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Sequential one-pot and three-component reactions of an *N*-heterocyclic carbene to form 4-(1,2,4-triazol-5-ylidene)pyrrolidine-2,5-diones: a tandem umpolung/annulation sequence via deoxy-Breslow intermediates

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ABSTRACT

The tandem sequence of the umpolung of α,β-unsaturated esters by an *N*-heterocyclic carbene (NHC) followed by annulation is demonstrated. The deoxy-Breslow intermediates are selectively generated from the reaction of NHC with methyl methacrylate, dimethyl itaconate, or methyl crotonate. Subsequently, they undergo annulation with isocyanates to give 4-(1,2,4-triazol-5-ylidene)pyrrolidine-2,5-diones in good isolated yields. In addition, the stoichiometric three-component reaction of NHC, methyl methacrylate, and phenyl isocyanate proceeded, accompanied by the formation of the 1:2 adduct of NHC with phenyl isocyanate.

1. Introduction

N-Heterocyclic carbenes[1] (NHCs), due to their strong electron donating ability,[2] readily react with various unsaturated electrophiles to generate zwitterionic adducts.[3] While the adducts of NHC with carbon dioxide,[4] carbon disulfide,[1b-d,5] and isothiocyanates[1b-d,6] are relatively stable and isolable, those with aldehydes,[7] activated olefins,[1,8,9] and isocyanates[1b,10] readily undergo proton transfer generating Breslow[7,11] or deoxy-Breslow[8,12] intermediates, or the further addition to the electrophile. Since the first report by Nair,[13a] the nucleophilic reactivity of NHCs has been extended to three-component reactions.[13] Specifically, NHCs selectively and sequentially react with two kinds of electrophiles (combinations of aldehydes,[13a-d,h-j] activated acetylenes,[13a-f,h-j] ketenes,[13e,f] allenoates,[13g,i] and isothiocyanates[13g]) to yield a variety of complex molecules, such as furan and furanone derivatives, in one pot. The three-component reaction may allow us to understand the reactivity of various adducts formed by NHCs and electrophiles.

NHC catalysis can offer new opportunities for the discovery of reactions, in particular, the umpolung of aldehydes.[7] Indeed, Breslow intermediates, the acyl anion and homoenolate equivalents, react with various electrophiles leading to widespread bond forming reactions. In contrast, the NHC-catalyzed umpolung of activated olefins is far less developed. Fu et al. first demonstrated the umpolung reaction of α,β-unsaturated carbonyl compounds via the deoxy-Breslow intermediate.[8a] We[8b] and Glorius[8c] extended this concept to the intermolecular bond forming reaction between β-carbons of methacrylates. Scheidt used the umpolung process for the rearrangement of vinyl sulfones[8d] and the related Rauhut–Currier reaction.[8e] The NHC-catalyzed umpolung of activated olefins is a promising procedure to introduce electrophiles at the β-carbons, thereby creating a new field of NHC catalysis. However, electrophiles are now limited to alkyl halides,[8a] tosylate,[8a] and electron-deficient alkenes.[8b-e] In this context, to expand the scope, we examined the reactions of the deoxy-Breslow intermediates with other electrophiles. Herein we report the sequential one-pot and three-component reactions of NHC, α,β-unsaturated esters, and isocyanates that involve the tandem umpolung/annulation sequence.

2. Results and discussion

2.1. Sequential one-pot reaction

We have previously reported the dimerization of methacrylates catalyzed by the isolated NHC (**1**) and detected the deoxy-Breslow intermediate (**2**) by electrospray ionization mass spectrometry (Scheme 1).[8b] In contrast, Glorius and co-workers used the in situ

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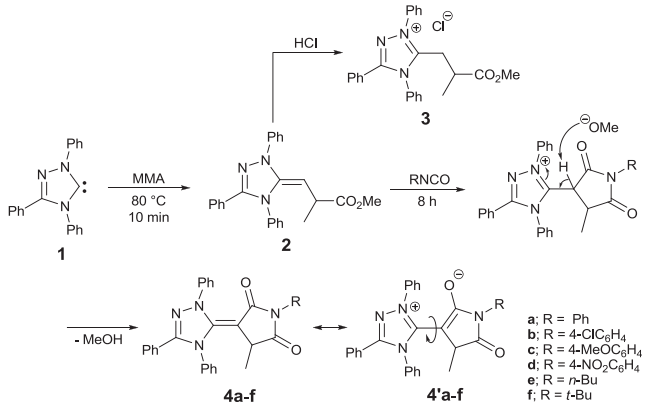
generated species, **1**, for the same reaction and isolated its corresponding $HClO_4$ adduct.[8c] Recently, Chen isolated the deoxy-Breslow intermediate derived from another NHC, imidazolium-2-ylidene, and MMA.[9e] When compared to the Breslow intermediates, the deoxy-variants are relatively stable.



Scheme 1. The sequential one-pot reaction of **1**, methyl methacrylate (MMA), and isocyanates.

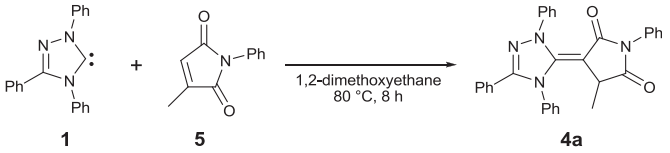
We first carried out the reaction of **1** with an equimolar amount of MMA in 1,2-dimethoxyethane at 80 °C for 10 min followed by the addition of HCl in methanol. The HCl adduct **3** was selectively formed and isolated in 80% yield, suggesting the selective generation of **2** without the further conjugate addition to MMA (Scheme 1). The addition of phenyl isocyanate (PhNCO) to **2** generated in situ produced **4a** in good yields (Table 1, entries 1 and 2).[14] Mechanistically, the umpolung β-carbon of **2** has sufficient nucleophilicity to attack the electrophilic carbon of PhNCO, followed by the ring closure and elimination of methanol. When the reaction time of **1** with MMA was extended to 8 h before the addition of PhNCO, the yield of **4a** decreased to 38% (entry 3), suggesting a decomposition of **2** during the prolonged reaction time. The reaction of **2** with PhNCO at 40 °C lowered the yield to 31% (entry 4), and no product was observed at 0 °C (entry 5). As an alternative pathway, the reaction of **1** with an equimolar amount of **5** at 80 °C directly produced **4a** in 70% yield through the conjugate addition and subsequent proton transfer (Scheme 2).[15]

