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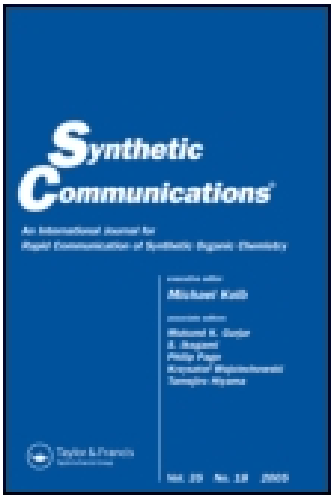

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Facile and Rapid Synthesis of α-Amidoester Derivatives Based on the Three-Component Passerini Reaction (P-3CR)

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Facile and Rapid Synthesis of α-Amidoester Derivatives Based on the Three-Component Passerini Reaction (P-3CR)

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Abstract: Modification of biologically active ethyl-3-bromopyruvate (Et-3-BrP), using the Passerini three-component reaction, to fully substitute α-amidoester (β-dicarbonyl) derivatives was investigated. The method is efficient for the one-step preparation of highly functionalized β-dicarbonyl derivatives containing *N*-protected amino acid residues and aliphatic, aromatic, and heteroaromatic carboxylic ester derivatives.

Keywords: Alkyl isocyanide, carboxylic acid, ethyl 3-bromopyruvate, Passerini three-component reaction (P-3CR)

INTRODUCTION

Bromopyruvate derivatives have good potential as pharmaceutical and biochemical agents because of their diverse biological profiles.[1] The ability to serve as α-dicarbonyl surrogates, with unique physical properties, has made them ideal functional groups for the development of novel SH blocking agent for proteins,[2] alkylating agents that looks like major metabolites except for one atom—bromide.[1]

In the past few years, combinatorial methods using multicomponent reactions have been closely examined as fast and convenient solutions for the synthesis of diverse classes of compounds.[3] Multicomponent

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reactions (MCRs), defined as one-pot reactions in which at least three functional groups join through covalent bonds, have been steadily gaining importance in synthetic organic chemistry.[4–6] Although several classes of compounds take part in MCRs, the most successful ones are isocyanide-based MCRs like the Passerini three-component reaction (P-3CR)[7a,b] and the Ugi four-component reaction (U-4CR).[4–6] This is attributable mainly to the presence of formal divalent carbon in these species.[7,8] Multicomponent reactions (MCRs), by virtue of their convergence, productivity, facile execution, and generally high yields of products, have attracted much attention from the point of view of combinatorial chemistry.[7,8]

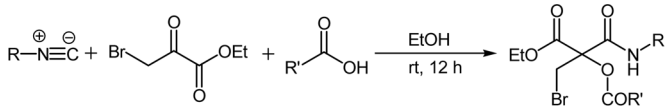
Recently, we have reported and developed the multicomponent reaction mediated by zwitterionic intermediates produced by isocyanide as a nuclephile and electrophile.[8a–g] During our studies, novel differentialy substituted β-dicarbonyl compound was synthesized by the Passerini reaction using ethyl 3-bromopyruvate as α-dicarbonyl. In this article, we present the results of an extended investigation of the reactivity of the ethyl 3-bromopyruvate with isocyanides in the presence of carboxylic acid, leading to the formation of 1-(bromomethyl)-2-(*tert*-butylamino)-1-(ethoxycarbonyl)-2-oxoethyl carboxylate derivatives.

RESULTS AND DISCUSSION

The reaction of alkyl isocyanide **1** with ethyl 3-bromopyruvate **2** in the presence of carboxylic acids **3** undergo a smooth 1:1:1 addition reaction in ethanol at ambient temperature to produce 1-(bromomethyl)-2-(*tert*-butylamino)-1-(ethoxycarbonyl)-2-oxoethyl carboxylate derivatives **4** in 63–92% yields (Table 1).

