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Tetrahedron
Tetrahedron 62 (2006) 5641–5644

Reaction between *tert*-butyl isocyanide, dialkyl acetylenedicarboxylates, and aromatic carboxylic acids: an efficient method for the synthesis of dialkyl (*E*)-2-{[benzoyl(*tert*-butyl)amino]carbonyl}-2-butenedioate derivatives

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Received 7 January 2006; revised 12 March 2006; accepted 30 March 2006
Available online 2 May 2006

Abstract—Protonation of the reactive intermediates produced in the reaction between *tert*-butyl isocyanide and dialkyl acetylenedicarboxylates by aromatic carboxylic acids leads to vinylnitrilium cations, which undergo nucleophilic reaction with conjugate bases of the carboxylic acids to produce dialkyl (*E*)-2-[(benzoyloxy)(*tert*-butylimino)methyl]-2-butenedioates and this intermediate rearranges to the dialkyl (*E*)-2-{[benzoyl(*tert*-butyl)amino]carbonyl}-2-butenedioate derivatives.
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1. Introduction

Within the last decade, the resurgence of interest in multicomponent reactions (MCRs) has been considered, not only because of their inherent atom efficiency and ease of implementation, but also because of their value to the pharmaceutical industry for construction of low molecular weight compound libraries through combinatorial strategies or parallel synthesis.[1,2] The ability of an isonitrile to undergo facile α-addition with a nucleophile and an electrophile under mild conditions made it a popular reactant for the development of novel MCRs.[3–9]

In the context of our on going studies on heterocyclic construction mediated by zwitterionic intermediates,[10] the possibility of trapping the 1:1 intermediate formed between dialkyl acetylenedicarboxylate and isocyanides with suitable O–H acids appeared attractive from the viewpoint of devising a novel MCR.[11]

Although the trapping of the 1:1 intermediate formed between dialkyl acetylenedicarboxylates and isocyanides with O–H, N–H, and C–H acids has been widely studied,[10–14] trapping of the initially formed 1:1 intermediate with carboxylic acids has not been reported.

We wish to report a simple one-pot three-component reaction between dialkyl acetylenedicarboxylates and *tert*-butyl isocyanide in the presence of aromatic carboxylic acids leading to yield dialkyl (*E*)-2-{[benzoyl(*tert*-butyl)amino]carbonyl}-2-butenedioate derivatives **3**.

2. Results and discussion

The reaction of *tert*-butyl isocyanide with dialkyl acetylenedicarboxylates **1** in the presence of aromatic carboxylic acids **2** undergo a smooth 1:1:1 addition reaction in dichloromethane at ambient temperature, to produce dialkyl (*E*)-2-{[benzoyl(*tert*-butyl)amino]carbonyl}-2-butenedioate derivatives **3** in 61–98% yields (Scheme 1).

The structures of compounds **3a–g** were deduced from their elemental analysis, IR, and high-field ^{1}H and ^{13}C NMR spectra. The mass spectrum of **3a** displayed the molecular ion (MC) peak at 376 *m*/*z*, which is consistent with the 1:1:1 adduct of dimethyl acetylenedicarboxylate, *tert*-butyl isocyanide, and benzoic acid. The ^{1}H NMR spectrum of **3a** exhibited four single sharp singlets readily recognized as arising from *tert*-butyl group (δ=1.62 ppm), methoxy (δ=3.65 and 3.84 ppm) protons along with an vinylic CH (δ=6.44 ppm). The phenyl moiety gave rise to characteristic signals in the aromatic region of the spectrum. The ^{1}H decoupled ^{13}C NMR spectrum of **3a** showed 14 distinct resonances in agreement with the dimethyl (*E*)-2-{[benzoyl(*tert*-butyl)amino]carbonyl}-2-butenedioate structure. Partial assignment of these resonances is given in Section 4.

