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Tandem Aza-Wittig/Carbodiimide-Mediated Annulation Applicable to 1,2-Diaza-1,3-dienes for the One-Pot Synthesis of Fully Substituted 1,2-Diaminoimidazoles

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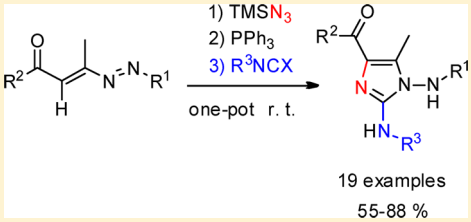
Supporting Information

ABSTRACT: One-pot sequential aza-Michael, Staudinger, and aza-Wittig reactions on 1,2-diaza-1,2-dienes (DDs) can afford fully substituted 1,2-diaminoimidazoles. A plausible mechanism for the imidazole core formation involving an intramolecular ring closure of the carbodiimide-derived phosphazene intermediate is given. The reported strategy has sufficient flexibility to allow substituted 1,2-diaminoimidazoles with orthogonal nitrogen-protective groups to be generated from a variety of heterocumulene moieties linked to the DDs skeleton.



The imidazole ring system is one of the most important substructures found in a large number of natural products and pharmacologically active compounds. For example, the amino acid histidine, the hypnotic agent etomidate,[1] the antiulcerative agent cimetidine,[2] the proton pump inhibitor omeprazole,[3] the fungicide ketoconazole,[4] and the benzodiazepine antagonist flumazenil[5] are imidazole derivatives. Recent advances in the imidazole-tailored ionic liquids,[6] stable nucleophilic carbene,[7] and organic catalyst[8] are other applications of imidazole derivatives. Consequently, new methodologies for the preparation of multisubstituted imidazoles are still desirable in synthetic organic and pharmaceutical chemistry.

Significantly, the class of 2-aminoimidazoles has a particular interest due to various biological properties, and among them, examples of 1-substituted 2-aminoimidazoles have been reported to possess antiviral[9] and anticancer activity[10] along with antagonistic effects against biofilm formation by *Salmonella typhimurium* and *Pseudomonas aeruginosa*.[11]

Because of these interesting biological activities, numerous synthetic routes to 2-aminoimidazoles have been reported. The most common methods for the direct synthesis of polysubstituted 2-aminoimidazoles involve condensation of α-aminocarbonyl compounds with cyanamide,[12] isothioureas or their synthetic equivalents,[13] or more recently, cyclocondensation of 2-aminopyrimidines with α-bromocarbonyl compounds followed by the hydrazine-mediated cleavage of imidazo[1,2-*a*]pyrimidin-1-ium salts.[14] Other general applicable strategies are the iminophosphorane-mediated cyclization of α-azido ester derivatives.[15]

Additionally, fully substituted 1,2-diaminoimidazoles with a distinct substitution pattern at N1 and at the 2-amino function are scarcely represented,[14−16] and new approaches should be developed for their synthesis.

In the course of our continuing interest in the construction of heterocycles based on 1,2-diaza-1,3-dienes (DDs) building blocks,[17] we recently focused our attention on development of synthetic procedures to obtain the imidazole core.[18] Here, we report a novel one-pot protocol for the synthesis of fully substituted 1,2-diaminoimidazoles combining sequential azidation, Staudinger and aza-Wittig reactions on 1,2-diaza-1,3-dienes.

As recent literature has thoroughly discussed,[19] phosphazenes have been shown to be useful intermediates in organic synthesis, particularly for the preparation C=N-containing heterocycles, including imidazoles.[15,16] Therefore, we envisioned DDs as powerful tools in a synthetic pathway involving a tandem aza-Wittig/heterocumulene-mediated annulation to give rise to fully substituted 1,2-diaminoimidazoles.

It is noteworthy that DDs **1** act as efficient partners in the aza-Michael additions from which arises a large variety of heterocycles by means of different intramolecular cyclizations where three atoms (C−C=N) of the azo-ene system are frequently involved.[17,18,20]

Based on our recent experience in the use of α-azidohydrazones obtained from DDs as valuable precursors for the construction of linked small heterocycles,[21] we reasoned that α-azidation reaction of **1** could be represented as the first step of our strategy. Thus, 1,4-addition of trimethylsililazide ($TMSN_3$)[22,23] **2** to DDs **1a−h** was carried out in the presence of a catalytic amount of $Cu(OAc)_2 \cdot H_2O$ in CH_2Cl_2 at room temperature (Table 1). After the disappearance of the starting **1a−h** (TLC check), the readily available crude α-azidohydrazone derivatives[21] **3a−h** were treated with PPh_3 for the