The structures of compounds **4a**–**g** were deduced from their elemental analyses, IR, and high-field ^{1}H and ^{13}C NMR spectra. The mass spectrum of **4a** displayed the molecular ion plus one ($M^+ + 1$) peak at $m/z = 446$, which is consistent with the 1:1:1 adduct of ethyl 3-bromopyruvate, *tert*-butyl isocyanide, and *p*-nitrobenzoic acid. The IR spectrum of **4a** exhibited absorption bands due to the NH at 3420 cm^{-1}, the carbonyl group of esters at 1760 and 1741 cm^{-1}, the aromatic bonds at 1677 and 1580 cm^{-1}, and the NO_2 groups at 1516 and 1360 cm^{-1}. In the ^{1}H NMR spectrum, a signal due to the *tert*-butyl protons was discernible as a sharp singlet at $\delta = 1.42$ ppm. The OEt protons afforded two separate multiplets at ($\delta = 1.27$ and 4.28–4.38) ppm. The diastereotopic CH_2Br protons afforded two separate doublets at $\delta = 4.12$ and 4.24 ppm with $J = 11.5$ Hz. The aryl moiety exhibited characteristic signals in the aromatic region of the spectrum. The ^{1}H-decoupled

Table 1. Reaction of alkyl isocyanides **1** and 3-bromopyruvate in the presence of carboxylic acids **3**



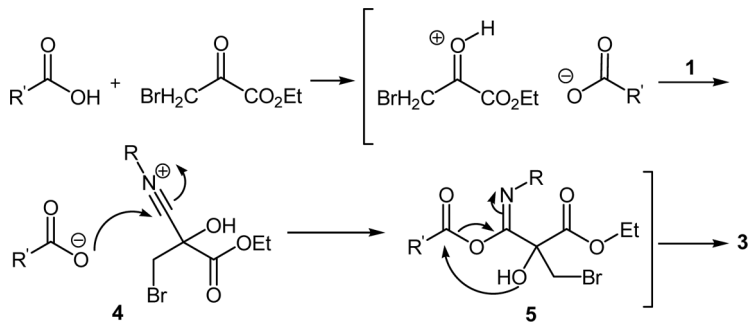
1 **2** **3** **4**

4	R	R′	Yield of 4%
a	^{t}Bu	*p*–$NO_2C_6H_4$	92
b	^{t}Bu	Furyl	87
c	Cy-Hex	*p*–$NO_2C_6H_4$	80
d	Cy-Hex	Furyl	77
e	Cy-Hex	$ClCH_2$	75
f	Cy-Hex	$C_6H_5CONHCH_2$	63
g	Cy-Hex	$C_6H_5CH_2$	67

^{13}C NMR spectrum of **4a** showed 13 distinct resonances in agreement with the 1-(bromomethyl)-2-(*tert*-butylamino)-1-(ethoxycarbonyl)-2-oxoethyl 4-nitrobenzoate structure.

Partial assignment of these resonances is given in the experimental section. The ^{1}H and ^{13}C NMR spectra of compounds **4b**–**g** are similar to those of **4a**.

Although we have not established the mechanism of the reaction between the isocyanide **1** and the ethyl 3-bromopyruvate **2** in the presence of the carboxylic acids **3** in an experimental manner, a possible explanation is proposed in Scheme 1.



Scheme 1. Plausible mechanism for the formation of β-dicarbonyl **3**.

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EXPERIMENTAL

Ethyl 3-bromopyruvate, carboxylic acids, and isocyanides were obtained from Merck (Germany) and Fluka (Switzerland) and were used without further purification. 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 70 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 meshes.

Typical Procedure for Preparation of Compound 4a

A solution of 0.08 g of *tert*-butyl isocyanide (1 mmol) in 3 mL dry EtOH was added dropwise to a magnetically stirred solution of 0.20 g of ethyl 3-bromopyruvate (1 mmol) and 0.17 g of 4-nitrobenzoic acid (1 mmol) in 3 mL dry EtOH at room temperature over 10 min. The reaction mixture was then allowed to stir for 12 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 (5:1) as eluent to give **4a** (0.4 g, 92%).