Keywords: Alkyl isocyanide; Dialkyl acetylenedicarboxylate; Aromatic carboxylic acid; Multicomponent reaction.
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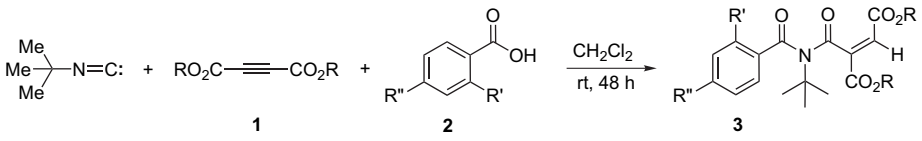
doi:10.1016/j.tet.2006.03.102



1 2 3

3	R	R'	R"	% Yield of 3
a	Me	H	H	95
b	Et	H	H	98
c	^{i}Pr	H	H	97
d	^{t}Bu	H	H	97
e	Me	H	NO_2	61
f	Me	OCOMe	H	74
g	Et	OCOMe	H	95

Scheme 1.

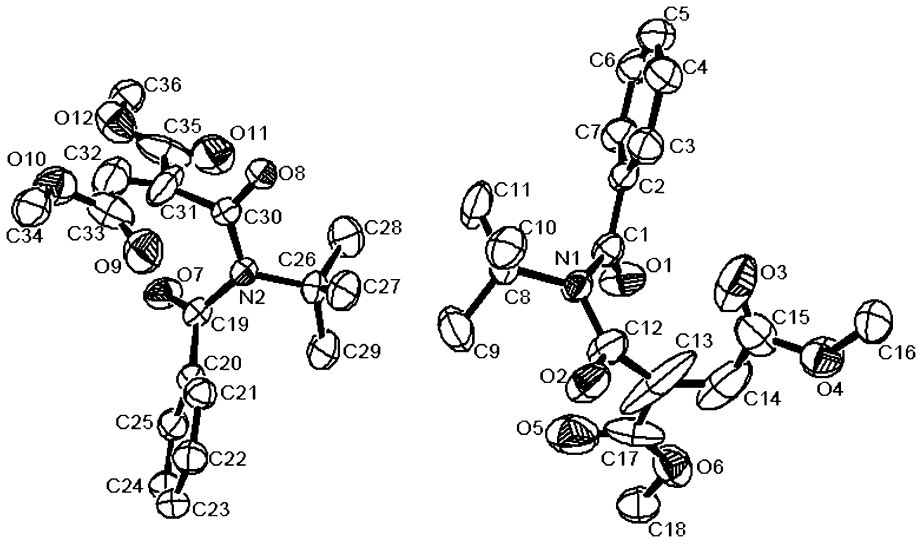
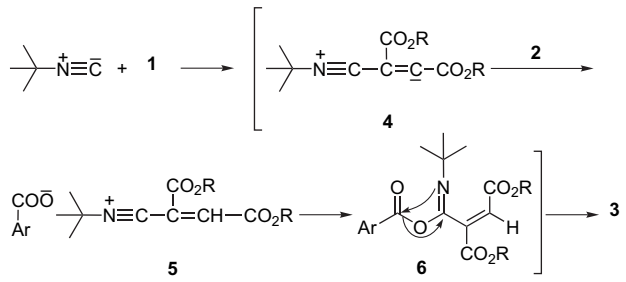


Figure 1. The molecular structure of compound **3a**.

Finally, **3a** was further confirmed by a single crystal X-ray diffraction analysis (Fig. 1).

The ^{1}H and ^{13}C NMR spectra of compounds **3b–g** are similar to those of **3a**, except for the aromatic moiety, and the ester groups, which exhibit characteristic signals with appropriate chemical shifts (see Section 4).

Although we have not established the mechanism of the reaction between the isocyanides and the acetylenic esters in the presence of the carboxylic acid derivatives **2** in an experimental manner, a possible explanation is proposed in Scheme 2.



Scheme 2.