Table 1
The sequential one-pot reaction of **1**, MMA, and isocyanates[a]

Entry	RNCO		Temp (°C)[b]	Yield (%)[c]
	R	Equiv		
1	Ph	1	80	75
2	Ph	3	80	81
3[d]	Ph	1	80	38
4	Ph	1	40	31
5	Ph	1	0	<1
6	4-ClC_6H_4	1	80	87
7	4-$MeOC_6H_4$	1	80	76
8	4-$NO_2C_6H_4$	1	80	72
9	*n*-Bu	1	80	73
10	*t*-Bu	1	80	22
11	*t*-Bu	3	80	26

[a] **1** (0.46 mmol), MMA (0.46 mmol), in 1,2-dimethoxyethane (0.9 mL). The reaction of **1** with MMA was carried out at 80 °C for 10 min, followed by the reaction with RNCO for 8 h.
[b] Temperature of the reaction of **2** with RNCO.
[c] Isolated yields of **4a**–**f**.
[d] The reaction of **1** and MMA was carried out for 8 h.

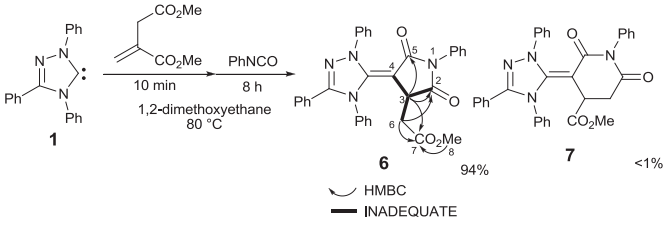
The aromatic isocyanates bearing electron-withdrawing and donating substituents at the *para* position and *n*-butyl isocyanate gave the products (**4a**–**e**) in good yields (entries 6–9); whereas the bulky *tert*-butyl isocyanate reduced the yield, even at an increased



Scheme 2. The direct synthesis of **4a** from **1** and **5**.

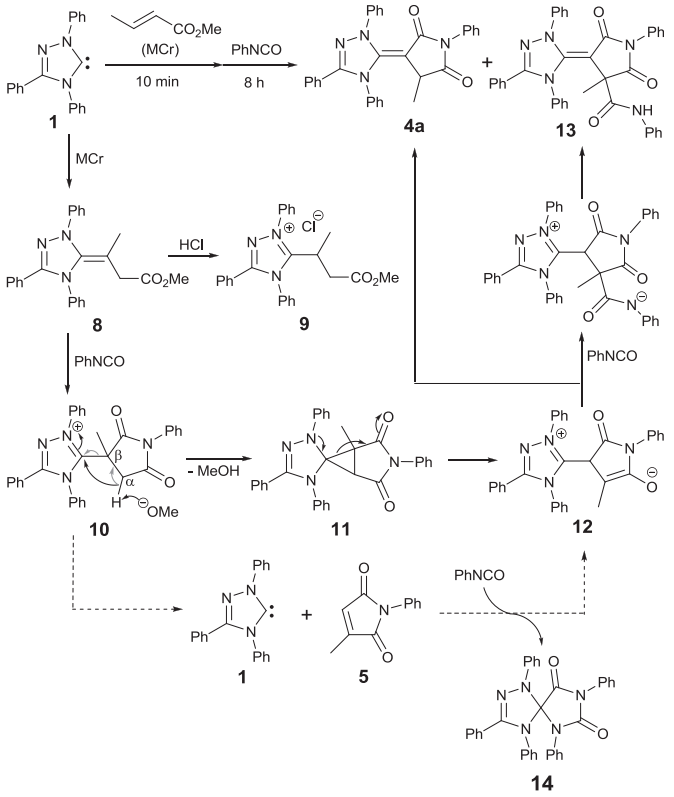
feed ratio (entries 10 and 11). Compounds **4a**–**f** show a single set of ^{13}C NMR signals, indicating that there are no diastereomers observed on the NMR timescale. It is reasonable to assume that the interconversion between **4** and **4′** allows the free rotation of the C–C bond formed from the carbene carbon and β-carbon of MMA (Scheme 1).[12,16]

We next examined the reaction of dimethyl itaconate (DMI), a substitute for MMA, as the two distinct methoxy carbonyl groups show promise for interesting reactivity. The analogous reaction proceeded to give a three-component product in 94% yield. Although there are two possible structural isomers, **6** and **7** (Scheme 3), the ^1H and ^{13}C NMR spectra indicated a single product. Compared to the ^{13}C NMR data of **4a**–**f**, similar resonances corresponding to the five-membered ring were observed.[17] In addition, the 2D INADEQUATE NMR spectrum showed a key correlation of the tertiary carbon (C3) with the imide carbonyl carbon (C2),[18] which does not appear in the six-membered ring of **7**, thereby identifying the structure of **6** (See Supplementary data).



Scheme 3. The sequential one-pot reaction of **1**, dimethyl itaconate (DMI), and PhNCO. The arrows and bold lines in **6** indicate the key HMBC and INADEQUATE correlations, respectively.

