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Cascade synthesis of substituted 4-amino-1,2,4-triazol-3-ones from aldehyde hydrazones and azodicarboxylates

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ABSTRACT

Substituted 4-amino-1,2,4-triazol-3-ones were synthesized from aldehyde hydrazones and azodicarboxylates in the presence of triphenylphosphine. The cascade reaction was conducted in a single step and the procedure is general and efficient.

1. Introduction

Triazolinones are an important class of organic compounds. As pharmacophores, they possess wide biological activity such as antitumor,[1] antifungal,[2] antioxidant,[3] antibacterial,[4] anti-inflammatory,[5] antihistamines,[6] and antiviral[7] activity. Consequently, a large amount of work has been devoted to the development of synthetic methods for construction of triazolinones, the majority of which involve intramolecular cyclocondensation of formyl semicarbazides,[8] intramolecular cyclocondensation of an amidrazone with phosgene or a phosgene surrogate,[9] Mitsunobu reaction of isocyanates and diisopropyl azodicarboxylate,[10] cyclization of semicarbazide[11] and intramolecular cyclocondensation of hydrazidehydrazones.[12]

The reaction of dialkyl azodicarboxylates and triphenylphosphine leading to the formation of Huisgen zwitterion,[13] which plays an important role in the Mitsunobu reaction.[14] Nair and co-workers used this zwitterion to synthesize a variety of important compunds.[15] Recently, we developed a cascade reaction of the Huisgen zwitterions with aziridines leading to pyrazolines.[16] Inspired by these works, we are interested in the reaction of aldehyde hydrazones with Huisgen zwitterion. We herein report the results of this effort.

2. Results and discussions

Initially, we chose to focus our attention on the reaction of benzaldehyde phenylhydrazone (**1a**, 1 equiv), diethyl azodicarboxylate (DEAD) (**2a**, 1 equiv), and triphenylphosphine (1 equiv). When the reaction was performed in toluene at 110 °C for 1 h, 4-ethyl(carbethoxy)-amino-2,5-diphenyl-2*H*-1,2,4-triazol-3(4*H*)-one (**3a**) was obtained with 6% yield (Table 1, entry 1). Intrigued by this result, we carried the reaction with 2 equiv of **2a** to establish the reaction conditions (Table 1). This revealed that treating the reaction solution of **1a** (1 equiv) and **2a** (2 equiv) in toluene with triphenylphosphine (1 equiv) at 80 °C for 1 h afforded **3a** in best yield (Table 1, entry 6). With regards to the reaction solvents, toluene was effective (Table 1, entries 1–8). CH_3CN (Table 1, entry 12) and hexane (Table 1, entry 15) gave low yields, while tetrahydrofuran (THF, Table 1, entry 9), dichloromethane (DCM, Table 1, entry 10), 1,2-dichloroethane (DCE, Table 1, entry 11), MeOH (Table 1, entry 13), and dimethylformamide (DMF, Table 1, entry 14) resulted in a complex mixture containing unknown side products and trace product.

To define the scope of the present procedure, we next turned our attention to the reactions of a variety of aldehyde hydrazones **1** and azodicarboxylates **2**. As shown in Table 2, aromatic aldehyde hydrazones **1a**–**1q** could react with **2** to afford the corresponding 4-alkyl(carbalkoxy)amino-1,2,4-triazol-3-ones **3a**–**3r** in good to excellent yields (71–98%). The R^1 group in aldehyde hydrazones **1** could be phenyl (Table 2, entries 1, 2, and 4–7), the electron-rich (Table 2, entry 3) or the electron-deficient phenyl (Table 2, entries

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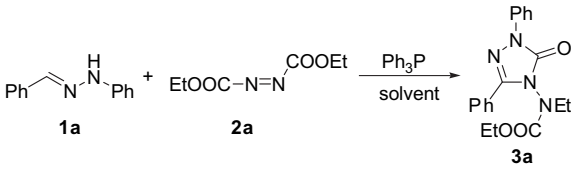
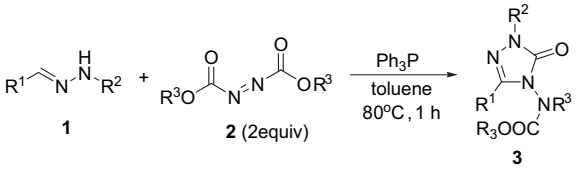
Table 1
Condition screening for the reaction of **1a** and **2a**

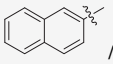
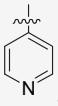


Entry	**1a**/**2a**/Ph_3P (molar ratio)	Solvent	Temp (°C)	Time (h)	Yield[a] (%)
1	1:1:1	PhMe	110	1	6
2	1:1:1	PhMe	95	1.5	21
3	1:1:1	PhMe	80	2	35
4	1:1:1	PhMe	60	3.5	31
5	1:1.5:1	PhMe	80	1.5	68
6	1:2:1	PhMe	80	1	90
7	1:2.2:1.1	PhMe	80	1	87
8	1:2:1	PhMe	50	1	82
9	1:2:1	THF	50	1	[b]
10	1:2:1	DCM	35	2	[b]
11	1:2:1	DCE	60	2	[b]
12	1:2:1	MeCN	50	0.5	10
13	1:2:1	MeOH	50	0.5	[b]
14	1:2:1	DMF	80	0.5	[b]
15	1:2:1	Hexane	50	1	25

[a] Yield refers to **1a**.
[b] A complex mixture of unknown side products afforded.