On the basis of the well-established chemistry of isocyanides,[15–20] it is reasonable to assume that the compound **3** apparently results from initial addition of the isocyanide to the acetylenic ester and subsequent protonation of the 1:1 adduct **4** by compound **2**, followed by attack of the carboxylate anion on the positively charged ion **5** to form imidoyl carboxylate **6**, which undergoes rearrangement[21–23] under the reaction condition employed, to produce the compound **3** (Scheme 2).

3. Conclusion

In summary, the reaction between isocyanides and dialkyl acetylenedicarboxylates in the presence of carboxylic acids is a regioselective reaction and provides a simple one-pot entry into the synthesis of dialkyl (*E*)-2-{[benzoyl(*tert*-butyl)-amino]carbonyl}-2-butenedioate derivatives of potential synthetic. The present method carries the advantage that, not only is the reaction performed under neutral condition, but also the substances can be mixed without any activation or modification.

4. Experimental

Dimethyl, diethyl and di(*tert*-butyl) acetylenedicarboxylates, and *tert*-butyl isocyanides were obtained from Merck

(Germany) and Fluka (Switzerland) and were used without further purification. Diisopropyl acetylenedicarboxylate was prepared according to the literature procedure.[24,25] Melting points were measured on an Electrothermal 9100 apparatus. Elemental analyses for C, H, and N were performed using a Heraeus CHN–O– Rapid analyzer. Mass spectra were recorded on a FINNIGAN-MATT 8430 mass spectrometer operating at an ionization potential of 20 eV. ^{1}H and ^{13}C NMR spectra were measured ($CDCl_3$ solution) with a Bruker DRX-500 AVANCE spectrometer at 500.1 and 125.8 MHz, respectively. IR spectra were recorded on a Shimadzu IR-460 spectrometer. Chromatography columns were prepared from Merck silica gel 230–240 mesh.

4.1. General procedure for preparation of compound 3a–d, exemplified on 3a

To a magnetically stirred solution of 0.14 g of dimethyl acetylenedicarboxylate (1 mmol) and 0.12 g of benzoic acid (1 mmol) in 5 mL dry CH_2Cl_2 was added dropwise a solution of 0.083 g of *tert*-butyl isocyanide (1 mmol) in 3 mL dry CH_2Cl_2 at room temperature over 10 min. The reaction mixture was then allowed to stir for 48 h. The solvent was removed under reduced pressure, and the residue was separated by silica gel (Merck 230–240 mesh) column chromatography using hexane–ethyl acetate mixture (5:2) as eluent.

4.1.1. Dimethyl (*E*)-2-{[benzoyl(*tert*-butyl)amino]carbonyl}-2-butenedioate 3a. Colorless crystals, mp 130–132 °C, solvent of crystallization ethyl acetate, yield 0.33 g, 95%. IR (KBr) (ν_{max} cm^{-1}): 1716 (OCNCO), 1680 (CO_2Me), 1650 (C=C), 1586 and 1435 (Ph), 1368, 1296, 1263, 1210, and 1178 (C–O). MS, *m*/*z* (%): 347 (M^+, 2), 233 (1), 232 (7), 226 (1), 171 (20), 105 (100), 77 (55), 57 (12), 41 (8). Anal. Calcd for $C_{18}H_{21}NO_6$ (347.36): C, 62.24; H, 6.09; N, 4.03%. Found: C, 62.21; H, 6.10; N, 4.00%. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ_H=1.62 (9H, s, C*Me*$_3$), 3.65 (3H, s, OMe), 3.77 (3H, s, OMe), 6.44 (1H, s, CH), 7.42 (2H, dd, $^3J_{HH}$=7.5 Hz, $^3J_{HH}$=7.5 Hz, 2CH$_{meta}$ of C_6H_5), 7.50 (1H, t, $^3J_{HH}$=7.4 Hz, CH$_{para}$ of C_6H_5), 7.80 (2H, d, $^3J_{HH}$=7.4 Hz, 2CH$_{ortho}$ of C_6H_5). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ_C=28.46 (C*Me*$_3$), 52.45 (OMe), 52.86 (OMe), 59.88 (*C*Me$_3$), 128.48 (2CH$_{meta}$ of C_6H_5), 128.64 (2CH$_{ortho}$ of C_6H_5), 130.64 (C=*C*H), 134.29 (CH$_{para}$ of C_6H_5), 135.81 (C$_{ipso}$ of C_6H_5), 141.20 (*C*=CH), 162.27 (PhCON*C*O), 162.99 (*C*O$_2$Me), 163.78 (*C*O$_2$Me), 175.21 (Ph*C*ON).