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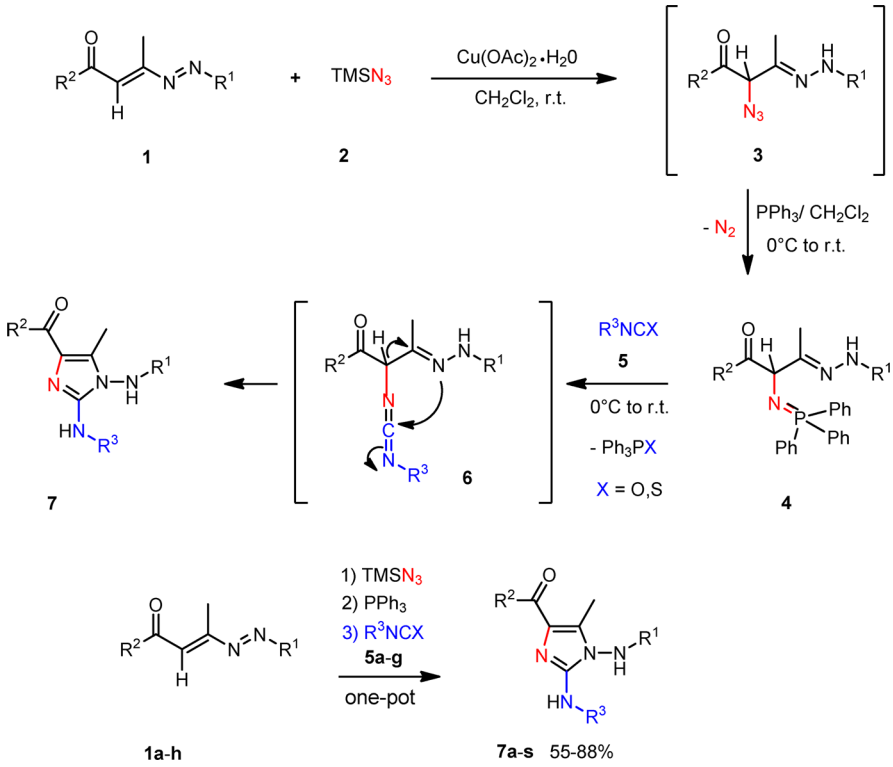
Table 1. Mechanism Pathway for One-Pot Synthesis of 1,2-Diaminoimidazoles 7a–s



entry	DD 1			heteroallene 5			1,2-diamino-imidazole 7	time (h)	yield[a] (%)
		R^1	R^2		R^3	X			
1	**1a**	CONHPh	$N(Me)_2$	**5a**	Ph	S	**7a**	7	65
2	**1a**	CONHPh	$N(Me)_2$	**5b**	Bn	S	**7b**	4	73
3	**1b**	CONHPh	$N(Et)_2$	**5a**	Ph	S	**7c**	7	61
4	**1c**	$CONH_2$	$N(Me)_2$	**5a**	Ph	S	**7d**	11	70
5	**1d**	CO_2Me	$N(Me)_2$	**5c**	Ph	O	**7e**	7	60
6	**1d**	CO_2Me	$N(Me)_2$	**5d**	3-Cl-Ph	O	**7f**	8	65
7	**1d**	CO_2Me	$N(Me)_2$	**5e**	Ts	O	**7g**	8	78
8	**1d**	CO_2Me	$N(Me)_2$	**5f**	*n*-Bu	O	**7h**	7	55
9	**1d**	CO_2Me	$N(Me)_2$	**5g**	4-Cl-Ph	O	**7i**	6	82
10	**1e**	CO_2Et	$N(Me)_2$	**5d**	3-Cl-Ph	O	**7j**	7	88
11	**1e**	CO_2Et	$N(Me)_2$	**5c**	Ph	O	**7k**	6	85
12	**1f**	CO_2t-Bu	Morph	**5c**	Ph	O	**7l**	5	83
13	**1f**	CO_2t-Bu	Morph	**5f**	*n*-Bu	O	**7m**	6	68
14	**1g**	CO_2t-Bu	$N(Me)_2$	**5c**	Ph	O	**7n**	6	71
15	**1g**	CO_2t-Bu	$N(Me)_2$	**5a**	Ph	S	**7n**	5	61
16	**1g**	CO_2t-Bu	$N(Me)_2$	**5d**	3-Cl-Ph	O	**7o**	8	67
17	**1g**	CO_2t-Bu	$N(Me)_2$	**5e**	Ts	O	**7p**	7	64
18	**1g**	CO_2t-Bu	$N(Me)_2$	**5f**	*n*-Bu	O	**7q**	6	60
19	**1g**	CO_2t-Bu	$N(Me)_2$	**5g**	4-Cl-Ph	O	**7r**	4	84
20	**1h**	4-NO_2–Ph	$N(Me)_2$	**5a**	Ph	S	**7s**	11	76

[a]Yield of isolated pure product based on DD **1**.

Staudinger reaction to deliver the related iminophosphoranes **4a–h** (monitored by TLC).

In view of a sequential one-pot procedure and to be sure of the hypothesized mechanistic pathway, only **4a** was isolated as crystalline solid (yield 96%) for the characterization of the phosphazene intermediate.

In all cases, **4a–h** were then coupled with the appropriate heteroallene (isocyanates or isothiocyanates) **5a–g** for the aza-Wittig reaction affording directly fully substituted 1,2-diaminoimidazoles **7a–s** in 55–88% overall yields (Table 1). Mechanistically, we propose that the conversion **4**→**7** involves the formation of the reactive carbodiimide-derived phosphazene intermediate **6** which undergoes a spontaneous ring closure by intramolecular nucleophilic attack of the hydrazone nitrogen at the central carbon of the heterocumulene moiety of **6**. Moreover, the reactions affording **7n** by use of isocyanate or its thio-analogue derivative (entries 14 and 15) were also performed. By comparison of the yields obtained (Table 1), phenylisocyanate seemed to be more efficient. This synthetic strategy, directly provides a precise substitution pattern at 2-

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amino function of the imidazole ring and constitutes an improvement over our previous results[12b] in which the selective *N*-alkylation in 2-position of 1,2-diaminoimidazoles, obtained by reaction of DDs and cyanamide, was uneffective due to competitive N1-alkylation. Due to the easy access of the starting materials, the good overall yields without the need to isolate intermediates, and due to the simplicity of the one-pot protocol, this synthetic strategy leads to a large variability of the substitution patterns both at the positions of the ring and at the 2-amino function and favorably implements the existing approach based on alkyl 2-amino-3-azidoacrylates.[16a]

In summary, combining sequential azidation, Staudinger and aza-Wittig reactions on 1,2-diaza-1,3-dienes in a one-pot protocol, fully substituted 1,2-diaminoimidazoles are directly accessible in good yields. The imidazole core formation could result from a spontaneous intramolecular ring closure of the carbodiimide-derived phosphazene intermediate formed. By suitable choice of the substituents both of the DD and heteroallene, selective protected 1,2-diaminoimidazoles can be obtained from which regioselective *N*-deprotection could be conveniently modulated.

