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Terephthaldehyde as a suitable building-block for synthesis of new Ugi adducts

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ABSTRACT

In this work, an efficient Ugi-four component reaction (U-4CR) with terephthaldehyde as oxo compound for synthesis of new original symmetrical *bis* (α-amino acyl amides) derivatives in good yields is reported. Diversity of aldehydes, amines, and isocyanides were examined in this protocol to give the corresponding products in one-pot operation. The structure of products was characterized using IR, ^{1}H and ^{13}C NMR, and CHN analysis.

KEYWORDS

Terephthaldehyde;
Ugi reaction;
Multicomponent;
Isocyanide.

INTRODUCTION

Multicomponent reactions (MCRs) are powerful tools for combinatorial library synthesis because of the fact that multiple bonds formed in a single operation and diversity can be achieved by simple varying each components[1]. Among MCRs, the Ugi four-component reaction is one of the most studied reactions owing to the efficiency, time-saving, and atom-economical process. In the archetypal Ugi 4CR, a primary amine, an oxo compound (aldehyde or ketone), a carboxylic acid and an isocyanide react in methanol to generate α-amino acyl amide. At the beginning of the 1990, the four-component nature of the Ugi reaction, along with the development of combinatorial chemistry in the pharmaceutical industry, set this reaction the leader of a major trend in organic chemistry[2].

Many researchers have focused on the U-4CR to prepare libraries of Ugi products. Various modifications of the classical Ugi-4CR have been described that involved the varying of one of the components or the introduction of a linkage between two of them leads to α-amino acyl amide derivatives[3]. Also combination of Ugi reaction with other common reactions in organic chemistry such as Heck and Michael addition is interesting for construction of biologically active compounds[4]. Recently, secondary diamines as components in the Ugi four-component reaction have been studied by Giovenzana *et al*.[5].

EXPERIMENTAL

All chemicals purchased from Merck and Fluka. All reactions were carried out under air. All NMR spectra were recorded on a Bruker AMX 300 MHz. Fourier transform-infrared (FT-IR) experiments were obtained in potassium bromide pellets on a Perkin-Elmer FT spectrum RX1over the range 400-4000 cm^{-1}. Elemental analyses performed by a perkin-Elmer 2004 (II) CHNS/O analyzer.

General reaction procedure

To a stirred solution of terephthaldehyde (1 eq.) in methanol (10 mL), an amine (2 eq.) was added. The mixture was stirred for 25 min to furnish the *bis* imine. Then, a carboxylic acid (2 eq.) was added. An isocyanide (2 eq.) was finally added slowly over 1 min and the reaction was allowed to stir for 24 h at 50 °C. Distilled water was added to the reaction and the solid impure product was collected by filtration. Purifications have been done with recrystallizations in mixture of ethanol and diethyl ether to afford a product as mixture of diastereomers.

Spectroscopic data for all products

(a) 1,4-bis [4-methylphenyl (phenyl) carboxamido (cyclohexylcarbamoyl) methyl] benzene (5a)

Brown powder; IR (KBr): ν_{max}= 3320, 3057, 2853, 1680, 1637, 1559 cm^{-1}; ^1H NMR (300.1 MHz, $CDCl_3$): δ= 0.88-2.18 (m, 26H), 3.86 (m, 2H), 5.89(s, 2H, 2CH), 6.08 (s, 2H), 6.81-7.3(m, 22H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$): δ= 20.9, 24.7, 25.5, 32.8, 48.6, 66.3, 127.6, 128.5, 129.0, 129.4, 129.7, 130.3, 135.0,135.9, 136.9, 138.7, 168.3, 171.3 ppm; Anal. Calcd (%) for $C_{50}H_{54}N_4O_4$: C, 77.49; H, 7.02; N, 7.23. Found: C, 76.99; H, 7.16; N, 6.90.

(b) 1,4-Bis [4-methylphenyl (phenyl) carboxamido (*t*-butyl carbamoyl) methyl]benzene (5b)

White powder ; mp 193-197 °C. IR (KBr): ν_{max}=3347, 3059, 2871, 1688, 1633, 1511 cm^{-1}; ^1H NMR (300.1 MHz, $CDCl_3$): δ= 1.35(s, 18H), 2.17(s, 6H), 5.86(s, 2H), 6.02(s, 2H), 6.81 (m, 8H), 7.13-7.30 (m, 14H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$): δ= 20.9, 28.6, 51.6, 66.7, 120.9, 127.6, 128.5, 129.1, 129.6, 129.8, 130.0, 135.1, 136.2, 138.7, 168.33, 171.21 ppm; Anal. Calcd (%) for $C_{46}H_{50}N_4O_4$: C, 76.43; H, 6.97; N, 7.75. Found: C, 75.99; H, 6.62; N, 7.43.