Crystal data for **3a** $C_{18}H_{21}NO_6$ (CCDC 288926): M_W=347.36, monoclinic, space group $P2_1/n$, a=10.6670(6) Å, b=12.5163(7) Å, c=26.5532(14) Å, β=99.2400(10)°, V=3499.2(3) Å^3, Z=8, D_c=1.319 mg/m^3, $F(000)$=1472, crystal dimension 0.28×0.23×0.12 mm, radiation, Mo Kα (λ=0.71073 Å), $1.55\leq 2\theta\leq 25.00$, intensity data were collected at 293 K with a Bruker APEX area-detector diffractometer, and employing $\omega/2\theta$ scanning technique, in the range of $-12\leq h\leq 12$, $-14\leq k\leq 14$, $-31\leq l\leq 31$; the structure was solved by a direct method, all non-hydrogen atoms were positioned and anisotropic thermal parameters refined from 33076 observed reflections with R(int)=0.0255 by a full-matrix least-squares technique converged to R=0.1069 and Rw=0.3149.

4.1.2. Diethyl (*E*)-2-{[benzoyl(*tert*-butyl)amino]carbonyl}-2-butenedioate 3b. Colorless crystals, mp 79–81 °C, yield 0.36 g, 98%. IR (KBr) (ν_{max} cm^{-1}): 1716 (OCNCO), 1690 (CO_2Et), 1661 (C=C), 1589 and 1443 (Ph), 1365, 1287, 1248, and 1182 (C–O). MS, *m*/*z* (%): 375 (M^+, 1), 329 (4), 319 (2), 302 (4), 279 (10), 246 (21), 224 (1), 199 (12), 190 (1), 176 (18), 167 (26), 149 (58), 113 (6), 105 (100), 77 (25), 71 (14), 57 (26), 43 (10), 41 (15). Anal. Calcd for $C_{20}H_{25}NO_6$ (375.42): C, 63.99; H, 6.71; N, 3.73%. Found: C, 64.00; H, 6.80; N, 3.70%. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ_H=1.26 (3H, t, $^3J_{HH}$=7.1 Hz, CH_3), 1.28 (3H, t, $^3J_{HH}$=7.1 Hz, CH_3), 1.62 (9H, s, C*Me*$_3$), 4.11 (2H, q, $^3J_{HH}$=7.1 Hz, OCH_2CH_3), 4.23 (2H, q, $^3J_{HH}$=7.1 Hz, OCH_2CH_3), 6.40 (1H, s, CH), 7.40 (2H, dd, $^3J_{HH}$=7.5 Hz, $^3J_{HH}$=7.5 Hz, 2CH$_{meta}$ of C_6H_5), 7.57 (1H, t, $^3J_{HH}$=7.4 Hz, CH$_{para}$ of C_6H_5), 7.83 (2H, d, $^3J_{HH}$=7.9 Hz, 2CH$_{ortho}$ of C_6H_5). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ_C=13.8 (*C*H$_3$CH$_2$), 14.08 (*C*H$_3$CH$_2$), 28.49 (C*Me*$_3$), 59.97 (*C*Me$_3$), 61.52 (O*C*H$_2$CH$_3$), 62.14 (O*C*H$_2$CH$_3$), 128.45 (C=*C*H), 128.57 (2CH$_{meta}$ of C_6H_5), 130.57 (2CH$_{ortho}$ of C_6H_5), 134.12 (CH$_{para}$ of C_6H_5), 136.08 (C$_{ipso}$ of C_6H_5), 141.80 (*C*=CH), 162.56 (PhCON*C*O), 162.61 (*C*O$_2$Et), 163.45 (*C*O$_2$Et), 175.25 (Ph*C*ON).