Moreover, the mild reaction conditions, good yields, accessible starting materials of the synthetic procedure here discussed, complements the existing routes for the synthesis of fully substituted 1,2-diaminoimidazoles.[16]

EXPERIMENTAL SECTION

General Methods. All chemicals and solvents were purchased from commercial suppliers and used as received. 1,2-Diaza-1,3-dienes (DDs) were prepared as reported[17,24] and used as *EE/EZ* isomer mixtures. $TMSN_3$,[23] $Cu(OAc)_2{\cdot}H_2O$, PPh_3, and isocyanate or isothiocyanate derivatives were commercial materials and were used without further purification. Melting points were determined in open capillary tubes and are uncorrected. FT-IR spectra were obtained as Nujol mulls or neat. Mass spectra (MS) were carried out by electron impact (EI) at an ionizing voltage of 70 eV. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded in DMSO-d_6 or in $CDCl_3$ as specified below. Dynamic ^{1}H NMR experiments were performed between 298−328 K to confirm the existence of a mixture of conformers for compounds **7a**−**s**. Chemical shifts (δ_H) and (δ_C) are reported in parts per million (ppm), and were referred to solvent signals as follows: δ = 2.50 ppm for proton (middle peak) and δ = 39.50 ppm for carbon in DMSO; δ = 7.26 ppm for proton and δ = 77.00 ppm for carbon (middle peak) in $CDCl_3$. All coupling constant (J values) are given in hertz (Hz). The following abbreviations are used to describe peak patterns where appropriate: s, singlet; d, doublet; dd, double−doublet; t, triplet; q, quartet; m, multiplet; br, broad. All the NH exchanged with D_2O. Precoated silica gel plates 0.25 mm were employed for analytical thin layer chromatography and silica gel 35−70 μm for column chromatography. All new compounds showed satisfactory elemental analysis. The nomenclature was generated using ACD/IUPACName (version 3.50, 5 Apr. 1998), Advanced Chemistry Development Inc., Toronto, ON (Canada).

General One-pot procedure for the synthesis of variously substituted 1,2-diaminoimidazoles 7a−s. In a 25-mL flask, DD **1a**−**h** (1.0 mmol) was dissolved in CH_2Cl_2 (4 mL) and the $TMSN_3$ **2** (1.1 mmol) was added. Catalyst $Cu(OAc)_2{\cdot}H_2O$ was then added (0.2 mmol) and the reaction mixture was stirred at room temperature until the complete formation of organic azide **3a**−**h** (TLC check). The reaction flask was then immersed in an ice bath (T = 0 °C), and a cooled solution of triphenylphosphine (1.0 mmol) in CH_2Cl_2 (1 mL) was added dropwise. The reaction was reported at room temperature and stirred until the disappeareance of organic azide **3a**−**h** (monitored by TLC). The formation of iminophosphorane **4a**−**h** was accompanied by the development of nitrogen gas from the reaction mixture. The reaction mixture was cooled again to 0 °C, and isocyanate or isothiocyanate derivative **5a**−**g** (1.1 mmol) was slowly added. Within 5 min, the reaction mixture was reported at room temperature and stirred until the complete formation of the triphenylphosphine oxide or triphenylphosphine thioxide as byproduct (TLC check). After removal of the solvent in vacuo, the residue was purified by column chromatography on silica gel (elution mixture: EtOAc/cyclohexane or EtOAc/MeOH) to give 1,2-diaminosubstituted imidazoles **7a**−**s**.

*Iminophosphorane derivative (**4a**):* yield 516.0 mg (96%); white powder; mp 112−115 °C (from CH_2Cl_2/Et_2O); IR (Nujol, ν, cm^{-1}) 3198, 3057, 3028, 2024, 1728, 1646, 1604, 1554, 1541, 1505; ^{1}H NMR (DMSO-d_6) δ 1.86 (s, 3H), 2.64 and 2.76 (2 s, 6H), 4.93 (d, ^3J = 10.8 Hz, 1H), 7.02 (t, J = 7.6 Hz, 1H), 7.30 (t, J = 7.6 Hz, 2H), 7.46 (d, J = 7.6 Hz, 2H), 7.72−7.84 (m, 15H), 8.61 (s, 1H), 9.83 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 13.2 (q), 35.6 (q), 36.4 (q), 58.8 (d), 119.0 (d), 121.5 (s, ^1J = 102.4 Hz), 122.5 (s), 128.8 (d), 129.7 (d, ^2J = 12.9 Hz), 133.6 (d, ^3J = 10.6 Hz), 134.7 (d), 138.8 (d), 143.9 (s), 152.9 (s), 167.7 (s); MS m/z 537 (M^+, 11), 493 (1), 465 (2), 445 (1), 373 (20), 352 (23), 329 (24), 304 (14), 277 (45), 262 (93), 183 (100). Anal. Calcd for $C_{31}H_{32}N_5O_2P$ (537.59): C, 69.26; H, 6.00; N, 13.03. Found: C, 69.10; H, 5.88; N, 13.08.