Given that the above reactions using MMA and DMI involved the abstraction of β-protons, we then turned our attention to the β-substituted olefin methyl crotonate (MCr). The reaction of **1** with MCr at 80 °C followed by the addition of HCl gave the HCl adduct (**9**) through the corresponding deoxy-Breslow intermediate (**8**) (Scheme 4). When **8**, generated in situ, was subsequently reacted with PhNCO, compounds **4a** and **13** were unexpectedly obtained. The yield of **13** increased with excess PhNCO (Table 2). The formation of **13** suggests that the enolate (**12**) is an intermediate. Mechanistically, the tandem umpolung/annulation sequence generates the intermediary species **10**, as in the case of MMA. Since the β-carbon of **10** is quaternary, the methoxide anion generated in situ abstracts the α-proton to give **12**. The proton transfer of **12** produces **4a**, while the further addition of **12** to PhNCO followed by the proton transfer resulted in **13**. There are two possible pathways for the transformation of **10** to **12**: (i) an intramolecular 1,2-migration of triazolinium ring via the three-membered ring **11**; or (ii) liberation of **1** and **5** followed by the intermolecular conjugate addition of **1** to the less hindered olefinic carbon of **5**. To gain a mechanistic insight into this process, the one-feed three-component reaction of **1**, **5**, and PhNCO was performed (Table 3). The stoichiometric reaction gave **4a** and **14** in 36% and 50% yields, respectively, without forming **13** (entry 1). In the presence of an excess of PhNCO, **14** was selectively obtained (entry 2). Given these results, if **10** liberated **1** and **5**, **14** would be formed instead of **13** by the reaction of the regenerated **1** with PhNCO. However, this was not the case.



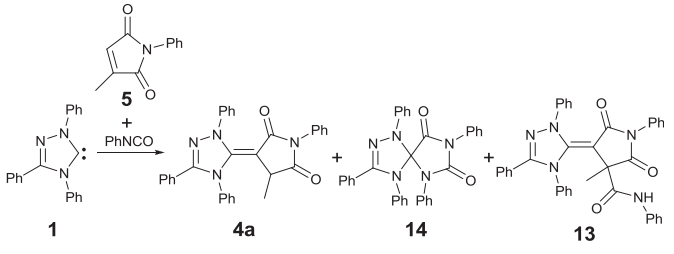
Scheme 4. The sequential one-pot reaction of **1**, methyl crotonate (MCr), and PhNCO. The proposed 1,2-migration mechanism of triazolinium ring (**10**→**12**).

Table 2
The sequential one-pot reaction of **1**, MCr, and PhNCO[a]

Entry	PhNCO (equiv)	Yield (%)[b]	
		4a	**13**[c]
1	1	24	11 (22)
2	10	11	50

[a] **1** (0.46 mmol), MCr (0.46 mmol), in 1,2-dimethoxyethane (0.9 mL) at 80 °C. The reaction of **1** with MCr was carried out for 10 min, followed by the reaction with RNCO for 8 h.
[b] Calculated by ^{1}H NMR spectra based on **1**.
[c] The value in parenthesis indicates the yield calculated based on PhNCO.

Table 3
Three-component reaction of **1**, **5**, and PhNCO[a]



Entry	**1**:**5**:PhNCO (equiv)	Yield (%)[b]		
		4a	**14**[c]	**13**
1	1:1:1	36	50 (>99)	<1
2	1:1:9	<1	>99	<1

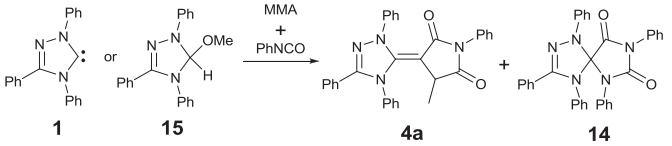
[a] **1** (0.46 mmol), **5** (0.46 mmol), in 1,2-dimethoxyethane (0.9 mL) at 80 °C for 8 h.
[b] Isolated yields calculated based on **1**.
[c] The value in parenthesis indicates the isolated yield calculated based on PhNCO.

Therefore, we reason that the transformation of **10** to **12** takes place intramolecularly via **11** without the liberation of **1** and **5**.

2.2. Three-component reaction

The sequential one-pot reactions were found to be highly selective, leading us to examine the one-feed three-component reaction of **1**, MMA, and PhNCO (Table 4). Although **14** was exclusively obtained at 40 °C (entry 1), the reaction at 80 °C gave **4a** and **14** in 31% and 37% yields, respectively, (entry 2). Increasing the MMA feed ratios to 2 and 10 neither increased the yield of **4a**, nor gave the MMA dimer or oligomers (entries 3 and 4). Alternatively, the addition of only 2 equiv of PhNCO led to the exclusive formation of **14** even in the presence of an excess amount of MMA (entries 5 and 6).

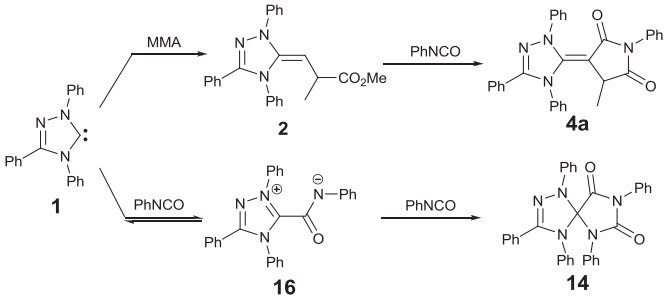
Table 4
Three-component reaction of NHC (**1**) or its precursor (**15**), MMA, and PhNCO[a]



Entry	NHC	NHC:MMA:PhNCO (equiv)	Temp (°C)	Yield (%)[b]	
				4a	**14**[c]
1	**1**	1:1:1	40	<1	50 (>99)
2	**1**	1:1:1	80	31	37 (74)
3	**1**	1:2:1	80	25	41 (82)
4	**1**	1:10:1	80	21	42 (84)
5	**1**	1:2:2	80	<1	94 (94)
6	**1**	1:10:2	80	<1	>99 (>99)
7	**15**	1:1:1	80	38	33 (66)
8	**15**	1:2:2	80	<1	>99 (>99)

[a] **1** or **15** (0.46 mmol), in 1,2-dimethoxyethane (0.9 mL) for 8 h.
[b] Isolated yields calculated based on NHC.
[c] The values in parentheses indicate the yields calculated based on PhNCO.