(c) 1,4-Bis [4-chlorophenyl (phenyl) carboxamido (cyclohexylcarbamoyl) methyl] benzene (5c)

White powder; IR (KBr): ν_{max}= 3410, 2855-3089, 1664, 1652, 1578, 622 cm^{-1}; ^1H NMR (300.1 MHz, $CDCl_3$): δ= 1.13-1.96(m, 20H), 3.83(m, 2H), 5.73(d, 2H, *J*= 8 Hz), 6.15(s, 2H), 6.90-7.20(m, 22H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$): δ= 24.5, 25.3, 32.8, 48.8, 65.4, 122.2, 127.8, 128.3, 129.1,130.2, 131.4, 132.9, 134.8, 135.4, 139.5, 168.1, 171.2 ppm. Anal. Calcd (%) for $C_{48}H_{48}Cl_2N_4O_4$: C, 70.67; H, 5.93; N, 6.87. Found: C, 70.34; H, 6.12; N, 6.78.

(d) 1,4-Bis [4-methylphenyl (4-nitrophenyl) carboxamido (cyclohexylcarbamoyl) methyl] benzene (5d)

White powder; IR (KBr): ν_{max}=3356,3036, 2855, 1686, 1641, 1518, 1329 cm^{-1}; ^1H NMR (300.1 MHz, $CDCl_3$) δ= 1.01-2.18(m, 26H), 3.83(m, 2H), 5.59(d, 2H, *J*=8.2 Hz), 6.11(s, 2H), 6.79(m, 8H), 7.16 (d, 4H, *J*=11.3 Hz), 7.41 (m, 4H), 8.00 (d, 4H, *J*=8.2 Hz) ppm;^{13}C NMR (75.5 MHz, $CDCl_3$): δ=20.9, 24.6, 25.4, 32.8, 48.8, 65.9, 122.9, 129.1, 129.4, 129.8, 130.4, 134.7, 137.1, 137.8, 142.2, 147.7, 167.7, 169.2 ppm. Anal. Calcd (%) for $C_{50}H_{52}N_6O_8$: C, 69.43; H, 6.06; N, 9.72. Found: C, 69.25; H, 6.01; N, 9.70.

(e) 1,4-Bis[4-chlorophenyl (4-nitrophenyl) carboxamido (cyclohexylcarbamoyl) methyl] benzene (5e)

White powder ; IR (KBr): ν_{max}=3343, 3063, 2855, 1685, 1639, 1520, 1342, 574 cm^{-1}; ^1H NMR (300.1 MHz, $CDCl_3$): δ= 1.01-1.99(m, 20H) 3.8(m, 2H), 5.48(d, 2H, *J*=8.0 Hz), 6.18(s, 2H), 6.95-7.13 (m, 12H), 7.41 (d, 4H, *J*=8.5 Hz), 8.01(d, 4H, *J*=8.5 Hz) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=24.7, 25.4, 32.8, 49.0, 64.8, 123.2, 128.8, 129.1, 130.6, 131.7, 133.9, 134.6, 138.0, 141.6, 148.0, 167.5, 169.1 ppm. Anal. Calcd (%) for $C_{48}H_{46}N_6O_8Cl_2$: C, 63.65; H, 5.12; N, 9.28. Found: C, 63.73; H, 5.17; N, 9.30.

(f) 1,4-Bis [4-chlorophenyl (phenyl) carboxamido (*t*-butyl carbamoyl) methyl] benzene (5f)

yellow powder; IR (KBr): ν_{max}=3326, 3082, 2926, 1685, 1628, 1541, 607 cm^{-1}; ^1H NMR (300.1 MHz, $CDCl_3$): δ= 1.39 (s, 18H),5.69 (brs, 2H), 6.09 (s, 2H), 6.8-7.27 (m, 22H, ArH) ppm;^{13}C NMR (75.5 MHz, $CDCl_3$): δ= 28.6, 51.7, 65.5, 127.8, 128.3, 128.6, 129.7, 130.3, 131.6, 132.9, 134.9, 135.4, 139.3, 168.2, 171.1 ppm; Anal. Calcd (%) for $C_{44}H_{44}Cl_2N_4O_4$: C, 69.19; H, 5.81; N, 7.34. Found: C, 69.51; H, 5.95; N, 7.21.