*2-Anilino-1-[(anilinocarbonyl)amino]-N,N,5-trimethyl-1H-imidazole-4-carboxamide (**7a**):* yield 245.9 mg (65%); white powder; mp 223−226 °C (from CH_2Cl_2/light petroleum ether); IR (Nujol, ν, cm^{-1}) 3357, 3282, 3200, 1713, 1622, 1604, 1575, 1550; ^{1}H NMR (DMSO-d_6) δ 2.18 (s, 3H), 2.93 and 3.36 (2 br s, 6H), 6.83 (t, J = 7.2 Hz, 1H), 6.99 (t, J = 7.2 Hz, 1H), 7.21−7.30 (m, 4H), 7.51 (d, J = 8.4 Hz, 2H), 7.72 (d, J = 8.4 Hz, 2H), 8.63 (s, 1H), 9.16 (1H, s, NH), 9.42 (1H, s, NH); ^{13}C NMR (DMSO-d_6) δ 8.9 (q), 35.3 (q), 38.4 (q), 116.2 (d), 118.7 (d), 119.8 (d), 122.3 (d), 124.8 (s), 128.6 (d), 128.7 (d), 129.3 (s), 139.3 (s), 141.3 (s), 142.3 (s), 153.7 (s), 164.8 (s); MS m/z 378 (M^+, 62), 285 (54), 214 (55), 186 (100), 170 (41), 119 (71). Anal. Calcd for $C_{20}H_{22}N_6O_2$ (378.42): C, 63.48; H, 5.86; N, 22.21. Found: C, 63.32; H, 5.95; N, 22.18.

*1-[(Anilinocarbonyl)amino]-2-(benzylamino)-N,N,5-trimethyl-1H-imidazole-4-carboxamide (**7b**):* yield 286.4 mg (73%); white powder; mp 192−195 °C (from MeOH/light petroleum ether); IR (Nujol, ν, cm^{-1}) 3262, 3208, 3145, 1736, 1680, 1668, 1652, 1612, 1571; ^{1}H NMR (DMSO-d_6) δ 2.11 (3H, s), 2.85 and 3.19 (2 br s, 6H), 4.36 (br s, 2H) 6.53 (t, J = 6.0 Hz, 1H), 6.98 (t, J = 7.2 Hz, 1H), 7.17−7.50 (m, 9H), 9.05 (s, 1H), 9.28 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 8.9 (q), 35.6 (q), 36.4 (q), 45.5 (t), 118.6 (d), 122.2 (d), 124.5 (d), 126.3 (d), 127.3 (s), 127.6 (d), 128.6 (d), 129.3 (s), 139.3 (s), 140.7 (s), 147.1 (s), 153.6 (s), 165.1 (s); MS m/z 392 (M^+, 50), 299 (39), 228 (40), 200 (100), 185 (27), 106 (13). Anal. Calcd for $C_{21}H_{24}N_6O_2$ (392.45): C, 64.27; H, 6.16; N, 21.41. Found: C, 64.38; H, 6.28; N, 21.33.

*2-Anilino-1-[(anilinocarbonyl)amino]-N,N-diethyl-5-methyl-1H-imidazole-4-carboxamide (**7c**):* yield 247.9 mg (61%); white powder; mp 180−183 °C (from EtOAc/light petroleum ether); IR (Nujol, ν, cm^{-1}) 3349, 3298, 3140, 1714, 1609, 1584, 1552, 1540; ^{1}H NMR (DMSO-d_6) δ 1.12 (br s, 3H), 1.27 (br s, 3H), 2.20 (s, 3H), 3.37 (br s, 2H), 3.79 (br s, 2H), 6.83 (t, J = 7.2 Hz, 1H), 6.99 (t, J = 7.6 Hz, 1H), 7.20−7.30 (m, 4H), 7.52 (d, J = 7.6 Hz, 2H), 7.74 (d, J = 7.6 Hz, 2H), 8.62 (s, 1H), 9.15 (s, 1H), 9.38 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 9.0 (q), 13.0 (q), 14.8 (q), 40.1 (t), 42.2 (t), 116.2 (d), 118.7 (d), 119.7 (d), 122.3 (d), 125.0 (s), 128.4 (d), 128.7 (d), 129.6 (s), 139.3 (s), 141.2 (s), 142.3 (s), 153.7 (s), 163.9 (s); MS m/z 406 (M^+, 15), 313 (6), 307 (17), 241 (10), 214 (23), 200 (100), 170 (11), 119 (24). Anal. Calcd for $C_{22}H_{26}N_6O_2$ (406.48): C, 65.01; H, 6.45; N, 20.68. Found: C, 65.12; H, 6.35; N, 20.59.

*1-[(Aminocarbonyl)amino]-2-anilino-N,N,5-trimethyl-1H-imidazole-4-carboxamide (**7d**):* yield 211.6 mg (70%); white powder; mp 234−237 °C (from EtOAc/light petroleum ether); IR (Nujol, ν, cm^{-1}) 3453, 3254, 3177, 1685, 1653, 1629, 1606, 1574, 1560, 1541; ^{1}H NMR (DMSO-d_6) δ 2.13 (s, 3H), 2.90 and 3.34 (2 br s, 6H), 6.39 (s, 2H) 6.80 (t, J = 7.5 Hz, 1H), 7.21 (t, J = 7.5 Hz, 2H), 7.70 (d, J = 7.5 Hz, 2H), 8.44 (s, 1H), 8.91 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 8.8 (q), 35.5 (q), 38.4 (q), 116.2 (d), 119.6 (d), 124.7 (s), 128.4 (d), 129.2 (s), 141.3 (s), 142.1 (s), 157.0 (s), 164.8 (s); MS m/z 302 (M^+, 80), 285 (10), 214 (27), 200 (35), 186 (100), 170 (30), 119 (21).