Table 2
Synthesis of triazolinones **3** from **1** and **2**[a]

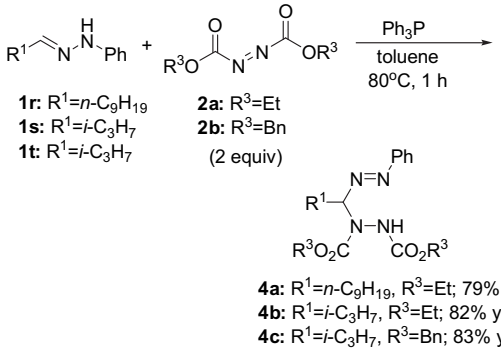


Entry	R^1/R^2	R^3	Yield[b] (%)
1	Ph/Ph (**1a**)	Et (**2a**)	**3a** 90
2	**1a**	Bn (**2b**)	**3b** 92
3	4-MeC_6H_4/Ph (**1b**)	**2a**	**3c** 84
4	Ph/4-ClC_6H_4 (**1c**)	**2a**	**3d** 85
5	Ph/4-$NO_2C_6H_4$ (**1d**)	**2a**	**3e** 71
6	Ph/4-$MeOC_6H_4$ (**1e**)	**2a**	**3f** 92
7	Ph/4-MeC_6H_4 (**1f**)	**2b**	**3g** 92
8	3-$NO_2C_6H_4$/4-MeC_6H_4 (**1g**)	**2a**	**3h** 95
9	4-$NO_2C_6H_4$/Ph (**1h**)	**2b**	**3i** 98
10	2-ClC_6H_4/Ph (**1i**)	**2a**	**3j** 93
11	4-BrC_6H_4/Ph (**1j**)	**2a**	**3k** 90
12	4-$NO_2C_6H_4$/Ph (**1k**)	**2a**	**3l** 97
13	4-ClC_6H_4/4-ClC_6H_4 (**1l**)	**2a**	**3m** 87
14	4-$NO_2C_6H_4$/4-$NO_2C_6H_4$ (**1m**)	**2a**	**3n** 78
15	4-$NO_2C_6H_4$/3,4-$(NO_2)_2C_6H_4$ (**1n**)	**2a**	**3o** 58
16	 /Ph (**1o**)	**2a**	**3p** 82
17	 / Ph (**1p**)	**2a**	**3q** 76
18	 / Ph (**1q**)	**2a**	**3r** 87

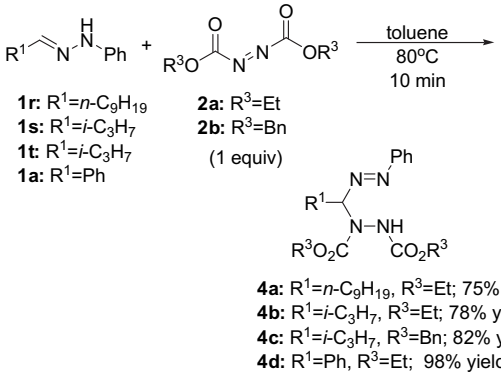
[a] Reaction conditions: **1** (0.5 mmol), **2** (1 mmol), PPh_3 (0.5 mmol), toluene (15 mL), 80 °C, 1 h.
[b] Yield refers to **1**.

8–15), naphthalenyl (Table 2, entry 16), or heterocycle (Table 2, entries 17 and 18). When R^2 is strongly electron-deficient (Table 2, entries 5, 14, and 15), lower yields were obtained than that in the case where R^2 is electron-rich (Table 2, entries 6–8).

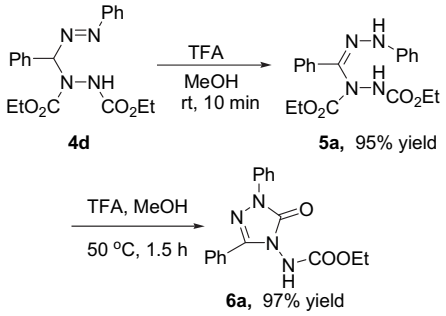
Aliphatic aldehyde hydrazones **1r**–**1t** were also examined under the established conditions. However, we obtained products **4a** (79% yield), **4b** (82% yield), and **4c** (83% yield) rather than the desired 1,2,4-triazol-3-ones **3** (Scheme 1). It was also found that PPh_3 was not necessary for this transformation. When the reaction was performed with 1 equiv of azodicarboxylates **2** under the PPh_3-free conditions, **4a**, **4b**, and **4c** were obtained in 75%, 78%, and 82% yields, respectively (Scheme 2). Under the same conditions, the reaction of **1a** and **2a** gave an analogue **4d** (Scheme 2). Treatment of **4d** with trifluoroacetic acid (TFA) at room temperature afforded diethyl 1-(phenyl(2-phenylhydrazono)-methyl) hydrazine-1,2-dicarboxylate (**5a**), which was quantitatively converted to 1,2,4-triazol-3-one **6a** in the presence of TFA at 50 °C (Scheme 3). In the presence of TFA in toluene or MeOH at 50 °C, **4d**, **4a**, and **4b** could be directly converted to 1,2,4-triazol-3-ones **6a** (95% yield), **6b** (94% yield), and **6c** (82% yield), respectively (Scheme 4).



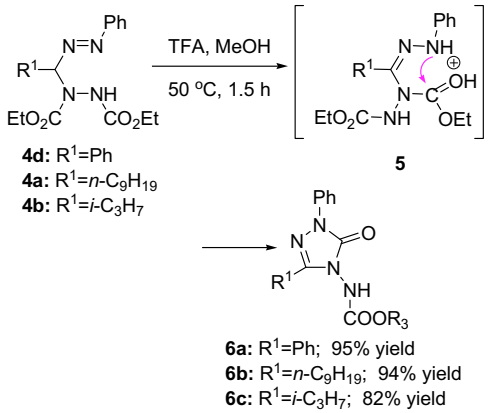
Scheme 1. Synthesis of **4a**–**4c** in the presence of PPh_3.



Scheme 2. Synthesis of **4a**–**4d** in the absence of PPh_3.



Scheme 3. Synthesis of **5a** and **6a**.



Scheme 4. Synthesis of 1,2,4-triazol-3-ones **6**.

The structures of products were characterized by ^{1}H NMR, ^{13}C NMR, IR, and HRMS spectra. The structure of compounds **3i**, **3l** (Fig. 1), and **5a** (Fig. 2) were unambiguously confirmed by X-ray analysis (see Supplementary data).[17]

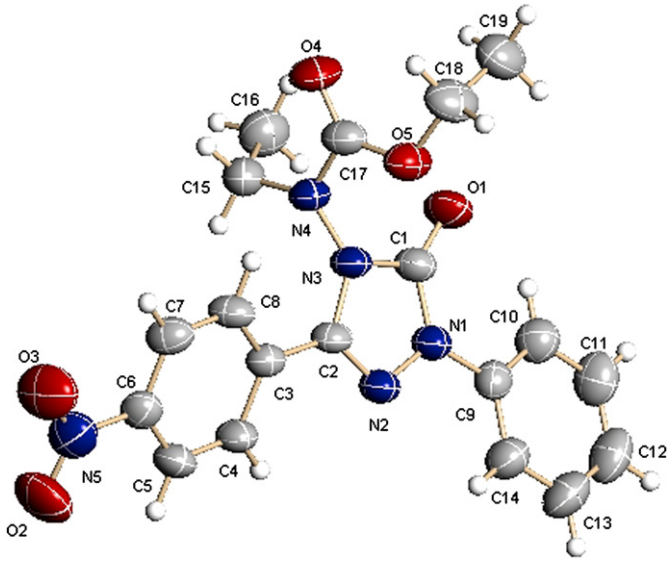


Figure 1. X-ray crystal structure of **3l**.