4.1.3. Diisopropyl (*E*)-2-{[benzoyl(*tert*-butyl)amino]carbonyl}-2-butenedioate 3c. Yellow oil, yield 0.40 g, 97%. IR (KBr) (ν_{max} cm^{-1}): 1713 (OCNCO), 1700 (CO_2^iPr), 1661 (C=C), 1590 and 1440 (Ph), 1286, 1258, 1248, and 1182 (C–O). MS, *m*/*z* (%): 403 (M^+, 2), 280 (2), 179 (12), 168 (3), 167 (35), 149 (100), 132 (2), 113 (11), 104 (4), 71 (31), 57 (57), 43 (36), 41 (32). Anal. Calcd for $C_{22}H_{29}NO_6$ (403.47): C, 65.49; H, 7.24; N, 3.47%. Found: C, 65.50; H, 7.30; N, 3.50%. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ_H=1.20 (6H, d, $^3J_{HH}$=6.3 Hz, CH*Me*$_2$), 1.22 (6H, d, $^3J_{HH}$=6.3 Hz, CH*Me*$_2$), 1.58 (9H, s, CMe$_3$), 4.91 (1H, hept, $^3J_{HH}$=6.2 Hz, *CH*Me$_2$), 5.03 (1H, hept, $^3J_{HH}$=6.2 Hz, *CH*Me$_2$), 6.31 (1H, s, C=CH), 7.36 (2H, t, $^3J_{HH}$=7.9 Hz, 2CH$_{meta}$ of C_6H_5), 7.53 (1H, t, $^3J_{HH}$=7.4 Hz, CH$_{para}$ of C_6H_5), 7.82 (2H, d, $^3J_{HH}$=7.6 Hz, 2CH$_{ortho}$ of C_6H_5). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ_C=21.43 (OCH*Me*$_2$), 21.66 (OCH*Me*$_2$), 28.50 (C*Me*$_3$), 59.66 (*C*Me$_3$), 69.09 (O*C*HMe$_2$), 70.16 (O*C*HMe$_2$), 128.52 (4CH of C_6H_5), 130.49 (C=*C*H), 133.98 (CH$_{para}$ of C_6H_5), 136.24 (C$_{ipso}$ of C_6H_5), 142.28 (*C*=CH), 162.10 (PhCON*C*O), 162.73 (*C*O$_2^i$Pr), 162.99 (*C*O$_2^i$Pr), 175.18 (Ph*C*ON).

4.1.4. Di(*tert*-butyl) (*E*)-2-{[benzoyl(*tert*-butyl)amino]carbonyl}-2-butenedioate 3d. Yellow oil, yield 0.42 g, 97%. IR (KBr) (ν_{max} cm^{-1}): 1709 (OCNCO), 1685 (CO_2^tBu), 1660 (C=C), 1590 and 1465 (Ph), 1399, 1364, 1270, and 1191 (C–O). MS, *m*/*z* (%): 431 (M^+, 2), 274 (12), 258 (14), 218 (16), 162 (24), 142 (16), 123 (14), 105 (100), 77 (24), 57 (83), 41 (24). Anal. Calcd for $C_{24}H_{33}NO_6$ (431.52): C, 66.80; H, 7.71; N, 3.25%. Found: C, 66.75; H, 7.60; N, 3.10%. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ_H=1.44 (9H, s, OCMe$_3$), 1.47 (9H, s, OCMe$_3$), 1.60 (9H, s, NCMe$_3$), 6.25 (1H, s, CH), 7.38 (2H, t, $^3J_{HH}$=7.8 Hz, 2CH$_{meta}$ of C_6H_5), 7.55 (1H, t, $^3J_{HH}$=7.4 Hz, CH$_{para}$ of C_6H_5), 7.89 (2H, d, $^3J_{HH}$=7.4 Hz, 2CH$_{ortho}$ of C_6H_5). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ_C=27.71 (OC*Me*$_3$), 28.01 (OC*Me*$_3$), 28.60 (NC*Me*$_3$), 59.49 (N*C*Me$_3$), 81.97 (O*C*Me$_3$), 83.01 (O*C*Me$_3$), 128.57