CONCLUSION

In summary, the reaction between isocyanides and ethyl 3-bromopyruvate in the presence of carboxylic acids provides a simple one-pot entry into the synthesis of α-amidoester derivatives of potential synthetic and pharmaceutical interest. The present method carries the advantage of being performed under neutral conditions and requires no activation or modification of the educts.

DATA

1-(Bromomethyl)-2-(*tert*-butylamino)-1-(ethoxycarbonyl)-2-oxoethyl 4-nitrobenzoate (4a)

Yield 0.4 g (92%); colorless crystals; mp 156–158°C; IR (KBr): 3420 (NH), 1760 and 1741 (C = O of esters), 1677 (CON), 1650 and 1580

(Ar), 1516 and 1360 (NO_2), 1271, 1223, 1192 and 1094 (C–O) cm^{-1}; ^1H NMR (500.1 MHz, $CDCl_3$): $\delta = 1.27$ (3 H, t, OCH_2CH_3), 1.42 [9H, s, $C(Me)_3$], 4.12 (1 H, d, $^2J_{HH} = 11.5$ Hz, CHBr), 4.24 (1 H, d, $^2J_{HH} = 11.5$ Hz, CHBr), 4.28–4.38 (2 H, m, OCH_2CH_3), 6.88 (1H, d, $^3J_{HH} = 7.5$ Hz, NH), 8.22 (2 H, d, $^3J_{HH} = 8.7$ Hz, 2 CH of Ar), 8.34 (2 H, d, $^3J_{HH} = 8.7$ Hz, 2 CH of Ar); ^{13}C NMR (125.7 MHz, $CDCl_3$): $\delta = 13.85$ (CH_3), 28.44 [$C(Me)_3$], 32.23 (CH_2Br), 52.32 [$C(Me)_3$,], 63.24 (OCH_2CH_3), 82.73 (C), 123.82 (2 CH of Ar), 131.03 (2 CH of Ar), 134.17 (C_{ipso}–C = O), 141.10 (C_{ipso}–NO_2), 162.24 (CO_2Ar), 162.65 (CO_2Et), 165.96 (CON); EI-MS, m/z (%): 446 ($M^+ + 1$, 2), 445 (M^+, 2), 372 (3), 266 (13), 220 (9), 150 (100), 120 (20), 104 (26), 76 (21), 58 (72), 32 (50). Anal. calcd. for $C_{17}H_{21}BrN_2O_7$ (445.26): C, 45.86; H, 4.75; N, 6.29%. Found: C, 48.90; H, 4.77; N, 6.30%.

1-(Bromomethyl)-2-(*tert*-butylamino)-1-(ethoxycarbonyl)-2-oxoethyl 2-Furoate (4b)

Yield 0.34 g (87%); green oil; IR (KBr): 3355 (NH), 1760 and 1741 (C = O of esters), 1670 (CON), 1657 and 1520 (Ar), 1283, 1254, 1207 and 1145 (C–O) cm^{-1}; ^1H NMR (500.1 MHz, $CDCl_3$): $\delta = 1.27$ (3 H, t, OCH_2CH_3), 1.42 [9H, s, $(C(Me)_3$], 4.22 (1 H, d, $^2J_{HH} = 11.3$ Hz, CHBr), 4.24–4.32 (2 H, m, OCH_2CH_3), 4.35 (1 H, d, $^2J_{HH} = 11.3$ Hz, CHBr), 7.59 (1H, dd, $^3J_{HH} = 3.5$ Hz, $^3J_{HH} = 1.6$ Hz, CH of furan), 6.78 (1H, s, NH), 7.31 (1H, d, $^3J_{HH} = 3.5$ Hz, CH of furan), 7.65 (1H, d, $^3J_{HH} = 1.6$ Hz, CH of furan); ^{13}C NMR (125.7 MHz, $CDCl_3$): $\delta = 13.83$ (CH_3), 28.42 C [$C(Me)_3$], 32.06 (CH_2Br), 52.14 [$C(Me)_3$], 62.98 (OCH_2CH_3), 82.37 (C), 112.39 (CH of furan), 120.07 (CH of furan), 143.13 (C_{ipso}–C = O), 147.38 (CH of furan), 155.49 (CO_2Et), 162.82 (CO_2 Et), 165.12 (CON); EI-MS, m/z (%): 392 ($M^+ + 2$, 2), 390 (M^+, 3), 336 (1), 319 (8), 291 (16), 245 (2), 211 (40), 165 (10), 95 (100), 57 (30), 39 (14). Anal. calcd. for $C_{15}H_{20}BrNO_6$ (390.29): C, 46.17; H 5.17; N 3.59%. Found: C, 46.25; H, 5.1; N, 3.5%.