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Anal. Calcd for $C_{14}H_{18}N_6O_2$ (302.33): C, 55.62; H, 6.00; N, 27.80. Found: C, 55.75; H, 5.92; N, 27.72.

*Methyl 2-anilino-4-[(dimethylamino)carbonyl]-5-methyl-1H-imidazol-1-ylcarbamate (**7e**):* yield 190.4 mg (60%); pale yellow powder; mp 183−185 °C (from EtOAc/Et_2O); IR (Nujol, ν, cm^{-1}) 3346, 3318, 1778, 1747, 1731, 1611, 1576, 1551; ^1H NMR (DMSO-d_6) δ 2.14 (s, 3H), 2.92 and 3.33 (2 br s, 6H), 3.75 (s, 3H), 6.84 (t, J = 7.7 Hz, 1H), 7.23 (t, J = 7.7 Hz, 2H), 7.70 (d, J = 7.7 Hz, 2H), 8.69 (s, 1H), 10.38 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 8.6 (q), 35.5 (q), 38.2 (q), 52.8 (q), 116.3 (d), 119.9 (d), 124.9 (s), 128.5 (d), 130.0 (s), 141.1 (s), 141.8 (s), 155.6 (s), 164.6 (s); MS m/z 317 (M^+, 82), 273 (11), 246 (45), 214 (26), 186 (100), 170 (29). Anal. Calcd for $C_{15}H_{19}N_5O_3$ (317.34): C, 56.77; H, 6.03; N, 22.07. Found: C, 56.65; H, 6.11; N, 22.14.

*Methyl 2-[(3-chlorophenyl)amino]-4-[(dimethylamino)carbonyl]-5-methyl-1H-imidazol-1-ylcarbamate (**7f**):* yield 228.6 mg (65%); pale yellow powder; mp 216−218 °C (from EtOAc/Et_2O); IR (Nujol, ν, cm^{-1}) 3303, 3086, 1746, 1620, 1607, 1566, 1550; ^1H NMR (DMSO-d_6) δ 2.14 (s, 3H), 2.93 and 3.32 (2 br s, 6H), 3.76 (s, 3H), 6.89 (d, J = 7.8 Hz, 1H), 7.25 (t, J = 7.8 Hz, 1H), 7.59 (d, J = 7.8 Hz, 1H), 7.96 (s, 1H), 9.00 (s, 1H), 10.45 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 8.6 (q), 35.4 (q), 38.9 (q), 52.9 (q), 114.9 (d), 115.7 (d), 119.5 (d), 124.9 (s), 128.7 (s), 130.2 (d), 133.1 (s), 141.2 (s), 142.4 (s), 155.6 (s), 164.4 (s); MS m/z 353 [M^+ + 2, (21)], 351 (M^+, 62), 280 (54), 248 (25), 220 (100), 203 (40), 153 (38). Anal. Calcd for $C_{15}H_{18}ClN_5O_3$ (351.78): C, 51.21; H, 5.16; N, 19.91. Found: C, 51.34; H, 5.07; N, 20.02.

*Methyl 4-[(dimethylamino)carbonyl]-5-methyl-2-[[(4-methylphenyl)sulfonyl]amino]-1H-imidazol-1-ylcarbamate (**7g**):* yield 308.4 mg (78%); pale yellow powder; mp 169−172 °C (from EtOAc/Et_2O); IR (Nujol, ν, cm^{-1}) 3222, 3163, 1757, 1662, 1618, 1587, 1530; ^1H NMR ($CDCl_3$) δ 2.15 (s, 3H), 2.36 (s, 3H), 3.02 (s, 6H), 3.75 (br s, 3H), 7.21 (d, J = 7.6 Hz, 2H), 7.78 (d, J = 7.6 Hz, 2H), 9.40 (br s, 1H), 9.77 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 9.0 (q), 21.4 (q), 37.2 (q), 53.4 (q), 113.0 (s), 126.1 (d), 128.4 (s), 129.2 (d), 132.0 (s), 139.7 (s), 142.3 (s), 146.5 (s), 155.4 (s), 160.9 (s); MS m/z 395 (M^+, 31), 324 (6), 264 (3), 240 (100), 197 (51), 167 (9). Anal. Calcd for $C_{16}H_{21}N_5O_5S$ (395.43): C, 48.60; H, 5.35; N, 17.71. Found: C, 48.49; H, 5.43; N, 17.78.

*Methyl 2-(butylamino)-4-[(dimethylamino)carbonyl]-5-methyl-1H-imidazol-1-ylcarbamate (**7h**):* yield 163.5 mg (55%); pale yellow crystals; mp 79−82 °C (from EtOAc/light petroleum ether); IR (Nujol, ν, cm^{-1}) 3263, 3176, 1746, 1732, 1697, 1606; ^1H NMR (DMSO-d_6) δ 0.87 (t, J = 7.2 Hz, 3H), 1.26−1.32 (m, 2H), 1.46−1.51 (m, 2H), 2.04 (s, 3H), 2.88−3.31 (m, 8H), 3.69 (s, 3H), 5.95 (br s, 1H), 10.11 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 8.7 (q), 13.8 (q), 19.5 (t), 31.3 (t), 35.4 (q), 38.3 (q), 41.8 (t), 52.6 (q), 124.8 (s), 127.7 (s), 147.0 (s), 155.6 (s), 165.1 (s); MS m/z 297 (M^+, 72), 253 (16), 224 (42), 194 (10), 166 (100), 152 (21). Anal. Calcd for $C_{13}H_{23}N_5O_3$ (297.35): C, 52.51; H, 7.80; N, 23.55. Found: C, 52.60; H, 7.69; N, 23.61.