This effect of the stoichiometry can be mechanistically explained as follows. The NHC **1** quickly adds to PhNCO to quantitatively generate the zwitterion, **16** (Scheme 5). In the presence of more than 2 equiv of PhNCO, **16** readily reacts further with PhNCO to yield **14**. In the case of an equimolar amount of PhNCO, compound **1** and PhNCO were partially regenerated from **16**, and the PhNCO was consumed by the reaction with **2** or **16**. The regenerated species **1** then reacted with MMA and PhNCO to yield **4a**.



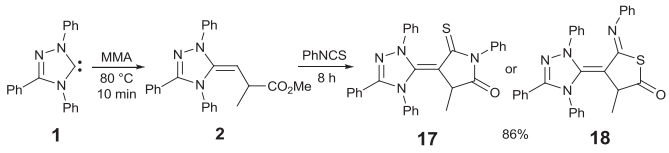
Scheme 5. Three-component reaction of **1**, MMA, and PhNCO through the equilibrium between **1** and **16**.

This reaction similarly proceeded using the methanol adduct of **1** (**15**) instead of the isolated **1**, and the same effect of the stoichiometry was observed (entries 7 and 8). In addition, **15** was found to react with PhNCO, even at room temperature, to quantitatively give **14**, suggesting that **16** was generated in situ under these conditions.

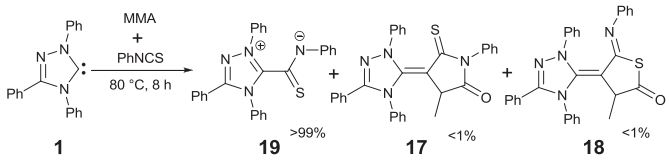
Therefore, **15** is regarded as a masked precursor of **1** and similarly used for this transformation.

2.3. Reactions using phenyl isothiocyanate (PhNCS)

PhNCS also underwent the sequential one-pot reaction to give a product (**17** or **18**) in 86% yield (Scheme 6), however, it was poorly soluble in common organic solvents.[19] On the other hand, the attempted three-component reaction gave the zwitterionic product **19** without forming **17** or **18** (Scheme 7). This result is in sharp contrast to that observed with PhNCO. Previously, Enders reported the stability and reactivity of **16** and **19**.[1b] Indeed, **16** was not isolable, while **19** was quite stable. Thus, we reason that there is an equilibrium between **1** and **16** and not between **1** and **19**, thereby not yielding the three-component products from PhNCS.



Scheme 6. The sequential one-pot reaction of **1**, MMA, and PhNCS.



Scheme 7. The attempted three-component reaction of **1**, MMA, and PhNCS.

3. Conclusions

We have demonstrated the sequential one-pot and three-component reactions that feature the unique tandem umpolung/annulation sequences. The deoxy-Breslow intermediates from MMA or DMI react with isocyanates to give compounds **4a**–**f** and **6** in good yields. Unexpectedly, **4a** was also obtained from MCr through the tandem sequence and intramolecular migration. These reactions are the first intermolecular reactions of the deoxy-Breslow intermediates with electrophiles other than activated olefins. It should also be noted that the stoichiometric three-component reaction of **1**, MMA, and PhNCO is the first multicomponent reaction of NHC via umpolung. Further study of reactions of the deoxy-Breslow intermediates with other electrophiles is now in progress.

4. Experimental section

4.1. General

All reactions were performed under nitrogen atmosphere using standard Schlenk techniques. MMA, MCr, DMI, and 1,2-dimethoxyethane were distilled from CaH_2 under reduced pressure before use. Other chemicals were used as received. Melting points were measured on a Yanaco micro melting point apparatus. ^1H and ^{13}C NMR spectra were recorded on Bruker Avance-600 (600 MHz for ^1H, 150 MHz for ^{13}C) or Avance III 500 MHz (500 MHz for ^1H, 125 MHz for ^{13}C) spectrometers. Chemical shifts were referenced internally to tetramethylsilane (0.0 ppm for ^1H), or $CDCl_3$ resonance (77.1 ppm for ^{13}C). Electrospray ionization mass spectrometry (ESI-MS) was performed on a Waters Synapt G2 HDMS tandem quadrupole orthogonal acceleration time-of-flight instrument equipped with a Z-spray nanoelectrospray ionization source. Infrared spectra were recorded on a FT/IR-460 Plus spectrometer equipped with a ZnSe crystal ATR accessory.

4.2. Synthesis of 3 and 9

To the solution of **1** (150 mg, 0.46 mmol) in 1,2-dimethoxyethane (0.9 mL), MMA (47.1 mg, 0.47 mmol) was added. After the reaction stirred at 80 °C for 10 min, HCl in methanol (5.0 mL, 0.46 mol/L) was added, and the reaction mixture was stirred at room temperature for 3 h. The crude product was purified by silica gel column chromatography using chloroform/methanol as the eluent to give **3** (158 mg, 0.36 mmol) in 80% yield. **9** was obtained in 90% yield from the analogous procedure with MCr.

*4.2.1. 5-(3-Methoxy-2-methyl-3-oxopropyl)-1,3,4-triphenyl-4H-1,2,4-triazol-1-ium chloride (**3**).* Mp=225–227 °C; ^1H NMR (600 MHz, $CDCl_3$): δ 8.21 (m, 3H), 7.98 (d, 1H, J=6.9 Hz), 7.95–7.28 (m, 12H), 4.08 (dd, 1H, J=16.1 Hz, 5.0 Hz), 3.54 (s, 3H), 3.22 (dd, 1H, J=16.1 Hz, 11.5 Hz), 2.27 (m, 1H), 1.00 (d, 3H, J=7.2 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ 174.0, 154.8, 152.8, 135.2, 131.9, 131.7, 131.7, 131.4, 130.5, 130.4, 129.9, 129.2, 128.7, 128.2, 128.0, 126.4, 122.7, 52.3, 35.7, 29.5, 17.2; HRMS (ESI) calcd for $C_{25}H_{24}ClN_3O_2$ $[M-Cl]^+$: 398.1868, found: 398.1866; IR (neat, cm^{-1}): 3051, 1735, 1553, 1506, 1459, 1198, 928, 767, 731, 638.