1-(Bromomethyl)-2-(cyclohexylamino)-1-(ethoxycarbonyl)-2-oxoethyl 4-Pitrobenzoate (4c)

Yield 0.37 g (80%); green oil; IR (KBr): 3425 (NH), 1750 and 1733 (C = O of esters), 1690 (CON), 1678 and 1580 (Ar), 1517 and 1368 (NO_2), 1298, 1253, 1190 and 1094 (C–O) cm^{-1}; ^1H NMR (500.1 MHz, $CDCl_3$): $\delta = 1.13$ (3 H, t, OCH_2CH_3), 1.14–2.07 (10 H, m, 5 CH_2 of Cy-Hex), 3.91 (1 H, m, NCH of Cy-Hex), 4.21 (1 H, d, $^2J_{HH} = 18.2$ Hz, CHBr),

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4.26 (1 H, d, $^2J_{HH} = 18.2$ Hz, CH Br), 4.34–4.44 (2 H, m, OCH_2CH$_3$), 6.99 (1H, d, $^3J_{HH} = 7.5$ Hz, NH), 8.29 (2 H, d, $^3J_{HH} = 7.0$ Hz, 2 CH Ar), 8.40 (2 H, d, $^3J_{HH} = 7.0$ Hz, 2 CH Ar); ^{13}C NMR (125.7 MHz, $CDCl_3$): $\delta = 13.88$ (CH_3), 24.54–32.49 (5 CH_2 of Cy-Hex), 32.70 (CH_2Br), 49.12 (NCH of Cy-Hex), 63.44 (OCH_2CH$_3$), 82.69 (C), 123.68 (CH of Ar), 131.03 (CH of Ar), 134.15 (C_{ipso}–C = O), 141.15 (C_{ipso}–NO_2), 162.47 (CO_2Ar), 162.77 (CO_2Et. 165.92 (CON); EI-MS, m/z (%): 473 ($M^+ + 2$, 23), 471 (M^+, 28), 372 (21), 266 (14), 150 (100), 104 (21), 83 (11), 55 (16). Anal. calcd. for $C_{19}H_{23}BrN_2O_7$ (471.30): C, 48.42; H, 4.92; N, 5.94%. Found: C, 48.35; H, 4.9. N; 5.86%.

1-(Bromomethyl)-2-(cyclohexylamino)-1-(ethoxycarbonyl)-2-oxoethyl 2-Furoate (4d)