*Methyl 2-[(4-chlorophenyl)amino]-4-[(dimethylamino)carbonyl]-5-methyl-1H-imidazol-1-ylcarbamate (**7i**):* yield 288.4 mg (82%); white powder; mp 198−200 °C (from EtOAc/Et_2O); IR (Nujol, ν, cm^{-1}) 3317, 3087, 1772, 1742, 1607, 1575, 1549, 1503; ^1H NMR (DMSO-d_6) δ 2.13 (s, 3H), 2.92 and 3.30 (2 br s, 6H), 3.75 (s, 3H), 7.29 (d, J = 7.6 Hz, 2H), 7.75 (d, J = 7.6 Hz, 2H), 8.92 (s, 1H), 10.43 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 8.6 (q), 35.4 (q), 38.3 (q), 52.9 (q), 117.8 (d), 123.4 (s), 125.0 (s), 128.4 (d), 128.5 (s), 140.0 (s), 141.5 (s), 155.6 (s), 164.5 (s); MS m/z 353 [M^+ + 2, (22)], 351 (M^+, 66), 319 (2), 307 (9), 292 (22), 280 (46), 248 (23), 220 (100), 203 (38), 152 (16), 127 (12). Anal. Calcd for $C_{15}H_{18}ClN_5O_3$ (351.78): C, 51.21; H, 5.16; N, 19.91. Found: C, 51.35; H, 5.24; N, 19.80.

*Ethyl 2-[(3-chlorophenyl)amino]-4-[(dimethylamino)carbonyl]-5-methyl-1H-imidazol-1-ylcarbamate (**7j**):* yield 321.9 mg (88%); white powder; mp 192−194 °C (from EtOAc/Et_2O); IR (Nujol, ν, cm^{-1}) 3328, 3085, 1735, 1618, 1605, 1580, 1574, 1552; ^1H NMR (DMSO-d_6) δ 1.28 (t, J = 6.4 Hz, 3H), 2.15 (s, 3H), 2.93 and 3.33 (2 br s, 6H), 4.15−4.17 (m, 2H), 6.88 (d, J = 8.0 Hz, 1H), 7.26 (t, J = 8.0 Hz, 1H), 7.59 (d, J = 8.0 Hz, 1H), 7.96 (s, 1H), 8.98 (s, 1H), 10.37 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 8.6 (q), 14.2 (q), 35.4 (q), 38.2 (q), 61.8 (t), 114.8 (d), 115.6 (d), 119.5 (d), 125.0 (s), 128.8 (s), 130.1 (d), 133.0 (s), 141.2 (s), 142.5 (s), 155.1 (s), 164.4 (s); MS m/z 367 [M^+ + 2, (22)], 365 (M^+, 71), 322 (8), 294 (46), 248 (36), 220 (100), 203 (42), 153 (15). Anal. Calcd for $C_{16}H_{20}ClN_5O_3$ (365.81): C, 52.53; H, 5.51; N, 19.14. Found: C, 52.41; H, 5.62; N, 19.09.

*Ethyl 2-anilino-4-[(dimethylamino)carbonyl]-5-methyl-1H-imidazol-1-ylcarbamate (**7k**):* yield 281.6 mg (85%); white powder; mp 176−179 °C (from EtOAc/Et_2O); IR (Nujol, ν, cm^{-1}) 3308, 3140, 1733, 1726, 1606, 1581, 1552; ^1H NMR (DMSO-d_6) δ 1.28 (t, J = 6.4 Hz, 3H), 2.14 (s, 3H), 2.92 and 3.34 (2 br s, 6H), 4.15−4.17 (m, 2H), 6.84 (t, J = 7.6 Hz, 1H), 7.23 (t, J = 7.6 Hz, 2H), 7.70 (d, J = 7.6 Hz, 2H), 8.68 (s, 1H), 10.32 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 8.6 (q), 14.3 (q), 35.4 (q), 38.6 (q), 61.7 (t), 116.3 (d), 119.9 (d), 125.0 (s), 128.5 (d), 130.0 (s), 141.1 (s), 141.8 (s), 155.2 (s), 164.6 (s); MS m/z 331 (M^+, 56), 288 (6), 260 (28), 214 (29), 186 (100), 169 (38), 119 (14). Anal. Calcd for $C_{16}H_{21}N_5O_3$ (331.37): C, 57.99; H, 6.39; N, 21.13. Found: C, 58.07; H, 6.27; N, 21.21.

*tert-Butyl [2-anilino-5-methyl-4-(morpholin-4-ylcarbonyl)-1H-imidazol-1-yl]carbamate (**7l**):* yield 333.2 mg (83%); white powder; mp 186−189 °C (from MeOH/Et_2O/light petroleum ether); IR (Nujol, ν, cm^{-1}) 3419, 3322, 1746, 1608, 1585, 1551, 1504; ^1H NMR (DMSO-d_6) δ 1.48 (s, 9H), 2.15 (s, 3H), 3.63−3.96 (m, 8H), 6.84 (t, J = 7.6 Hz, 1H), 7.22 (t, J = 7.6 Hz, 2H), 7.66 (d, J = 7.6 Hz, 2H), 8.67 (s, 1H), 10.01 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 8.6 (q), 27.8 (q), 42.8 (t), 47.2 (t), 66.4 (t), 81.2 (s), 116.3 (d), 120.0 (d), 124.3 (s), 128.5 (d), 132.0 (s), 141.0 (s), 142.0 (s), 154.1 (s), 163.6 (s); MS m/z 401 (M^+, 24), 345 (42), 301 (27), 285 (20), 260 (38), 232 (100), 200 (29), 170 (17), 119 (15). Anal. Calcd for $C_{20}H_{27}N_5O_4$ (401.46): C, 59.84; H, 6.78; N, 17.44. Found: C, 59.73; H, 6.88; N, 17.36.