*4.2.2. 5-(4-Methoxy-4-oxobutan-2-yl)-1,3,4-triphenyl-4H-1,2,4-triazol-1-ium chloride (**9**).* Mp=120–122 °C; ^1H NMR (600 MHz, $CDCl_3$): δ 8.16–8.01 (m, 4H), 7.68–7.47 (m, 8H), 7.41–7.32 (m, 2H), 7.25 (t, 2H, J=7.6 Hz), 3.61 (s, 3H), 3.59 (m, 1H), 2.96 (dd, 1H, J=8.4 Hz, 17.5 Hz), 2.33 (dd, 1H, J=7.6 Hz, 17.5 Hz), 1.47 (d, 3H, J=7.2 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ 171.1, 156.3, 153.5, 135.2, 131.7, 131.7, 131.6, 131.3, 130.1, 130.1, 129.7, 129.7, 128.6, 128.4, 128.4, 127.4, 122.8, 52.0, 36.9, 28.0, 18.3; HRMS (ESI) calcd for $C_{25}H_{24}ClN_3O_2$ $[M-Cl]^+$: 398.1868, found: 398.1895; IR (neat, cm^{-1}): 3051, 2951, 1732, 1504, 1362, 1198, 1178, 926, 764, 724, 693.

4.3. General procedure for the sequential one-pot reaction (4a–f, 6)

To the solution of **1** (150 mg, 0.46 mmol) in 1,2-dimethoxyethane (0.9 mL), MMA (45.6 mg, 0.46 mmol) was added. After the reaction stirred for 10 min at 80 °C, PhNCO (53.3 mg, 0.45 mmol) was then added, and the reaction solution was stirred for 8 h. An excess amount of ethyl acetate was added to the solution, and the precipitated **4a** (162 mg, 0.33 mmol, 75%) was collected by filtration. Compounds **4b**–**f** and **6** were obtained from the analogous procedure.

*4.3.1. 3-Methyl-1-phenyl-4-(1,3,4-triphenyl-1H-1,2,4-triazol-5(4H)-ylidene)pyrrolidine-2,5-dione (**4a**).* Mp=257–258 °C; ^1H NMR (600 MHz, $CDCl_3$): δ 7.68 (d, 2H, J=7.6 Hz), 7.52–7.45 (m, 5H), 7.43–7.36 (m, 4H), 7.32–7.27 (m, 6H), 7.18 (t, 1H, J=7.6), 7.13 (d, 2H J=7.9 Hz), 2.81 (q, 1H, J=7.0 Hz), 1.16 (d, 3H, J=7.0 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ 177.7, 164.6, 151.1, 150.2, 139.3, 135.0, 133.4, 130.9, 130.0, 129.9, 129.2, 129.1, 128.6, 128.6, 128.2, 126.9, 126.6, 124.8, 123.3, 70.4, 39.0, 18.4; HRMS (ESI) calcd for $C_{31}H_{24}N_4O_2$ $[M+H]^+$: 485.1978, found: 485.1970; IR (neat, cm^{-1}): 1720, 1667, 1532, 1492, 1376, 1274, 1122, 1099, 691.

*4.3.2. 1-(4-Chlorophenyl)-3-methyl-4-(1,3,4-triphenyl-1H-1,2,4-triazol-5(4H)-ylidene)pyrrolidine-2,5-dione (**4b**).* The crude product was purified by silica gel column chromatography using chloroform/ethyl acetate as the eluent. Mp=231–233 °C; ^1H NMR (600 MHz, $CDCl_3$): δ 7.66 (d, 2H, J=7.7 Hz), 7.52–7.43 (m, 5H),

7.42–7.34 (m, 4H), 7.31–7.21 (m, 6H), 7.11 (d, 2H, *J*=8.4 Hz), 2.79 (q, 1H, *J*=7.0 Hz), 1.15 (d, 3H, *J*=7.0 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ 177.4, 163.9, 151.0, 150.2, 139.1, 134.7, 132.2, 131.9, 130.9, 130.0, 129.8, 129.1, 129.0, 128.6, 128.6, 128.5, 128.2, 127.6, 124.5, 123.2, 69.9, 38.9, 18.3; HRMS (ESI) calcd for $C_{31}H_{23}ClN_4O_2$ $[M+H]^+$: 519.1588, found: 519.1589; IR (neat, cm^{-1}): 1721, 1666, 1531, 1490, 1374, 1363, 1275, 1090, 835, 706, 690.

*4.3.3. 1-(4-Methoxyphenyl)-3-methyl-4-(1,3,4-triphenyl-1H-1,2,4-triazol-5(4H)-ylidene)pyrrolidine-2,5-dione (**4c**).* Mp=259–260 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.67 (d, 2H, *J*=7.8 Hz), 7.52–7.23 (m, 13H), 7.04 (d, 2H, *J*=8.6 Hz), 6.83 (d, 2H, *J*=8.6 Hz), 3.73 (s, 3H), 2.79 (q, 1H, *J*=7.0 Hz), 1.15 (d, 3H, *J*=7.0 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ 177.9, 164.8, 158.3, 151.0, 150.0, 139.2, 134.9, 130.8, 129.9, 129.8, 129.1, 129.1, 128.6, 128.0, 127.7, 126.2, 124.7, 123.2, 1134.0, 70.4, 55.3, 28.9, 18.3; HRMS (ESI) calcd for $C_{32}H_{26}N_4O_3$ $[M+H]^+$: 515.2083, found: 515.2080; IR (neat, cm^{-1}): 1719, 1666, 1538, 1510, 1494, 1257, 1083, 708, 693.