Yield 0.32 g (77%); green oil; IR (KBr): 3425 (NH), 1750 and 1733 (C = O of esters), 1690 (CON), 1678 and 1580 (Ar), 1298, 1253, 1190 and 1094 (C–O) cm^{-1}; ^{1}H NMR (500.1 MHz, $CDCl_3$): $\delta = 1.26$ (3 H, t, OCH$_2$CH_3), 1.28–1.81 (10 H, m, 5 CH_2 of Cy-Hex), 3.85 (1 H, m, NCH of Cy-Hex), 4.24 (1 H, d, $^2J_{HH} = 15.3$ Hz, CHBr), 4.27–4.30, (2 H, m, OCH_2CH$_3$), 4.26 (1 H, d, $^2J_{HH} = 15.3$ Hz, CH Br), 6.59 (1H, dd, $^3J_{HH} = 4.8$ Hz, $^4J_{HH} = 1.7$ Hz, CH of furan), 6.83 (1H, s, NH), 7.32 (1H, d, $^3J_{HH} = 4.2$ Hz, CH of furan), 7.62 (1H, d, $^3J_{HH} = 4.9$ Hz, CH of furan); ^{13}C NMR (125.7 MHz, $CDCl_3$): $\delta = 13.83$ (CH_3), 24.46–32.20 (5 CH_2 of Cy-Hex), 40.88 (CH_2Br), 48.87 (NCH of Cy-Hex), 53.40 (OCH_2CH$_3$), 82.40 (C), 143.11 (C_{ipso}–C = O), 147.40 (CH of furan), 155.50 (CO_2Et), 162.99 (CO_2Et), 165.02 (CON); MS-EI, m/z (%): 418 ($M^+ + 2$, 26), 416 (M^+, 25), 317 (10), 211 (100), 165 (32), 137 (16), 95 (85), 39 (14). Anal. calcd. for $C_{17}H_{22}BrNO_6$ (416.27): C, 49.05; H, 5.33, N, 3.36%. Found: C, 49.25; H, 5.15; N, 3.35%.

Ethyl 2-(Bromomethyl)-2-[(chloroacetyl)oxy]-3-(cyclohexylamino)-3-oxopropanoate (4e)

Yield 0.3 g (75%); green oil; IR (KBr): 3355 (NH), 1760 and 1741 (C = O of esters), 1670 (CON), 1657 and 1520 (Ar), 1272, 1254, 1207 and 1145 (C–O) cm^{-1}; ^{1}H NMR (500.1 MHz, $CDCl_3$): $\delta = 1.28$ (3 H, t, OCH$_2$CH_3), 1.33–1.70 (10 H, m, 5 CH_2 of Cy-Hex), 3.79 (1 H, m, NCH of Cy-Hex), 3.91 (1 H, d, $^2J_{HH} = 11.7$ Hz, CHBr), 4.03 (1 H, d, $^2J_{HH} = 11.7$ Hz, CH Br), 4.12 (2H, s, CH_2Cl), 4.24–4.31 (2 H, m, OCH_2CH$_3$), 6.79 (1H, d, $^3J_{HH} = 7.1$ Hz, NH); ^{13}C NMR (125.7 MHz, $CDCl_3$): $\delta = 13.82$ (CH_3), 24.41–32.35 (5 CH_2 of Cy-Hex), 36.91

(CH_2 Br), 40.66 (CH_2Cl) 48.93 (NCH of Cy-Hex), 63.66 (OCH_2CH_3), 83.02 (C) 162.54 (CO_2Et), 164.80 (CO_2 Et), 169.84 (CON); EI-MS, m/z (%): 400 ($M^+ + 1$, 4), 398 (M^+, 3), 318 (3), 271 (5), 240 (15), 193 (30), 147 (25), 117 (40), 83 (37), 56 (53), 32(100). Anal. calcd. for $C_{14}H_{21}BrClNO_5$ (398.68): C, 42.18; H, 5.31; N, 3.51%, Found: C, 42.15; H, 5.27, N, 3.50%.