*tert-Butyl [2-(butylamino)-5-methyl-4-(morpholin-4-ylcarbonyl)-1H-imidazol-1-yl]carbamate (**7m**):* yield 259.4 mg (68%); beige powder; mp 139−141 °C (from EtOAc/Et_2O); IR (Nujol, ν, cm^{-1}) 3373, 3206, 1748, 1703, 1605, 1596, 1510; ^1H NMR (DMSO-d_6) δ 0.86 (t, J = 7.2 Hz, 3H), 1.25−1.49 (m, 13H), 2.07 (s, 3H), 3.10 (br s, 2H), 3.57−3.77 (m, 8H), 5.87 (br s, 1H), 9.80 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 8.7 (q), 13.7 (q), 19.4 (t), 27.8 (q), 31.2 (t), 41.7 (t), 46.5 (t), 66.4 (t), 80.7 (s), 124.1 (s), 129.0 (s), 147.1 (s), 154.0 (s), 163.7 (s); MS m/z 381 (M^+, 18), 325 (39), 281 (19), 265 (22), 240 (41), 212 (100), 195 (30), 168 (53). Anal. Calcd for $C_{18}H_{31}N_5O_4$ (381.47): C, 56.67; H, 8.19; N, 18.36. Found: C, 56.79; H, 8.28; N, 18.28.

*tert-Butyl [2-anilino-4-[(dimethylamino)carbonyl]-5-methyl-1H-imidazol-1-yl]carbamate (**7n**):* yield 255.2 mg (71% from **5c**); white powder; mp 176−178 °C (from MeOH/EtOAc/light petroleum ether); IR (Nujol, ν, cm^{-1}) 3427, 3299, 1752, 1741, 1728, 1604, 1584, 1540; ^1H NMR (DMSO-d_6) δ 1.48 (s, 9H), 2.13 (s, 3H), 2.92 and 3.32 (2 br s, 6H), 6.83 (t, J = 7.7 Hz, 1H), 7.22 (t, J = 7.7 Hz, 2H), 7.70 (d, J = 7.7 Hz, 2H), 8.64 (s, 1H), 9.99 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 8.6 (q), 27.8 (q), 35.4 (q), 38.6 (q), 81.1 (s), 116.3 (d), 119.8 (d), 125.0 (s), 128.5 (d), 131.5 (s), 141.2 (s), 141.8 (s), 154.2 (s), 164.7 (s); MS m/z 359 (M^+, 27), 303 (59), 259 (24), 244 (28), 200 (23), 186 (100), 119 (11). Anal. Calcd for $C_{18}H_{25}N_5O_3$ (359.42): C, 60.15; H, 7.01; N, 19.49. Found: C, 60.01; H, 7.12; N, 19.53.

*tert-Butyl [2-[(3-chlorophenyl)amino]-4-[(dimethylamino)-carbonyl]-5-methyl-1H-imidazol-1-yl]carbamate (**7o**).* yield 263.9 mg (67%); pale yellow crystals; mp 170−174 °C (from MeOH/light petroleum ether); IR (Nujol, ν, cm^{-1}) 3275, 3133, 1730, 1623, 1615, 1601, 1579, 1528; ^1H NMR (DMSO-d_6) δ 1.48 (s, 9H), 2.14 (s, 3H), 2.93 and 3.32 (2 br s, 6H), 6.88 (d, J = 8.0 Hz, 1H), 7.24 (t, J = 8.0 Hz, 1H), 7.59 (d, J = 8.0 Hz, 1H), 7.96 (s, 1H), 8.96 (s, 1H), 10.05 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 8.6 (q), 27.8 (q), 35.4 (q), 38.3 (q), 81.3 (s), 114.8 (d), 115.6 (d), 119.4 (d), 125.0 (s), 128.8 (s), 130.1 (d), 133.0 (s), 141.3 (s), 142.6 (s), 154.1 (s), 164.5 (s); MS m/z 395 [M^+ + 2 (5)], 393 (M^+, 17), 337 (63), 320 (2), 293 (24), 278 (41), 266 (50), 249 (9), 234 (27), 220 (100), 204 (17), 153 (10). Anal. Calcd for $C_{18}H_{24}ClN_5O_3$ (393.86): C, 54.89; H, 6.14; N, 17.78. Found: C, 55.01; H, 6.05; N, 17.71.

*tert-Butyl (4-[(dimethylamino)carbonyl]-5-methyl-2-[[(4-methylphenyl)sulfonyl]amino]-1H-imidazol-1-yl)carbamate (**7p**):*

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yield 280.0 mg (64%); pale yellow powder; mp 150−152 °C (from MeOH/Et_2O); IR (Nujol, ν, cm^{-1}) 3608, 3488, 3290, 3118, 1732, 1658, 1627, 1597, 1511; ^1H NMR ($CDCl_3$) δ 1.45 (s, 9H), 2.17 (s, 3H), 2.35 (s, 3H), 3.04 (s, 6H), 7.19 (d, J = 8.0 Hz, 2H), 7.78 (d, J = 8.0 Hz, 2H), 8.31 (s, 1H), 9.74 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 9.1 (q), 21.3 (q), 27.8 (q), 37.2 (q), 82.9 (s), 112.7 (s), 126.0 (d), 127.4 (s), 129.1 (s), 140.1 (s), 142.0 (s), 146.5 (s), 154.1 (s), 161.1 (s); MS m/z 437 (M^+, 11), 381 (7), 337 (47), 293 (2), 264 (4), 226 (32), 182 (100), 155 (14). Anal. Calcd for $C_{19}H_{27}N_5O_5S$ (437.51): C, 52.16; H, 6.22; N, 16.01. Found: C, 52.22; H, 6.12; N, 15.90.