On the bases of these results, we proposed a possible mechanism for the formation of 4-alkyl(carbalkoxy)-amino-1,2,4-triazol-3-ones **3** (Scheme 5). Firstly, the reaction of triphenylphosphine with DEAD leads to Huisgen zwitterions **A**.[13] **A** nucleophilically attacks the carbon atom of C=N in hydrazone **1** to give **B**, which isomerizes to **C** in turn. The nitrogen anion in **C** nucleophilically attacks the carboxylic carbon and further cyclizes to form **E**. **E** subsequently releases Ph_3PO, following by an intramolecular nucleophilic substitution, to form intermediate **G**. Nucleophilical addition of **G** to another DEAD, following by proton exchange and elimination of 2H-DEAD, yields the dehydrogenated product **3**. Regarding to formation of **B** and **D**, the substrates bearing an electron-deficient R^1 and/or an electron-rich R^2 (Table 2, entries 8, 9, and 12) should be reactive than that bearing an electron-rich R^1 and/or an electron-deficient R^2 (Table 2, entries 5, 14, and 15).

The formation of **5** (R^1=aryl) from hydrazones **1** (R^1=aryl) and azodicarboxylates **2** has been reported by Gillis and Daniher.[12] The reaction firstly yielded **4** (R^1=aryl) via a cyclic mechanism,[12,18] which subsequently isomerized to more stable **5** (R^1=aryl). The resulting **5** (R^1=aryl) could easily cyclize to 1,2,4-triazol-3-ones **6** (R^1=aryl).[12]

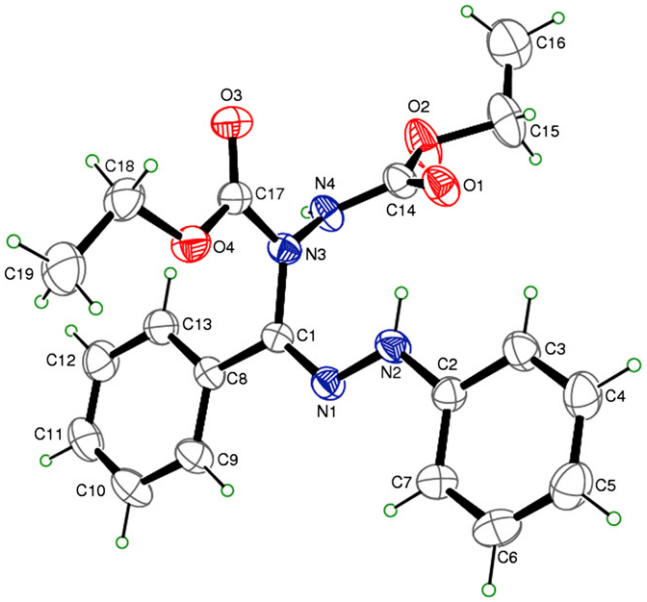
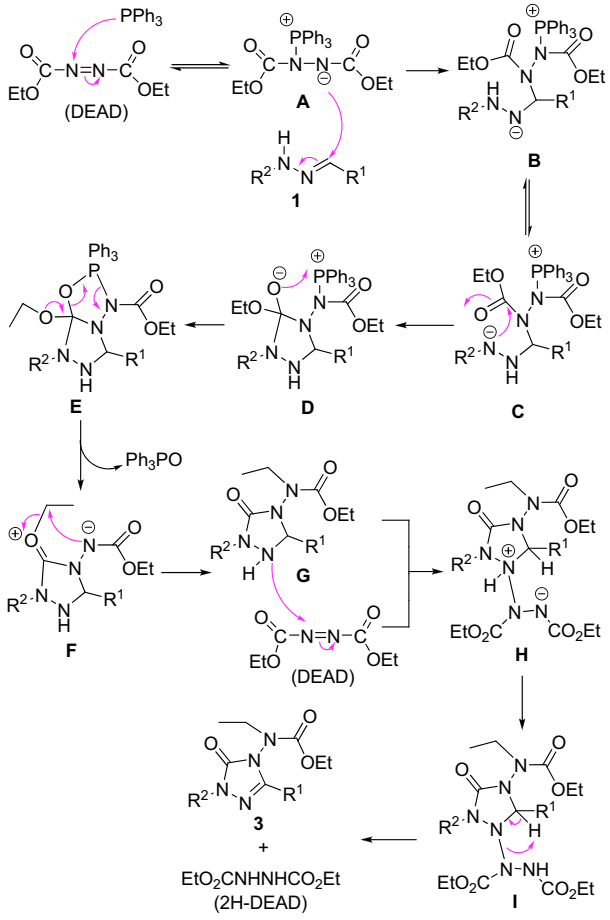


Figure 2. X-ray crystal structure of **5a**.



Scheme 5. A plausible mechanism for the synthesis of 1,2,4-triazol-3-ones **3**.

In our reaction system containing PPh_3, there are two competitive reactions. The first one is the reaction between hydrazones **1** and Huisgen zwitterions **A**, and the second one is the formation of **4.** We obtained **3** as the major product when R^1=aryl. It is probably because the presence of the aromatic group increases the acidity of

proton, which facilitates the deprotonation and aromatization. So the electron-deficient R^1 may help to obtain the desired products **3** (see Table 2, entries 8, 9, and 12). Whereas, when R^1=alkyl, the second reaction leading to **4** is quicker than the first one.

3. Conclusion

In summary, we have developed a synthesis of substituted 4-amino-1,2,4-triazol-3-ones **3** from aldehyde hydrazones **1** and azodicarboxylates **2** in the presence of triphenylphosphine. The single step reaction involves a Huisgen zwitterion formation and a subsequent domino process. The procedure is efficient and general, and the substrates are readily available. This method will find its applications in organic synthesis.