(C=*C*H), 129.93 (2CH$_{meta}$ of C_6H_5), 130.56 (2CH$_{ortho}$ of C_6H_5), 133.88 (C_{ipso} of C_6H_5), 136.39 (CH$_{para}$ of C_6H_5), 142.57 (*C*=CH), 161.67 (PhCON*C*O), 162.73 (*C*O$_2^t$Bu), 163.06 (*C*O$_2^t$Bu), 175.32 (Ph*C*ON).

4.1.5. Dimethyl (*E*)-2-{[*tert*-butyl(4-nitrobenzoyl)amino]-carbonyl}-2-butenedioate 3e. Yellow oil, yield 0.24 g, 61%. IR (KBr) (ν_{max} cm^{-1}): 1717 (OCNCO), 1664 (CO_2Me), 1660 (C=C), 1596 and 1429 (Ar), 1521 and 1351 (NO_2), 1300, 1266, 1210, and 1190 (C–O). MS, *m*/*z* (%): 392 (M$^+$, 2), 260 (1), 228 (6), 171 (100), 150 (57), 138 (71), 121 (10), 104 (24), 84 (576), 59 (57), 41 (38). Anal. Calcd for $C_{18}H_{20}N_2O_8$ (392.36): C, 55.10; H, 5.14; N, 7.14%. Found: C, 5; H, 5.10; N, 7.10%. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ_H=1.60 (9H, s, C*Me*$_3$), 3.74 (3H, s, O*Me*), 3.79 (3H, s, O*Me*), 6.48 (1H, s, C*H*), 8.02 (2H, d, $^3J_{HH}$=8.8 Hz, 2CH of C_6H_4), 8.27 (2H, d, $^3J_{HH}$=8.9 Hz, 2CH of C_6H_4). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ_C=28.73 (C*Me*$_3$), 52.62 (O*Me*), 53.11 (O*Me*), 60.69 (*C*Me$_3$), 123.73 (2CH of C_6H_4), 128.44 (C=*C*H), 131.34 (2CH of C_6H_4), 141.17 (*C*=CH), 141.61 (*C*–CON), 150.74 (*C*–NO_2), 162.75 (ArCON*C*O), 162.97 (*C*O$_2$Me), 163.94 (*C*O$_2$Me), 174.11 (Ar*C*ON).