*tert-Butyl [2-(butylamino)-4-[(dimethylamino)carbonyl]-5-methyl-1H-imidazol-1-yl]carbamate (**7q**):* yield 203.6 mg (60%); colorless crystals; mp 115−116 °C (from Et_2O); IR (Nujol, ν, cm^{-1}) 3368, 3139, 1740, 1613, 1581, 1517; ^1H NMR (DMSO-d_6) δ 0.86 (t, J = 7.6 Hz, 3H), 1.26−1.47 (m, 13H), 2.04 (s, 3H), 2.86−3.26 (m, 8H), 5.78 (br s, 1H), 9.76 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 8.6 (q), 13.7 (q), 19.4 (t), 27.8 (q), 31.3 (t), 35.3 (q), 38.0 (q), 41.8 (t), 80.7 (s), 124.8 (s), 127.8 (s), 147.0 (s), 154.1 (s), 165.1 (s); MS m/z 339 (M^+, 28), 283 (57), 266 (3), 239 (21), 224 (29), 210 (38), 195 (20), 166 (100), 151 (16). Anal. Calcd for $C_{16}H_{29}N_5O_3$ (339.43): C, 56.62; H, 8.61; N, 20.63. Found: C, 56.70; H, 8.50; N, 20.56.

*tert-Butyl [2-[(4-chlorophenyl)amino]-4-[(dimethylamino)carbonyl]-5-methyl-1H-imidazol-1-yl]carbamate (**7r**):* yield 330.8 mg (84%); white powder; mp 180−184 °C (from THF/light petroleum ether); IR (Nujol, ν, cm^{-1}) 3409, 3106, 1743, 1718, 1700, 1685, 1600, 1576, 1538; ^1H NMR (DMSO-d_6) δ 1.48 (s, 9H), 2.13 (s, 3H), 2.92 and 3.29 (2 br s, 6H), 7.27 (d, J = 8.8 Hz, 2H), 7.76 (d, J = 8.8 Hz, 2H), 8.87 (s, 1H), 10.03 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 8.6 (q), 27.8 (q), 35.4 (q), 38.3 (q), 81.2 (s), 117.9 (d), 123.3 (s), 125.0 (s), 128.3 (d), 128.6 (s), 140.1 (s), 141.6 (s), 154.2 (s), 164.6 (s); MS m/z 395 [M^+ + 2, (7)], 393 (M^+, 17), 337 (45), 293 (31), 278 (33), 266 (49), 234 (31), 220 (100), 204 (19), 153 (11), 126 (9). Anal. Calcd for $C_{18}H_{24}ClN_5O_3$ (393.86): C, 54.89; H, 6.14; N, 17.78. Found: C, 54.76; H, 6.21; N, 17.70.

*2-Anilino-N,N,5-trimethyl-1-[(4-nitrophenyl)amino]-1H-imidazole-4-carboxamide (**7s**):* yield 289.1 mg (76%); yellow brown powder; mp 236−239 °C (from EtOAc/Et_2O); IR (Nujol, ν, cm^{-1}) 3255, 3097, 1665, 1650, 1618, 1591, 1574, 1558, 1505; ^1H NMR (DMSO-d_6) δ 2.10 (s, 3H), 2.94 and 3.38 (2 br s, 6H), 6.62 (d, J = 7.4 Hz, 2H), 6.83 (t, J = 7.6 Hz, 1H), 7.22 (t, J = 7.6 Hz, 2H), 7.71 (d, J = 7.6 Hz, 2H), 8.16 (d, J = 7.4 Hz, 2H), 8.73 (s, 1H), 10.02 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 8.8 (q), 35.4 (q), 38.5 (q), 111.5 (d), 116.4 (d), 120.1 (d), 125.9 (s), 126.1 (d), 128.0 (s), 128.5 (d), 140.0 (s), 140.9 (s), 141.9 (s), 152.6 (s), 164.5 (s); MS m/z 380 (M^+, 55), 309 (11), 243 (85), 200 (100), 186 (30), 170 (30), 138 (7). Anal. Calcd for $C_{19}H_{20}N_6O_3$ (380.40): C, 59.99; H, 5.30; N, 22.09. Found: C, 60.13; H, 5.38; N, 22.01.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Copies of ^1H and ^{13}C NMR spectra of products **4a** and **7a−s**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(23) **Attention**: The main concern about this one-pot procedure is that it may pose a serious safety issue. In fact, it is well documented in the literature that ionic azides react with dichloromethane to form explosive azidochloromethane and/or diazidomethane. See: (a) Conrow, R. E.; Dean, W. D. *Org. Process Res. Dev.* **2008**, *12*, 1285−1286. (b) Hassner, A.; Stern, M.; Gottlieb, H. E. *J. Org. Chem.* **1990**, *55*, 2304−2306. Luckily, under our reaction conditions (short reaction times, stoichiometric amount of $TMSN_3$), the possible competitive nucleophilic substitution on CH_2Cl_2 is effectively suppressed since the Michael addition is the favorite and exclusive pathway. **Caution:** organic azides are potentially explosive compounds (when dry) and should be handled with great care. During our experiments we used $TMSN_3$ and we encountered no problem.
(24) (a) Sommer, S. *Tetrahedron Lett.* **1977**, *18*, 117. (b) Attanasi, O. A.; Filippone, P.; Mei, A.; Santeusanio, S. *Synthesis* **1984**, 671.

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