4. Experimental section

4.1. General considerations

IR spectra were recorded on a FTIR spectrometer (KBr) and reported in reciprocal centimeters (cm^{-1}). NMR spectra were recorded for ^1H NMR at 500 MHz and for ^{13}C NMR at 125 MHz. NMR spectra data were recorded at 75 °C and were reported as follows: chemical shift, integration, multiplicity (s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, br=broad), and coupling constant in hertz. For ^{13}C NMR, TMS (δ=0) or $CDCl_3$ (δ=77.25) was used as internal standard and spectra were obtained with complete proton decoupling. High resolution mass spectral (HRMS) data were obtained using electron spray ionization. Mp data were measured with micro melting point apparatus. Elemental analyses were recorded on an automatic analyzer.

4.2. Preparation of 3 and 4

4.2.1. General procedure. To a solution of **1** (0.5 mmol) and **2** (1 mmol) in anhydrous toluene (10 mL) was added a solution of PPh_3 (0.5 mmol) in anhydrous toluene (5 mL). The mixture was stirred at 80 °C for 1 h. The solvent was evaporated in vacuum and the residue was purified by silica gel column chromatography using hexane/EtOAc (10:1 to 6:1) as the eluent.

*4.2.2. General procedure for the synthesis of **4** in the absence of PPh_3.* The solution of **1** (0.5 mmol) and **2** (0.5 mmol) in anhydrous toluene (10 mL) was stirred at 80 °C for 10 min. The solvent was evaporated in vacuum and the residue was purified by silica gel column chromatography using hexane/EtOAc (6:1) as the eluent.

*4.2.2.1. 4-Ethyl(carbethoxy)amino-2,5-diphenyl-2H-1,2,4-triazol-3(4H)-one (**3a**).* Colorless gum; ^1H NMR (500 MHz, DMSO): δ 7.99 (m, 2H), 7.75 (m, 2H), 7.60 (m, 3H), 7.50 (m, 2H), 7.31 (m, 1H), 4.20 (m, 2H), 3.73 (m, 2H), 1.17 (m, 3H), 1.07 (t, J=7.2 Hz, 3H); ^{13}C NMR (125 MHz, DMSO): δ 154.6, 149.7, 145.4, 137.5, 131.2, 129.2, 129.1, 127.3, 125.8, 125.2, 118.4, 63.1, 45.6, 14.2, 12.6; HRMS (ESI) calcd for $C_{19}H_{20}N_4O_3$ ([M+Na]$^+$): 375.1428, found: 375.1442; IR (KBr) ν (cm^{-1}): 2981, 1732, 1597, 1496, 1455, 1268.

*4.2.2.2. 4-Benzyl(carbobenzoxy)amino-2,5-diphenyl-2H-1,2,4-triazol-3(4H)-one (**3b**).* Colorless gum; ^1H NMR (500 MHz, DMSO): δ 7.91 (m, 2H), 7.50 (m, 3H), 7.31 (m, 10H), 7.16 (m, 1H), 7.09 (m, 4H), 5.30 (m, 2H), 5.02 (d, J=14.2 Hz, 1H), 4.69 (d, J=14.2 Hz, 1H); ^{13}C NMR (125 MHz, DMSO): δ 154.9, 149.2, 145.4, 137.4, 135.6, 133.8, 130.9, 129.5, 129.2, 128.6, 128.5, 128.3, 128.2, 128.1, 127.8, 127.3, 125.9, 154.8, 118.5, 68.7, 53.9; HRMS (ESI) calcd for $C_{29}H_{24}N_4O_3$ ([M+Na]$^+$): 499.1741, found: 499.1752; IR (KBr) ν (cm^{-1}): 3064, 3034, 2958, 1732, 1597, 1496, 1455, 1219.

*4.2.2.3. 4-Ethyl(carbethoxy)amino-2-phenyl-5-(4-methylphenyl)-2H-1,2,4-triazol-3(4H)-one (**3c**).* Colorless gum; ^1H NMR (500 MHz, DMSO): δ 7.98 (m, 2H), 7.64 (d, J=8.2 Hz, 2H), 7.51 (m, 2H), 7.39 (d, J=8.0 Hz, 2H), 7.30 (m, 1H), 4.20 (m, 2H), 3.72 (m, 2H), 2.40 (s, 3H), 1.17 (m, 3H), 1.07 (t, J=7.2 Hz, 3H); ^{13}C NMR (125 MHz, DMSO): δ 154.6, 149.6, 145.4, 141.3, 137.6, 129.7, 129.2, 127.1, 125.7, 122.3, 118.4, 63.0, 45.6, 21.0, 14.2, 12.6; HRMS (ESI) calcd for $C_{20}H_{22}N_4O_3$ ([M+Na]$^+$): 389.1584, found: 389.1590; IR (KBr) ν (cm^{-1}): 2964, 1739, 1597, 1502, 1459, 1263.

*4.2.2.4. 4-Ethyl(carbethoxy)amino-2-(4-chlorophenyl)-5-phenyl-2H-1,2,4-triazol-3(4H)-one (**3d**).* White solid; mp 114–115 °C; ^1H NMR (500 MHz, DMSO): δ 8.00 (m, 2H), 7.74 (m, 2H), 7.58 (m, 5H), 4.20 (m, 2H), 3.72 (m, 2H), 1.17 (m, 3H), 1.07 (m, 3H); ^{13}C NMR (125 MHz, DMSO): δ 154.5, 149.5, 145.6, 136.3, 131.3, 130.0, 129.2, 129.1, 127.3, 124.9, 119.9, 63.1, 45.7, 14.2, 12.6; HRMS (ESI) calcd for $C_{19}H_{19}ClN_4O_3$ ([M+Na]$^+$): 409.1038, found: 409.1043; IR (KBr) ν (cm^{-1}): 2990, 1740, 1716, 1597, 1496, 1460, 1270.

