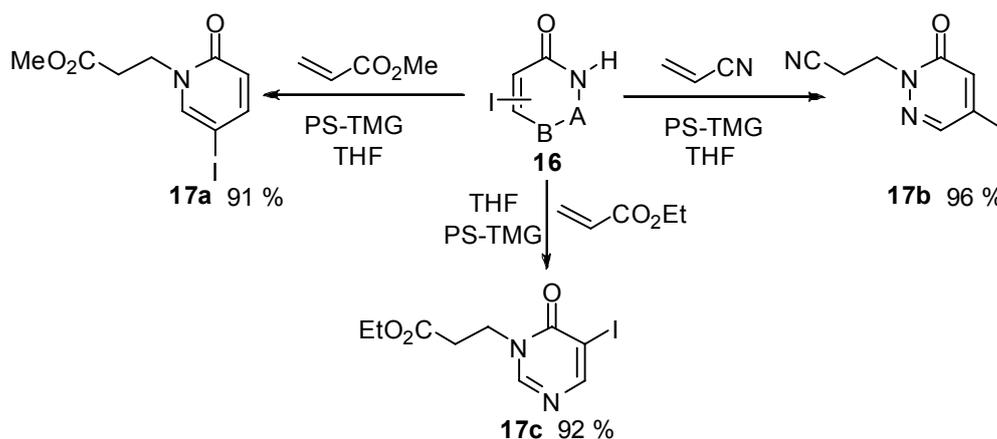
**Scheme 5.** PS-TMG-catalyzed Knoevenagel reaction

The reaction of  $\alpha,\beta$ -unsaturated enones [e.g., cyclopentenone and (E)-benzylidene acetone] with different malonic acid derivatives (**12**) was employed as a model transformation to evaluate the effectiveness of **3** as a base in the Michael reaction (scheme 6). All experiments were performed at 30 °C in the presence of 25% mol of PS-TMG and led to complete conversion of the enone (**14**) after 6–8 h. As evidenced from the experimental results compiled in scheme 6, Ps-TMG accelerates exclusively the 1,4-addition and avoids side reactions. In contrast to the results recently published<sup>10</sup> (employing PS-TBD), we did not find significant differences between experiments performed in tetrahydrofuran or under solvent free conditions.



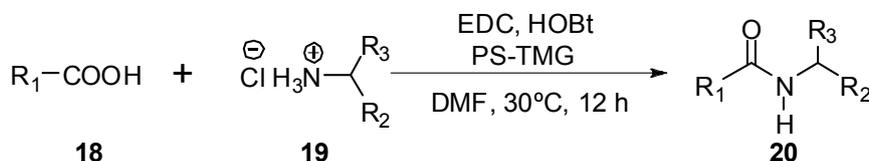
**Scheme 6.** PS-TMG-catalyzed Michael additions to enones

Encouraged by the excellent results obtained in the Michael reaction (scheme 6), further experimental work was aimed at evaluating the role of PS-TMG as a catalyst for the aza-Michael reaction<sup>12</sup> (scheme 7). Three azinones (**16**) [5-iodopyridin-2(1*H*)-one, 5-iodopyridazin-3(2*H*)-one and 4-iodopyrimidin-4(3*H*)-one] and three Michael acceptors (**17**) (acrylonitrile, ethyl acrylate and methyl acrylate) were reacted at 50 °C in the presence of 20% of **3**. The highly effective catalysis shown by Ps-TMG in these experiments afforded the desired  $\beta$ -heteroaryl malonic adducts **17a-c**<sup>13</sup> in high yields (91–96%) and with short reaction times (4–6 h) (scheme 7).



**Scheme 7.** PS-TMG-catalyzed aza-Michael addition to azinones

The suitability of PS-TMG to deprotonate amine hydrochlorides was successfully exploited in the widely employed carbodiimide-mediated amide synthesis (scheme 8). Direct coupling of equimolar amounts of carboxylic acids (**18**) (benzoic or acetic) and the corresponding protected amino acid hydrochloride (**19**) employing 1.5 equivalents of PS-TMG and a slight excess (1.2 equiv.) of EDC and HOBT in DMF, afforded the expected amides (**20**) in excellent isolated yields (table 3).