*4.3.4. 3-Methyl-1-(4-nitrophenyl)-4-(1,3,4-triphenyl-1H-1,2,4-triazol-5(4H)-ylidene)pyrrolidine-2,5-dione (**4d**).* The crude product was purified by silica gel column chromatography using dichloromethane/ethyl acetate as the eluent. Mp=223–224 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.14 (d, 2H, *J*=9.2 Hz), 7.68 (d, 2H, *J*=7.7 Hz), 7.56–7.39 (m, 11H), 7.31 (d, 4H, *J*=4.3 Hz), 2.82 (q, 1H, *J*=7.1 Hz), 1.17 (d, 3H, *J*=7.1 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ 177.1, 163.0, 151.2, 150.5, 145.2, 139.5, 138.9, 134.6, 131.1, 130.2, 129.9, 129.3, 129.1, 128.6, 128.5, 126.2, 124.4, 123.8, 123.4, 69.4, 39.0, 18.4; HRMS (ESI) calcd for $C_{31}H_{23}N_5O_4$ $[M+H]^+$: 530.1828, found: 530.1827; IR (neat, cm^{-1}): 1733, 1674, 1533, 1493, 1339, 1125, 822, 742, 708, 694.

*4.3.5. 1-n-Butyl-3-methyl-4-(1,3,4-triphenyl-1H-1,2,4-triazol-5(4H)-ylidene)pyrrolidine-2,5-dione (**4e**).* The crude product was purified by silica gel column chromatography using chloroform/ethyl acetate as the eluent. Mp=200–202 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.62 (d, 2H, 7.5 Hz), 7.48–7.41 (m, 5H), 7.39–7.32 (m, 4H), 7.28 (s, 4H), 3.30 (t, 2H, *J*=6.7 Hz), 2.61 (q, 1H, *J*=6.7 Hz), 1.36 (m, 2H), 1.15 (m, 2H), 1.07 (d, 3H, *J*=6.7 Hz), 0.82 (t, 3H, *J*=7.1 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ 178.5, 165.7, 150.7, 149.4, 139.3, 134.9, 130.6, 129.7, 129.6, 128.9, 128.9, 128.4, 127.7, 124.7, 122.9, 70.9, 38.7, 37.3, 30.3, 19.8, 18.1, 13.7; HRMS (ESI) calcd for $C_{29}H_{28}N_4O_2$ $[M+H]^+$: 465.2290, found: 465.2290; IR (neat, cm^{-1}): 2960, 2930, 1714, 1659, 1537, 1494, 1445, 1271, 1032, 691.

*4.3.6. 1-tert-Butyl-3-methyl-4-(1,3,4-triphenyl-1H-1,2,4-triazol-5(4H)-ylidene)pyrrolidine-2,5-dione (**4f**).* The crude product was purified by silica gel column chromatography using chloroform/ethyl acetate as the eluent. Mp=88–90 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.61 (d, 2H, *J*=7.8 Hz), 7.48–7.25 (m, 5H), 2.52 (q, 1H, *J*=6.9 Hz), 1.40 (s, 9H), 0.99 (d, 3H, *J*=6.8 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ 179.3, 167.7, 150.8, 149.2, 139.6, 135.3, 130.7, 129.6, 129.6, 129.1, 128.9, 128.9, 128.9, 128.5, 128.4, 127.9, 127.4, 125.0, 122.8, 71.8, 56.5, 39.2, 29.0, 18.5; HRMS (ESI) calcd for $C_{29}H_{28}N_4O_2$ $[M+H]^+$: 465.2290, found: 465.2290; IR (neat, cm^{-1}): 2960, 2924, 2853, 1718, 1661, 1495, 1255, 1102, 1017, 702, 690.

*4.3.7. Methyl 2-(2,5-dioxo-1-phenyl-4-(1,3,4-triphenyl-1H-1,2,4-triazol-5(4H)-ylidene)pyrrolidin-3-yl)acetate (**6**).* The crude product was purified by silica gel column chromatography using chloroform/ethyl acetate as the eluent. Mp=186–188 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.67 (d, 2H, *J*=7.6 Hz), 7.52–7.12 (m, 18H), 3.65 (s, 3H), 3.05 (dd, 1H, *J*=3.5 Hz, 5.4 Hz), 2.79 (dd, 1H, *J*=3.5 Hz, 15.6 Hz), 2.30 (dd, 1H, *J*=2.3 Hz, 15.6 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ 175.8, 171.2, 164.9, 151.1, 149.7, 139.0, 134.8, 133.5, 130.9, 130.1, 129.7, 129.2, 129.1, 128.6, 128.6, 128.3, 127.0, 126.6, 124.6, 123.5, 66.5, 51.7, 40.7, 36.1; HRMS (ESI) calcd for $C_{33}H_{26}N_4O_4$ $[M+H]^+$: 543.2032, found: 543.2032; IR (neat, cm^{-1}): 3066, 1731, 1668, 1531, 1493, 1387, 1122, 907, 725, 690.

4.4. General procedure for the three-component reaction

The mixture of MMA (47.0 mg, 0.47 mmol) and PhNCO (54.1 mg, 0.45 mmol) in 1,2-dimethoxyethane (0.9 mL) was added to **1** (150 mg, 0.46 mmol) at 80 °C. The mixture was stirred for 8 h. An excess amount of ethyl acetate was added to the solution, and precipitated **4a** (67.4 mg, 0.14 mmol, 31%) was collected by filtration. The filtrate was concentrated under reduced pressure, and the residual solution was then poured into hexane. The precipitated **14** (89.9 mg, 0.17 mmol, 37%) was collected by filtration.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2012.08.076. These data include MOL files and InChiKeys of the most important compounds described in this article.