*4.2.2.5. 4-Ethyl(carbethoxy)amino-2-(4-nitrophenyl)-5-phenyl-2H-1,2,4-triazol-3(4H)-one (**3e**).* Yellow solid; mp 136–137 °C; ^1H NMR (500 MHz, DMSO): δ 8.39 (d, J=9.2 Hz, 2H), 8.27 (m, 2H), 7.77 (m, 2H), 7.62 (m, 3H), 4.21 (m. 2H), 3.74 (m, 2H), 1.17 (m, 3H), 1.09 (t, J=7.2 Hz, 3H); ^{13}C NMR (125 MHz, DMSO): δ 154.4, 149.8, 146.7, 144.6, 142.4, 131.7, 129.2, 127.5, 125.2, 124.7, 118.1, 63.2, 45.8, 14.2, 12.7; HRMS (ESI) calcd for $C_{19}H_{19}N_5O_5$ ([M+Na]$^+$): 420.1278, found: 420.1287; IR (KBr) ν (cm^{-1}): 2988, 1743, 1712, 1597, 1519, 1498, 1454, 1280.

*4.2.2.6. 4-Ethyl(carbethoxy)amino-2-(4-methoxyphenyl)-5-phenyl-2H-1,2,4-triazol-3(4H)-one (**3f**).* Colorless gum; ^1H NMR (500 MHz, DMSO): δ 7.85 (m, 2H), 7.74 (m, 2H), 7.58 (m, 3H), 7.08 (m, 2H), 4.20 (m, 2H), 3.82 (s, 3H), 3.72 (m, 2H), 1.17 (m, 3H), 1.06 (t, J=7.2 Hz, 3H); ^{13}C NMR (125 MHz, DMSO): δ 157.6, 154.6, 149.6, 145.0, 131.1, 130.8, 129.1, 127.2, 125.3, 120.4, 114.6, 63.0, 55.6, 45.6, 14.2, 12.6; HRMS (ESI) calcd for $C_{20}H_{22}N_4O_4$ ([M+Na]$^+$): 405.1533, found: 405.1541; IR (KBr) ν (cm^{-1}): 2980, 1738, 1514, 1453, 1249.

*4.2.2.7. 4-Benzyl(carbobenzoxy)amino-2-(4-methylphenyl)-5-phenyl-2H-1,2,4-triazol-3(4H)-one (**3g**).* Colorless gum; ^1H NMR (500 MHz, DMSO): δ 7.99 (m, 2H), 7.49 (m, 1H), 7.33 (m, 11H), 7.18 (m, 1H), 7.09 (m, 4H), 5.31 (m, 2H), 5.03 (d, J=14.3 Hz, 1H), 4.69 (d, J=14.3 Hz, 1H), 2.35 (s, 3H); ^{13}C NMR (125 MHz, DMSO): δ 154.9, 149.1, 145.2, 135.6, 135.3, 135.0, 133.8, 130.8, 129.6, 129.5, 128.6, 128.5, 128.3, 128.2, 128.1, 127.7, 127.2, 124.8, 118.6, 68.6, 53.9, 20.5; HRMS (ESI) calcd for $C_{30}H_{26}N_4O_3$ ([M+Na]$^+$): 513.1897, found: 513.1899; IR (KBr) ν (cm^{-1}): 2963, 1738, 1514, 1497, 1453, 1261.

*4.2.2.8. 4-Ethyl(carbethoxy)amino-2-(4-methylphenyl)-5-(3-nitrophenyl)-2H-1,2,4-triazol-3(4H)-one (**3h**).* White solid; mp 131–132 °C; ^1H NMR (500 MHz, DMSO): δ 8.51 (s, 1H), 8.41 (d, J=7.6 Hz, 1H), 8.18 (d, J=7.8 Hz, 1H), 7.89 (t, J=8.0 Hz, 1H), 7.84 (d, J=8.2 Hz, 2H), 7.32 (d, J=8.2 Hz, 2H), 4.22 (m. 2H), 3.77 (m, 2H), 2.35 (s, 3H), 1.18 (m, 3H), 1.10 (t, J=7.2 Hz, 3H); ^{13}C NMR (125 MHz, DMSO): δ 154.6, 149.4, 148.4, 143.2, 135.6, 134.9, 133.2, 131.1, 129.6, 126.6, 125.6, 121.7, 118.6, 63.3, 45.8, 20.5, 14.2, 12.7; HRMS (ESI) calcd for $C_{20}H_{21}N_5O_5$ ([M+Na]$^+$): 434.1435, found: 434.1445; IR (KBr) ν (cm^{-1}): 2986, 1742, 1535,1513, 1267.

*4.2.2.9. 4-Benzyl(carbobenzoxy)amino-5-(4-nitrophenyl)-2-phenyl-2H-1,2,4-triazol-3(4H)-one (**3i**).* Pale brown solid; mp 137–138 °C; ^1H NMR (500 MHz, DMSO): δ 8.11 (d, J=8.8 Hz, 2H), 7.91 (d, J=7.9 Hz, 2H), 7.53 (m, 4H), 7.32 (m, 6H), 7.10 (m, 5H), 5.34 (m. 2H), 5.15 (d, J=14.2 Hz, 1H), 4.65 (d, J=14.2 Hz, 1H); ^{13}C NMR (125 MHz, DMSO): δ 154.8, 149.0, 148.7, 143.6, 137.1, 135.5, 133.7, 130.4, 129.7,

129.3, 128.5, 128.4, 128.3, 128.2, 128.0, 126.3, 123.7, 118.7, 68.9, 53.8; HRMS (ESI) calcd for $C_{29}H_{23}N_5O_5$ ([M+Na]$^+$): 544.1591, found: 544.1599; IR (KBr) ν (cm^{-1}): 3064, 1731, 1599, 1518, 1448, 1301.

*4.2.2.10. 4-Ethyl(carbethoxy)amino-5-(2-chlorophenyl)-2-phenyl-2H-1,2,4-triazol-3(4H)-one (**3j**).* Colorless gum; ^{1}H NMR (500 MHz, DMSO): δ 7.94 (m, 2H), 7.70 (m, 2H), 7.56 (m, 4H), 7.32 (m, 1H), 4.17 (q, J=7.0 Hz, 2H), 4.36 (m, 2H), 1.19 (t, J=7.0 Hz, 3H), 1.05 (t, J=7.2 Hz, 3H); ^{13}C NMR (125 MHz, DMSO): δ 154.3, 149.3, 144.2, 137.4, 133.6, 133.2, 132.0, 130.3, 129.3, 127.6, 126.0, 124.2, 128.5, 63.1, 45.9, 40.1, 12.7; HRMS (ESI) calcd for $C_{19}H_{19}ClN_4O_3$ ([M+Na]$^+$): 409.1038, found: 409.1044; IR (KBr) ν (cm^{-1}): 2981, 1739, 1598, 1502, 1460, 1269.