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Ethyl 2-{[2-(Benzoylamino)acetyl]oxy}-2-(bromomethyl)-3-(cyclohexylamino)-3-oxo Propanoate (4f)

Yield 0.33 g (70%); yellow powder, mp 223–225°C; IR (KBr): 3235 and 3120 (NH), 1783 (CO_2C^t), 1731 (CO_2Et), 1675 (CON), 1658 (PhCON), 1651 (C = C), 1277, 1250, 1168, 1080 (C–O) cm^{-1}; ^1H NMR (500.1 MHz, $CDCl_3$): $\delta = 0.93$ (3H, t, OCH_2CH_3), 1.22–1.44 (10H, m, CH_2 of CyHex), 3.79 (1H, d, $^2J_{HH} = 10.6$ Hz, CH_2Br), 3.855 (2H, d, $^2J_{HH} = 10.6$, CH_2Br), 3.92 (2H, d, $^2J_{HH} = 10.7$ Hz, CH_2N), 4 (2H, d, $^2J_{HH} = 10.7$ Hz, CH_2N), 4.31 (1H, m, CH of CyHex), 4.37 (2H, m, OCH_2CH_3), 5.35 (1H, d, $^2J_{HH} = 14.8$ Hz, NH), 7.64–7.78 (5H, m, 5 CH of Ph); ^{13}C NMR (125.7 MHz, $CDCl_3$): $\delta = 11.26$ (OCH_2CH_3), 23.57–33.37 (CH_2 of CyHex), 39.69 (CH_2Br), 63.58 (CH_2NH), 63.78 (CH of CyHex), 64.085 (CH_3CH_2O), 68.35 (C), 129.58 (2CH of Ph), 131.93 (2CH of Ph), 133.47 (CH of Ph), 145.1 (C_{ipso} of Ph), 161 (CO), 164.5 (CO), 168 (CO); EI-MS, m/z (%); 483 (M^+, 2), 321 (4), 345 (3), 3.67 (3), 289 (12), 271 (28), 243 (19), 191 (36), 149 (100), 167 (24), 121 (24), 105 (21), 69 (28), 43 (35). Anal. calcd. for $C_{21}H_{27}BrN_2O_6$ (483.36): C, 52.18; H, 5.63; N, 5.80%. Found: C, 52.14; H, 5.67; N, 5.82%.

Ethyl 2-(Bromomethyl)-3-(cyclohexylamino)-3-oxo-2-[(2-phenylacetyl)oxy]propanoate (4g)

Yield 0.29 g (67%); colorless oil; IR (KBr): 3365 (NH), 1755 and 1721 (C = O of esters), 1676 (CON), 1660 and 1511 (Ar), 1275, 1240, 1211 and 1149 (C–O) cm^{-1}; ^1H NMR (500.1 MHz, $CDCl_3$): $\delta = 1.22$ (3 H, t, OCH_2CH_3), 1.28–1.77 (10 H, m, 5 CH_2 of Cy-Hex), 3.65 (2H, s, $PhCH_2$), 3.70 (1 H, m, NCH of Cy-Hex), 3.82 (1 H, s, CH_2Br), 4.27–4.29, (2 H, m, OCH_2CH_3), 6.17 (1H, d, $^3J_{HH} = 8.0$ Hz, NH), 7.29 (2H, t, $^3J_{HH} = 7.4$ Hz, CH of Ph), 7.34 (1H, d, $^3J_{HH} = 6.9$ Hz, CH of Ph). 7.39 (2H, t, $^3J_{HH} = 6.8$ Hz, CH of Ph); ^{13}C NMR (125.7 MHz, $CDCl_3$): $\delta = 13.77$ (CH_3), 24.50–32.37 (5 CH_2 of Cy-Hex), 32.60 (CH_2Br), 40.87 (NCH of Cy-Hex), 48.70 ($PhCH_2$), 62.89 (OCH_2CH_3), 82.26 (C), 127.31 (2CH of Ph), 128.86 (2CH of Phr), 129.45 (CH of Ph) 133.40 (C_{ipso}–C = O),

147.40 (*C*H of furan), 162.97, 162.99 (2 O*C*=O), 168.67 (CON); EI-MS, m/z (%): ($M^+ + 2$, 10), 440 (M^+, 10), 322 (20), 235 (80), 119 (18), 91 (100). Anal. calcd. for $C_{20}H_{26}BrNO_5$ (440.33): C, 54.55; H, 5.95; N, 3.18%. Found: C, 54.52; H, 6; N, 3.17%.

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