References and notes

1. For seminal studies of NHC 1 by Enders, see: (a) Enders, D.; Breuer, K.; Raabe, G.; Runsink, J.; Teles, J. H.; Melder, J.-P.; Ebel, K.; Brode, S. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1021–1023; (b) Enders, D.; Breuer, K.; Runsink, J.; Teles, J. H. *Liebigs Ann.* **1996**, 2019–2028; (c) Enders, D.; Breuer, K.; Teles, J. H.; Ebel, K. *J. Prakt. Chem.* **1997**, *339*, 397–399; (d) Enders, D.; Breuer, K.; Kallfass, U.; Balensiefer, T. *Synthesis* **2003**, 1292–1295.
2. (a) Maji, B.; Breugst, M.; Mayr, H. *Angew. Chem., Int. Ed.* **2011**, *50*, 6915–6919; (b) Dröge, T.; Glorius, F. *Angew. Chem., Int. Ed.* **2010**, *49*, 6940–6952; (c) Domingo, L. R.; Aurell, M. J.; Arnó, M. *Tetrahedron* **2009**, *65*, 3432–3440.
3. For reviews, see: (a) Nair, V.; Bindu, S.; Sreekumar, V. *Angew. Chem., Int. Ed.* **2004**, *43*, 5130–5135; (b) Kirmse, W. *Eur. J. Org. Chem.* **2005**, 237–260; (c) Delaude, L. *Eur. J. Inorg. Chem.* **2009**, 1681–1699.
4. For selected examples, see: (a) Kuhn, N.; Steimann, M.; Weyers, G. *Z. Naturforsch., Teil B* **1999**, *54*, 427–433; (b) Holbrey, J. D.; Reichert, W. M.; Tkatchenko, I.; Bouajila, E.; Walter, O.; Tommasi, I.; Rogers, R. D. *Chem. Commun.* **2003**, 28–29; (c) Duong;, H. A.; Tekavec, T. N.; Arif, A. M.; Louie, J. *Chem. Commun.* **2004**, 112–113; (d) Tommasi, I.; Sorrentino, F. *Tetrahedron Lett.* **2006**, *47*, 6453–6456; (e) Zhou, H.; Zhang, W.-Z.; Wang, Y.-M.; Qu, J.-P.; Lu, X.-B. *Macromolecules* **2009**, *42*, 5419–5421; (f) Van Ausdall, B. R.; Glass, J. L.; Wiggins, K. M.; Aarif, A. M.; Louie, J. *J. Org. Chem.* **2009**, *74*, 7935–7942; (g) Ajitha, M. J.; Suresh, C. H. *J. Org. Chem.* **2012**, *77*, 1087–1094.
5. For selected examples, see: (a) Kuhn, N.; Bohnen, H.; Henkel, G. *Z. Naturforsch., Teil B* **1994**, *49*, 1473–1480; (b) Kuhn, N.; Niquet, E.; Steimann, M.; Walker, I. *Z. Naturforsch., Teil B* **1999**, *54*, 1181–1187; (c) Faust, R.; Göbelt, B. *Chem. Commun.* **2000**, 919–920; (d) Delaude, L.; Demonceau, A.; Wouters, J. *Eur. J. Inorg. Chem.* **2009**, 1882–1891.
6. (a) Cheng, Y.; Liu, M.-F.; Fang, D.-C.; Lei, X.-M. *Chem.—Eur. J.* **2007**, *13*, 4282–4292; (b) Liu, M.-F.; Wang, B.; Cheng, Y. *Chem. Commun.* **2006**, 1215–1217; (c) Zhu, Q.; Liu, M.-F.; Wang, B.; Cheng, Y. *Org. Biomol. Chem.* **2007**, *5*, 1282–1286; (d) Xue, J.; Yang, Y.; Huang, X. *Synlett* **2007**, 1533–1536; (e) Ma, Y. G.; Cheng, Y. *Chem. Commun.* **2007**, 5087–5089; (f) Li, J.-Q.; Liao, R.-Z.; Ding, W.-J.; Cheng, Y. *J. Org. Chem.* **2007**, *72*, 6266–6269; (g) Cheng, Y.; Kang, Z.-M.; Ma, Y.-G.; Peng, J.-H.; Liu, M.-F. *Tetrahedron* **2008**, *64*, 7362–7368; (h) Cheng, Y.; Wang, B.; Wang, X.-R.; Zhang, J.-H.; Fang, D.-C. *J. Org. Chem.* **2009**, *74*, 2357–2367; (i) Norris, B. C.; Bielawski, C. W. *Macromolecules* **2010**, *43*, 3591–3593; (j) Norris, B. C.; Sheppard, D. G.; Henkelman, G.; Bielawski, C. W. *J. Org. Chem.* **2011**, *76*, 301–304; (k) Katritzky, A. R.; Jishkariani, D.; Sakhuja, R.; Hall, C. D.; Steel, P. J. *J. Org. Chem.* **2011**, *76*, 4082–4087; (l) Chia, E. Y.; Naeem, S.; Delaude, L.; White, A. J. P.; Wilton-Ely, J. D. E. T. *Dalton Trans.* **2011**, *40*, 6645–6658.
7. For reviews of NHC-catalyzed umpolung reactions of aldehyde, see: (a) Enders, D.; Balensiefer, T. *Acc. Chem. Res.* **2004**, *37*, 534–541; (b) Enders, D.; Niemeier, O.; Henseler, A. *Chem. Rev.* **2007**, *107*, 5606–5655; (c) Marion, N.; Díez-González, S.; Nolan, S. P. *Angew. Chem., Int. Ed.* **2007**, *46*, 2988–3000; (d) Nair, V.; Vellalath, S.; Babu, B. P. *Chem. Soc. Rev.* **2008**, *37*, 2691–2698; (e) Phillips, E. M.; Chan, A.; Scheidt, K. A. *Aldrichimica Acta* **2009**, *42*, 54–66; (f) Moore, J. L.; Rovis, T. *Top. Curr. Chem.* **2010**, *291*, 77–144; (g) Vora, H. U.; Rovis, T. *Aldrichimica Acta* **2011**,

44, 3–11; (h) Biju, A. T.; Kuhl, N.; Glorius, F. *Acc. Chem. Res.* **2011**, *44*, 1182–1195; (i) Grossmann, A.; Enders, D. *Angew. Chem., Int. Ed.* **2012**, *51*, 314–325; (j) Bugaut, X.; Glorius, F. *Chem. Soc. Rev.* **2012**, *41*, 3511–3522.