*4.2.2.11. 4-Ethyl(carbethoxy)amino-5-(4-bromophenyl)-2-phenyl-2H-1,2,4-triazol-3(4H)-one (**3k**).* Colorless gum; ^{1}H NMR (500 MHz, DMSO): δ 7.97 (d, J=7.8 Hz, 2H), 7.80 (d, J=8.6 Hz, 2H), 7.70 (d, J=8.5 Hz, 2H), 7.52 (m, 2H), 7.31 (m, 1H), 4.20 (m, 2H), 3.74 (m, 2H), 1.17 (m, 3H), 1.09 (t, J=7.2 Hz, 3H); ^{13}C NMR (125 MHz, DMSO): δ 157.4, 152.5, 147.4, 140.3, 135.2, 132.1, 132.0, 128.8, 127.9, 127.2, 121.4, 66.1, 48.6, 17.1, 15.5; HRMS (ESI) calcd for $C_{19}H_{19}BrN_4O_3$ ([M+Na]$^+$): 453.0533, found: 453.0536; IR (KBr) ν (cm^{-1}): 2980, 1741, 1598, 1491, 1460, 1267.

*4.2.2.12. 4-Ethyl(carbethoxy)amino-5-(4-nitrophenyl)-2-phenyl-2H-1,2,4-triazol-3(4H)-one (**3l**).* Pale yellow solid; mp 115–117 °C; ^{1}H NMR (500 MHz, DMSO): δ 8.40 (d, J=8.6 Hz, 2H), 8.05 (d, J=8.6 Hz, 2H), 7.98 (d, J=8.2 Hz, 2H), 7.53 (m, 2H), 7.32 (m, 1H), 4.21 (m. 2H), 3.78 (q, J=7.2 Hz, 2H), 1.17 (m, 3H), 1.12 (t, J=7.2 Hz, 3H); ^{13}C NMR (125 MHz, DMSO): δ 154.5, 149.5, 149.1, 143.5, 137.3, 130.8, 129.3, 128.5, 126.2, 124.3, 118.6, 63.3, 45.7, 14.2, 12.6; HRMS (ESI) calcd for $C_{19}H_{19}N_5O_5$ ([M+Na]$^+$): 420.1278, found: 420.1283; IR (KBr) ν (cm^{-1}): 2989, 1744, 1719, 1597, 1519, 1460, 1269.

*4.2.2.13. 4-Ethyl(carbethoxy)amino-5-(4-chlorophenyl)-2-(4-chlorophenyl)-2H-1,2,4-triazol-3(4H)-one (**3m**).* White solid; mp 124–125 °C; ^{1}H NMR (500 MHz, DMSO): δ 8.00 (m, 2H), 7.77 (d, J=8.6 Hz, 2H), 7.66 (d, J=6.8 Hz, 2H), 7.56 (m, 2H), 4.20 (m. 2H), 3.74 (m, 2H), 1.16 (m, 3H), 1.08 (t, J=7.2 Hz, 3H); ^{13}C NMR (125 MHz, DMSO): δ 154.8, 149.8, 145.0, 136.8, 136.6, 130.4, 129.8, 129.6, 129.4, 124.1, 120.2, 63.6, 46.0, 14.6, 13.0; HRMS (ESI) calcd for $C_{19}H_{18}Cl_2N_4O_3$ ([M+Na]$^+$): 443.0648, found: 443.0649; IR (KBr) ν (cm^{-1}): 2996, 1742, 1716, 1597, 1493, 1445, 1271.

*4.2.2.14. 4-Ethyl(carbethoxy)amino-5-(4-nitrophenyl)-2-(4-nitrophenyl)-2H-1,2,4-triazol-3(4H)-one (**3n**).* Pale yellow solid; mp 174–176 °C; ^{1}H NMR (500 MHz, DMSO): δ 8.43 (m, 4H), 8.28 (m, 2H), 8.07 (m, 2H), 4.25 (m, 2H), 3.80 (m, 2H), 1.18 (m, 3H), 1.13 (t, J=7.2 Hz, 3H); ^{13}C NMR (125 MHz, DMSO): δ 154.4, 149.6, 149.4, 144.8, 142.1, 130.3, 128.2, 125.2, 124.4, 118.4, 63.5, 45.8, 14.2, 12.7; HRMS (ESI) calcd for $C_{19}H_{18}N_6O_7$ ([M+Na]$^+$): 465.1129, found: 465.1144; IR (KBr) ν (cm^{-1}): 2963, 1754, 1715, 1593, 1518, 1274.

*4.2.2.15. 4-Ethyl(carbethoxy)amino-5-(4-nitrophenyl)-2-(2,4-dinitrophenyl)-2H-1,2,4-triazol-3(4H)-one (**3o**).* Pale yellow solid; mp 132–133 °C; ^{1}H NMR (500 MHz, DMSO): δ 8.84 (d, J=2.6 Hz, 1H), 8.71 (m, 1H), 8.44 (m, 2H), 8.25 (d, J=9.0 Hz, 1H), 8.03 (m, 2H), 4.23 (m, 2H), 3.76 (m, 2H), 1.21 (t, J=7.0 Hz, 3H), 1.11 (t, J=7.0 Hz, 3H); ^{13}C NMR (125 MHz, DMSO): δ 154.2, 149.6, 149.5, 146.1, 146.0, 142.3, 132.9, 130.0, 128.8, 128.6, 127.2, 124.5, 121.4, 63.6, 45.7, 14.0, 12.5; HRMS (ESI) calcd for $C_{19}H_{17}N_7O_9$ ([M+Na]$^+$): 510.0980, found: 510.0992; IR (KBr) ν (cm^{-1}): 2979, 1761, 1729, 1603, 1491, 1267.