**Scheme 8.** PS-TMG as a base in amide synthesis

**Table 3.** PS-TMG as a base in amide synthesis

Compound	R <sub>1</sub>	R <sub>2</sub>	R <sub>3</sub>	Yield (%)
<b>20a</b>	Ph	H	COOMe	90
<b>20b</b>	Ph	Me	COOMe	87
<b>20c</b>	Me	H	COOMe	93
<b>20d</b>	Me	Me	COOMe	88

One of the most relevant advantages of the use of supported organic reagents is the possibility of recovering and re-using them in new transformations. As a consequence, after each reaction depicted in schemes 1–7 the PS-TMG was thoroughly washed (THF, MeOH) and then submitted to a new reaction. These experiments showed that the recovered Ps-TMG employed in Knoevenagel, Michael and aza-Michael reactions retained a high catalytic efficiency (up to 4 reaction cycles). However, the resin employed for amide and/or ester formation (schemes 2, 3, 4 and 7) showed a sharp drop in catalytic activity on re-use. In any case, complete regeneration of the activity of the base can be achieved by treatment of **3** with ammonia solution at room temperature (1–2 h), followed by filtration, washing (MeOH, THF) and drying under vacuum.

In summary, some of the potential applications of polystyrene-supported 1,1,3,3-tetramethylguanidine (PS-TMG) have been validated in a set of powerful organic reactions. In light of these findings, PS-TMG can be considered as a new member of the family of organic superbases and, consequently, is an attractive candidate to replace the bases usually employed in organic synthesis (e.g., pyridine, DMAP or DIPEA) in the implementation of environmentally friendly preparative process.

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- (8) **Representative experimental procedure to prepare 3**: A kimble vial containing a suspension of 1 g of Merrieffield resin (4.0 mmol/g, 2% DVB) in THF (3 mL) was vortexed for 5 min. Tetramethylguanidine (2.5 mL) was added and the mixture was heated at 60 °C for 8 h. The slurry was transferred to a fritted polypropylene tube and washed free of the excess reagents using the following sequence of solvents, with intermittent shaking (5 min): THF (2 × 5 mL), DMF (2 × 5 mL), MeOH (2 × 5 mL), H<sub>2</sub>O (2 × 5 mL), MeOH/THF (1/1) (2 × 5 mL) and DCM (2 × 5 mL). The resin was dried under vacuum and the process (synthesis + washing) was repeated twice. The loading of **3** was found to be superior to 3.75 mmol/g as determined by Cl analysis employing wavelength dispersive X-ray fluorescence spectrometry (WD-XRF).<sup>9</sup>
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- (13) Spectroscopic data for representative compounds: 2-Morpholino-*N*-phenylacetamide (**10a**): <sup>1</sup>H-NMR (300 MHz, DMSO-d<sub>6</sub>): 9.43 (bs, 1H), 7.59 (m, 2H), 7.35–7.16 (m, 3H), 3.18 (s, 2H), 2.77 (t, *J* = 7.2 Hz, 4H), 2.64 (t, *J* = 7.2 Hz, 6H). HRMS(EI): C<sub>12</sub>H<sub>16</sub>N<sub>2</sub>O<sub>2</sub>, calcd for 220.2676, found 220.2911. 2-Diethylamino-*N*-phenylacetamide (**10c**): <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>) 9.41 (bs, 1H), 7.56–7.45 (m, 2H), 7.33–7.17 (m, 3H), 3.17 (s, 2H), 2.65 (q, *J* = 7.2 Hz, 4H), 1.11 (t, *J* = 7.2 Hz, 6H). HRMS(EI): C<sub>12</sub>H<sub>18</sub>N<sub>2</sub>O, calcd for 206.2841, found 207.3015. 3-(5-Iodo-2-oxo-2H-pyridin-1-yl)-propionic acid methyl ester (**17a**). <sup>1</sup>H-NMR (CDCl<sub>3</sub> 300 MHz), δ (ppm): 7.65 (d *J*=2.5 Hz, 1H), 7.40 (dd *J*=2.5, *J*=9.5 Hz, 1H), 6.32 (d *J*=9.5 Hz, 1H), 3.82 (s, 3H). HRMS (EI): C<sub>9</sub>H<sub>10</sub>INO<sub>3</sub> calcd 307.0850, found: 307.1021. 3-(4-Iodo-6-oxo-6H-pyridazin-1-yl)-propionitrile (**17b**). <sup>1</sup>H-NMR (CDCl<sub>3</sub> 300 MHz), δ (ppm): 7.94 (d, *J*=1.9, 1H), 7.45 (d, *J*=1.9, 1H), 4.33 (t, *J*=6.7 Hz, 2H), 2.86 (t, *J*=6.7 Hz, 2H). HRMS (EI): C<sub>7</sub>H<sub>6</sub>IN<sub>3</sub>O calcd 274.9556, found: 275.9571.