4.1.6. Dimethyl (*E*)-2-{[[2-(acetyloxy)benzoyl](*tert*-butyl)-amino]carbonyl}-2-butendioate 3f. Colorless crystals, mp 150–151 °C, yield 0.30 g, 74%. IR (KBr) (ν_{max} cm^{-1}): 1764 (OCOMe), 1718 (OCNCO), 1663 (CO_2Me), 1650 (C=C), 1593 and 1469 (Ar), 1365, 1300, 1259, and 1184 (C–O). MS, *m*/*z* (%): 405 (M$^+$, 2), 358 (2), 326 (1), 307 (6), 291 (3), 270 (7), 248 (8), 214 (8), 171 (71), 121 (100), 92 (16), 57 (12), 43 (14), 41 (6). Anal. Calcd for $C_{20}H_{23}NO_8$ (405.40): C, 59.25; H, 5.72; N, 3.46%. Found: C, 59.10; H, 5.80; N, 3.35%. ^{1}H NMR (500 MHz, $CDCl_3$): δ_H=1.69 (9H, s, C*Me*$_3$), 2.29 (3H, s, OCO*Me*), 3.58 (3H, s, OMe), 3.84 (3H, s, O*Me*), 6.53 (1H, s, C*H*), 7.17 (1H, d, $^3J_{HH}$=8.0 Hz, CH of C_6H_4), 7.30 (1H, dd, $^3J_{HH}$=7.6 Hz, CH of C_6H_4), 7.60 (1H, t, $^3J_{HH}$=7.7 Hz, CH of C_6H_4), 7.64 (1H, d, $^3J_{HH}$=8.0 Hz, CH of C_6H_4). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ_C=20.55 (*C*H$_3$COO), 28.58 (C*Me*$_3$), 52.41 (O*Me*), 52.65 (O*Me*), 60.47 (*C*Me$_3$), 124.87, 125.22, and 134.45 (4CH of C_6H_4), 128 (C_{ipso}–CON), 129.31 (C=*C*H), 131.47 (*C*=CH), 150.25 (C_{ipso}–OCOMe), 162.53 (ArCON*C*O), 163.77 (*C*O$_2$Me), 168.95 (2*C*O$_2$Me), 172.00 (Ar*C*ON).

4.1.7. Diethyl (*E*)-2-{[[2-(acetyloxy)benzoyl](*tert*-butyl)-amino]carbonyl}-2-butendioate 3g. Yellow oil, yield 0.40 g, 95%. IR (KBr) (ν_{max} cm^{-1}): 1766 (OCOMe), 1714 (OCNCO), 1663 (CO_2Et), 1650 (C=C), 1594 and 1468 (Ar), 1366, 1300, 1248, and 1178 (C–O). MS, *m*/*z* (%): 433 (M$^+$, 2), 344 (2), 335 (1), 318 (2), 298 (4), 262 (8), 241 (8), 215 (2), 199 (7), 163 (40), 143 (22), 121 (100), 92 (14), 57 (12), 41 (6). Anal. Calcd for $C_{22}H_{27}NO_8$ (433.45): C, 60.96; H, 6.28; N, 3.23%. Found: C, 60.80; H, 6.10; N, 3.10%. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ_H=1.22 (3H, t, $^3J_{HH}$=7.1 Hz, CH_3CH_2), 1.31 (3H, t, $^3J_{HH}$=7.1 Hz, CH_3CH_2), 1.64 (9H, s, CMe_3), 2.25 (3H, s, OCOMe), 3.98 (2H, q, $^3J_{HH}$=7.1 Hz, OCH_2CH_3), 4.25 (2H, q, $^3J_{HH}$=7.1 Hz, OCH_2CH_3), 6.45 (1H, s, CH), 7.13 (1H, d, $^3J_{HH}$=8.0 Hz, CH of C_6H_4), 7.24 (1H, t, $^3J_{HH}$=7.6 Hz, CH of C_6H_4), 7.56 (1H, t, $^3J_{HH}$=7.6 Hz, CH of C_6H_4), 7.67 (1H, d, $^3J_{HH}$=8.0 Hz, CH of C_6H_4). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ_C=13.74 (*C*H$_3$CH$_2$), 14.15 (*C*H$_3$CH$_2$), 20.54 (*C*H$_3$COO), 28.54 (C*Me*$_3$), 60.29 (*C*Me$_3$), 61.54 (O*C*H$_2$CH$_3$), 61.94 (O*C*H$_2$CH$_3$), 124.70 (CH of C_6H_4), 125.31 (CH of C_6H_4), 128.13 (C=*C*H), 128.23 (C_{ipso}–CON), 129.35 (CH of C_6H_4), 131.54 (*C*=CH), 134.30 (CH of C_6H_4), 150.22 (C_{ipso}–OCOMe), 162.12 (ArCON*C*O), 162.72 (CO_2Et), 163.47 (CO_2Et), 168.86 (ArO*C*OMe), 172.21 (Ar*C*ON).

Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2006.03.102.

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