*4.2.2.16. 4-Ethyl(carbethoxy)amino-5-(naphthalen-2-yl)-2-phenyl-2H-1,2,4-triazol-3(4H)-one (**3p**).* Colorless gum; ^{1}H NMR (500 MHz, DMSO): δ 8.31 (s, 1H), 8.10 (d, J=8.6 Hz, 1H), 8.03 (m, 4H), 7.87 (m, 1H), 7.65 (m, 2H), 7.53 (m, 2H), 7.31 (m, 1H), 4.23 (m, 2H), 3.79 (m, 2H), 1.18 (m, 3H), 1.11 (t, J=7.2 Hz, 3H); ^{13}C NMR (125 MHz, DMSO): δ 154.6, 149.8, 145.3, 137.6, 133.9, 132.5, 129.2, 128.9, 128.7, 128.0, 127.8, 127.4, 127.2, 125.9, 123.7, 122.5, 118.5, 63.1, 45.8, 14.2, 12.6; HRMS (ESI) calcd for $C_{23}H_{22}N_4O_3$ ([M+Na]$^+$): 425.1584, found: 425.1588; IR (KBr) ν (cm^{-1}): 3061, 2979, 1732, 1598, 1501, 1266.

*4.2.2.17. 4-Ethyl(carbethoxy)amino-5-(furan-2-yl)-2-phenyl-2H-1,2,4-triazol-3(4H)-one (**3q**).* Colorless liquid; ^{1}H NMR (500 MHz, DMSO): δ 7.93 (m, 3H), 7.50 (m, 2H), 7.73 (m, 1H), 7.03 (m, 1H), 6.73 (m, 1H), 4.17 (m, 2H), 3.86 (m, 1H), 3.73 (m, 1H), 1.17 (m, 6H); ^{13}C NMR (125 MHz, DMSO): δ 154.2, 149.2, 146.1, 139.2, 138.3, 137.4, 129.2, 125.9, 118.4, 113.1, 112.2, 62.9, 45.3, 14.2, 12.5; HRMS (ESI) calcd for $C_{17}H_{18}N_4O_4$ ([M+Na]$^+$): 365.1220, found: 365.1219; IR (KBr) ν (cm^{-1}): 2982, 1740, 1597, 1503, 1460, 1270.

*4.2.2.18. 4-Ethyl(carbethoxy)amino-5-(pyridin-4-yl)-2-phenyl-2H-1,2,4-triazol-3(4H)-one (**3r**).* Colorless liquid; ^{1}H NMR (500 MHz, DMSO): δ 8.82 (m, 2H), 7.98 (m, 2H), 7.72 (m, 2H), 7.53 (m, 2H), 7.34 (m, 1H), 4.21 (m, 2H), 3.77 (m, 2H), 1.17 (m, 3H), 1.13 (t, J=7.2 Hz, 3H); ^{13}C NMR (125 MHz, DMSO): δ 154.5, 150.8, 149.6, 143.2, 137.3, 132.4, 129.3, 126.3, 120.7, 118.7, 63.3, 45.7, 14.2, 12.6; HRMS (ESI) Calcd for $C_{18}H_{19}N_5O_3$ ([M+Na]$^+$): 376.1380, found: 376.1390; IR (KBr) ν (cm^{-1}): 2981, 1740, 1597, 1499, 1446, 1268.

*4.2.2.19. Diethyl 1-(1-(phenyldiazenyl)decyl)hydrazine-1,2-dicarboxylate (**4a**).* Pale yellow solid; mp 58–59 °C; ^{1}H NMR (500 MHz, DMSO): δ 9.06 (br, 1H), 7.66 (m, 2H), 7.52 (m, 3H), 5.56 (s, 1H), 4.09 (m, 4H), 1.92 (m, 1H), 1.80 (m, 1H), 1.49 (m, 2H), 1.26 (m, 18H), 0.86 (t, J=7.0 Hz, 3H); ^{13}C NMR (125 MHz, DMSO): δ 156.5, 155.7, 151.5, 131.0, 129.1, 122.3, 86.0, 61.9, 60.8, 31.3, 29.6, 28.9, 28.8, 28.7, 28.6, 24.5, 22.0, 14.4, 14.3, 13.8; HRMS (ESI) calcd for $C_{22}H_{36}N_4O_4$ ([M+Na]$^+$): 443.2629, found: 443.2639; IR (KBr) ν (cm^{-1}): 3293, 2922, 1755, 1684, 1502, 1468, 1418, 1228.

*4.2.2.20. Diethyl 1-(2-methyl-1-(phenyldiazenyl)propyl)hydrazine-1,2-dicarboxylate (**4b**).* Pale yellow solid; mp 82–83 °C; ^{1}H NMR (500 MHz, DMSO): δ 9.10 (br, 1H), 7.68 (m, 2H), 7.52 (m, 3H), 5.15 (d, J=7.7 Hz, 1H), 4.09 (q, J=7.0 Hz, 4H), 2.49 (m, 1H), 1.14 (m, 9H), 0.83 (d, J=6.0 Hz, 3H); ^{13}C NMR (125 MHz, DMSO): δ 156.4, 155.8, 151.6, 131.0, 129.1, 122.3, 91.3, 61.9, 60.8, 28.7, 19.2, 18.3, 14.4, 14.3; HRMS (ESI) calcd for $C_{16}H_{24}N_4O_4$ ([M+Na]$^+$): 359.1690, found: 359.1691; IR (KBr) ν (cm^{-1}): 3293, 2981, 2936, 1753, 1683, 1528, 1497, 1417, 1223.

*4.2.2.21. Dibenzyl 1-(2-methyl-1-(phenyldiazenyl)propyl)hydrazine-1,2-dicarboxylate (**4c**).* Pale yellow solid; mp 93–94 °C; ^{1}H NMR (500 MHz, DMSO) δ 9.45 (br, 1H), 7.63 (m, 2H), 7.48 (m, 3H), 7.29 (m, 10H), 5.20 (s, 1H), 5.12 (m, 4H), 2.51 (m, 1H), 1.10 (d, J=5.0 Hz, 3H), 0.82 (d, J=5.0 Hz, 3H); ^{13}C NMR (125 MHz, DMSO) δ 156.4, 155.7, 151.5, 136.6, 136.3, 131.0, 129.1, 128.3, 127.9, 127.6, 127.3, 122.4, 91.5, 67.4, 66.4, 28.7, 19.2, 18.3; HRMS (ESI) calcd for $C_{26}H_{28}N_4O_4$ ([M+Na]$^+$): 483.2003, found: 483.2007; IR (KBr) ν (cm^{-1}): 3280, 2962, 1744, 1689, 1499, 1411, 1221.