8. For NHC-catalyzed umpolung reactions of activated olefins: (a) Fischer, C.; Smith, S. W.; Powell, D. A.; Fu, G. C. *J. Am. Chem. Soc.* **2006**, *128*, 1472–1473; (b) Matsuoka, S.; Ota, Y.; Washio, A.; Katada, A.; Ichioka, K.; Takagi, K.; Suzuki, M. *Org. Lett.* **2011**, *13*, 3722–3725; (c) Biju, A. T.; Padmanaban, M.; Wurz, N. E.; Glorius, F. *Angew. Chem., Int. Ed.* **2011**, *50*, 8412–8415; (d) Atienza, R. L.; Roth, H. S.; Scheidt, K. A. *Chem. Sci.* **2011**, *2*, 1772–1776; (e) Atienza, R. L.; Scheidt, K. A. *Aust. J. Chem.* **2011**, *64*, 1158–1164.
9. For reactions of NHC with activated olefins without involving umpolung: (a) He, L.; Jian, T.-Y.; Ye, S. *J. Org. Chem.* **2007**, *72*, 7466–7468; (b) Raveendran, A. E.; Paul, R. R.; Suresh, E.; Nair, V. *Org. Biomol. Chem.* **2010**, *8*, 901–905; (c) Zhang, Y.; Miyake, G. M.; Chen, E. Y.-X. *Angew. Chem., Int. Ed.* **2010**, *49*, 10158–10162; (d) Matsuoka, S.; Shimakawa, S.; Takagi, K.; Suzuki, M. *Tetrahedron Lett.* **2011**, *52*, 6835–6838; (e) Zhang, Y.; Chen, E. Y.-X. *Angew. Chem., Int. Ed.* **2012**, *51*, 2465–2469.
10. (a) Takamizawa, A.; Hirai, K.; Matsumoto, S.; Ishiba, T. *Chem. Pharm. Bull.* **1968**, *16*, 2130–2136; (b) Takamizawa, A.; Hirai, K.; Matsumoto, S.; Ishiba, T. *Chem. Pharm. Bull.* **1969**, *17*, 462–466; (c) Regitz, M.; Hocker, J.; Schössler, W.; Weber, B.; Liedhegener, A. *Justus Liebigs Ann. Chem.* **1971**, *748*, 1–19; (d) Schössler, W.; Regitz, M. *Chem. Ber.* **1974**, *107*, 1931–1948; (e) Rigby, J. H.; Wang, Z. *Org. Lett.* **2002**, *4*, 4289–4291; (f) Duong, H. A.; Cross, M. J.; Louie, J. *Org. Lett.* **2004**, *6*, 4679–4681; (g) Schmidt, A.; Habeck, T.; Lindner, A. S.; Snovydovych, B.; Namyslo, J. C.; Adam, A.; Gjikaj, M. *J. Org. Chem.* **2007**, *72*, 2236–2239.
11. Breslow, R. *J. Am. Chem. Soc.* **1958**, *80*, 3719–3726.
12. The deoxy-Breslow intermediates were also obtained from the reaction of NHC with alkyl halides, see: (a) Knappke, C. E. I.; Neudörfl, J. M.; Jacobi von Wangelin, A. *Org. Biomol. Chem.* **2010**, *8*, 1695–1705; (b) Knappke, C. E. I.; Arduengo, A. J., III; Jiao, H.; Neudörfl, J.-M.; Jacobi von Wangelin, A. *Synthesis* **2011**, 3784–3795 Recently, their nucleophilic reactivities have been studied in details, see; (c) Maji, B.; Horn, M.; Mayr, H. *Angew. Chem., Int. Ed.* **2012**, *51*, 6231–6235.
13. (a) Nair, V.; Bindu, S.; Sreekumar, V.; Rath, N. P. *Org. Lett.* **2003**, *5*, 665–667; (b) Ma, C.; Yang, Y. *Org. Lett.* **2005**, *7*, 1343–1345; (c) Nair, V.; Sreekumar, V.; Bindu, S.; Suresh, E. *Org. Lett.* **2005**, *7*, 2297–2300; (d) Ma, C.; Ding, H.; Wu, G.; Yang, Y. *J. Org. Chem.* **2005**, *70*, 8919–8923; (e) Ma, C.; Ding, H.; Zhang;, Y.; Bian, M. *Angew. Chem., Int. Ed.* **2006**, *45*, 7793–7797; (f) Ding, H.; Zhang, Y.; Bian, M.; Yao, W.; Ma, C. *J. Org. Chem.* **2008**, *73*, 578–584; (g) Wang, B.; Li, J.-Q.; Cheng, Y. *Tetrahedron Lett.* **2008**, *49*, 485–489; (h) Nair, V.; Mathew, S. C.; Vellalath, S.; Pillai, A. N.; Suresh, E. *Synthesis* **2008**, 551–554; (i) Pan, H.-R.; Li, Y.-J.; Yan, C.-X.; Xing, J.; Cheng, Y. *J. Org. Chem.* **2010**, *75*, 6644–6652; (j) Pan, H.-R.; Wang, X.-R.; Yan, C.-X.; Sun, Z.-X.; Cheng, Y. *Org. Biomol. Chem.* **2011**, *9*, 2166–2174.
14. The analogous reaction using 1,3-bis(2,4,6-trimethylphenyl)imidazol-2-ylidene did not proceed.
15. The analogous reactions of **1** with maleimides, see: Ref. 1b.
16. For the similar interconversions, see: (a) Fürstner, A.; Alcarazo, M.; Goddard, R.; Lehmann, C. W. *Angew. Chem., Int. Ed.* **2008**, *47*, 3210–3214; (b) DiRocco, D. A.; Oberg, K. M.; Rovis, T. *J. Am. Chem. Soc.* **2012**, *134*, 6143–6145.
17. The ^{13}C NMR chemical shifts of C-2, 3, 4, and 5 of **6** are 175.8, 40.7, 66.5, 164. 9 ppm, respectively, and the corresponding peaks of **4a**–**f** are observed within 177.1–179.3, 38.6–39.1, 69.4–71.8, 163.0–167.7 ppm.
18. The signals of three carbonyl carbons (C-2, 5, 7) of **6** were assigned by HMBC experiments (See Scheme 3 and Supplementary data).
19. The characterization was limited to ^{1}H NMR, ESI-MS, and IR. We have been unsuccessful in obtaining a suitable single crystal for X-ray analysis to date, and thus, the chemical structure (**17** or **18**) could not be determined.