*4.2.2.22. Diethyl 1-(phenyl(phenyldiazenyl)methyl)hydrazine-1,2-dicarboxylate (**4d**)*[19]. Yellow solid; mp 95–96 °C; ^{1}H NMR (500 MHz, DMSO) δ 9.16 (br, 1H), 7.75 (m, 2H), 7.55 (m, 3H), 7.43 (m, 2H), 7.34 (m, 3H), 6.71 (s, 1H), 4.20 (m, 2H), 3.81 (m, 2H), 1.15 (m, 3H), 1.02 (m, 3H); ^{13}C NMR (125 MHz, DMSO) δ 155.7, 151.4, 131.3, 129.2, 128.9, 128.4, 128.1, 122.4, 87.7, 62.1, 60.5, 14.3; HRMS (ESI) calcd for $C_{19}H_{22}N_4O_4$ ([M+Na]$^+$): 393.1533, found: 393.1523; IR (KBr) ν (cm^{-1}): 3294, 2982, 1756, 1683, 1498, 1416, 1314, 1225.

4.3. Preparation of 5a and 6a

4.3.1. General procedure. To a solution of **4d** (1 mmol) in MeOH (15 mL) was added TFA (1 mmol). The mixture was stirred at room temperature for 10 min. The solvent was evaporated in vacuum and residual oil was purified by silica gel column chromatography using hexane/EtOAc (7:1) as the eluent to give pure **5a**. Compound **5a** (0.5 mmol) was dissolved in MeOH (10 mL). TFA (0.5 mmol) was added and the resulting mixture was stirred at 50 °C for 1.5 h. The solvent was evaporated in vacuum and product was purified by silica gel column chromatography using hexane/EtOAc (5:1) as the eluent to give pure **6a**.

*4.3.2. General procedure for the synthesis of **6** from **4**.* The solution of **4** (0.5 mmol) and TFA (0.5 mmol) in MeOH was stirred at 50 °C for 1.5 h. The solvent was evaporated in vacuum and residue was purified by silica gel column chromatography using hexane/EtOAc (5:1) as the eluent to afford pure **6**.

*4.3.2.1. Diethyl 1-(phenyl(2-phenylhydrazono)methyl)hydrazine-1,2-dicarboxylate (**5a**).* White solid; mp 123–124 °C; ^{1}H NMR (500 MHz, DMSO): δ 9.98 (br, 2H), 7.74 (m, 2H), 7.39 (m, 2H), 7.30 (m, 3H), 7.15 (m, 2H), 6.84 (m, 1H), 4.20 (q, J=7.0 Hz, 2H), 4.11 (m, 2H), 1.23 (t, J=6.8 Hz, 3H), 1.00 (m, 3H); ^{13}C NMR (125 MHz, DMSO): δ 158.3, 153.8, 144.3, 134.0, 132.7, 129.3, 128.4, 128.2, 125.5, 120.3, 113.0, 62.7, 62.1, 14.3, 14.1; HRMS (ESI) calcd for $C_{19}H_{22}N_4O_4$ ([M+Na]$^+$): 393.1533, found: 393.1522; IR (KBr) ν (cm^{-1}): 3281, 3245, 2984, 1736, 1705, 1559, 1496, 1448, 1260.

*4.3.2.2. 4-Carbethoxyamino-2,5-diphenyl-2H-1,2,4-triazol-3(4H)-one (**6a**).* White solid; mp 144–145 °C; ^{1}H NMR (500 MHz, DMSO): δ 8.63 (br, 1H), 8.02 (d, J=8.0 Hz, 2H), 7.84 (d, J=6.9 Hz, 2H), 7.46 (m, 5H), 7.23 (m, 1H), 4.18 (q, J=6.9 Hz, 2H), 1.20 (m, 3H); ^{13}C NMR (125 MHz, DMSO): δ 155.7, 151.3, 146.1, 137.8, 131.2, 129.2, 129.0, 127.9, 126.1, 125.4, 119.1, 63.4, 14.4; HRMS (ESI) calcd for $C_{17}H_{16}N_4O_3$ ([M+Na]$^+$): 347.1115, found: 347.1106; IR (KBr) ν (cm^{-1}): 3211, 1753, 1712, 1495, 1458, 1241.

*4.3.2.3. 4-Carbethoxyamino-5-nonyl-2-phenyl-2H-1,2,4-triazol-3(4H)-one (**6b**).* White solid; mp 65–66 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.70 (br, 1H), 7.93 (d, J=8.2 Hz, 2H), 7.40 (m, 2H), 7.21 (m, 1H), 4.19 (q, J=6.8 Hz, 2H), 2.55 (t, J=7.8 Hz, 2H), 1.72 (m, 2H), 1.40 (m, 2H), 1.31 (m, 13H), 0.88 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 155.6, 151.0, 148.7, 137.8, 129.1, 125.8, 118.9, 63.2, 32.1, 29.6, 29.5, 29.4, 29.3, 25.7, 25.0, 22.9, 14.4, 14.3; HRMS (ESI) calcd for $C_{20}H_{30}N_4O_3$ ([M+Na]$^+$): 397.2210, found: 397.2213; IR (KBr) ν (cm^{-1}): 3175, 2926, 1754, 1705, 1549, 1502, 1256.

*4.3.2.4. 4-Carbethoxyamino-2-phenyl-5-tert-butyl-2H-1,2,4-triazol-3(4H)-one (**6c**).* White solid; mp 113–114 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.60 (br, 1H), 7.95 (m, 2H), 7.41 (m, 2H), 7.19 (m, 1H), 4.21 (q, J=7.0 Hz, 2H), 2.94 (m, 1H), 1.32 (d, J=7.0 Hz, 6H), 1.22 (t, J=7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 155.8, 152.5, 151.2, 137.9, 129.1, 125.8, 118.9, 63.3, 25.6, 19.7, 14.4; HRMS (ESI) calcd for $C_{14}H_{18}N_4O_3$ ([M+Na]$^+$): 313.1271, found: 313.1263; IR (KBr) ν (cm^{-1}): 3206, 2978, 1749, 1704, 1497, 1460, 1246.

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Supplementary data

Copies of ^{1}H and ^{13}C NMR spectra for all products. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2010.01.087.

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17. CCDC 761051, CCDC 761049, and CCDC 761050 contain the supplementary crystallographic data for compounds **3i**, **3l**, and **5a**, respectively. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.
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