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(g) 1,4-Bis[4-boromophenyl (4-nitrophenyl) carboxamido (*t*-butyl carbamoyl) methyl] benzene (5g)

yellow powder; IR (KBr): ν_{max}=3347, 3079, 2870, 1687, 1652, 1523, 1346, 551 cm^{-1}; ^1H NMR (300.1 MHz, $CDCl_3$): δ= 1.36 (s, 18H), 5.48 (brs, 2H), 6.06 (s, 2H), 6.86 (m, 4H), 7.09-7.17 (8H, m), 7.41 (d, 4H, *J*= 8.8 Hz), 8.02 (d, 4H, *J*= 8.8 Hz) ppm;^{13}C NMR (75.5 MHz, $CDCl_3$): δ= 28.6, 52.1, 65.6, 121.9, 123.2, 129.2, 130.5, 131.9 (2C), 134.6, 138.8, 141.6, 148.0, 167.6, 168.9 ppm. Anal. Calcd (%) for $C_{44}H_{42}Br_2N_6O_{8:}$ C, 56.06; H, 4.49; N, 8.92. Found: C, 56.33; H, 4.13; N, 8.65.

(h) 1,4-Bis [4-chlorophenyl (4-nitrophenyl) carboxamido (*t*-butyl carbamoyl) methyl] benzene (5h)

white powder; IR (KBr): ν_{max}=3354, 3071, 2931, 1692, 1633, 1661, 1525, 1348, 569 cm^{-1}; ^1H NMR (300.1 MHz, $CDCl_3$): δ= 1.35 (s, 18H), 5.40 (s, 2H), 6.10 (s, 2H), 6.91-7.13 (m, 12H), 7.41 (d, 4H, *J*= 8.8 Hz), 8.01 (d, 4H, *J*= 8.8 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ= 28.6, 52.0, 65.3, 123.2, 128.7, 129.2, 130.5, 131.7, 133.8, 134.6, 138.1, 141.7, 148.0, 167.7, 168.9 ppm. Anal. Calcd (%) For $C_{44}H_{42}N_6O_8Cl_{2:}$ C, 61.90; H, 4.96; N, 9.84. Found: C, 61.66; H, 4.94; N, 9.82.

(i) 1,4-Bis[4-methylphenyl (methyl) carboxamido (*t*-butyl carbamoyl) methyl] benzene (5i)

white powder; IR (KBr): ν_{max}= 3312, 3065, 2928, 1690, 1633, 1510 cm^{-1}; ^1H NMR (300.1 MHz, $CDCl_3$): 1.31 (s, 18H), 1.82 (s, 6H), 2.28 (s, 6H), 5.60 (brs, 2H), 5.86 (s, 2H), 6.91-6.98 (m, 12H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ= 21.1, 23.0, 28.6, 51.6, 64.8, 129.6, 129.8, 134.9, 137.9, 138.0, 147.1, 168.6, 171.4 ppm; Anal. Calcd (%) for $C_{36}H_{46}N_4O_4$: C, 72.21; H, 7.74; N, 9.36. Found: C, 71.95; H, 7.94; N, 9.76.

(j) 1,4-Bis [2-methylphenyl (4-nitrophenyl) carboxamido (cyclohexylcarbamoyl) methyl] bezene (5j)

white powder; IR (KBr): ν_{max}=3329, 3072, 2854, 1679, 1626, 1520, 1345 cm^{-1}; ^1H NMR (300.1 MHz, $CDCl_3$): δ= 1.02-1.92 (m, 26H), 3.84 (m, 2H), 5.48 (d, 2H, *J*= 8.2 Hz), 6.06 (s, 2H), 6.72-7.96 (m, 16H), 7.98 (4H, d, *J*=8.6 Hz) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ= 18.2, 24.6, 25.43, 32.8, 48.7, 65.7, 122.8, 126.6, 127.1, 128.8, 129.8, 130.6, 131.0, 134.0, 135.9, 138.1, 142.0, 147.9, 166.9, 169.0 ppm. Anal. Calcd (%) for $C_{50}H_{52}N_6O_8$: C, 69.43; H, 6.06; N, 9.72. Found: C, 69.31; H, 6.26; N, 9.66.

(k) 1,4-Bis [4-methylphenyl (triflouromethyl) carboxamido (cyclohexyl carbamoyl) methyl] benzene (5k)

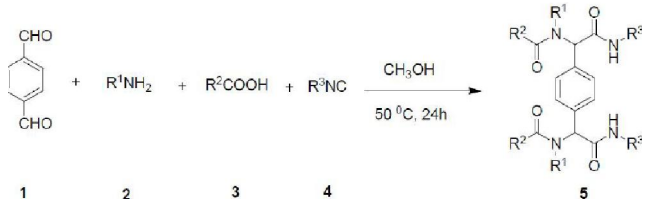
white powder; IR (KBr): ν_{max}= 3301, 3074, 2856, 1698, 1657, 1513cm^{-1}; ^1H NMR (300.1 MHz, $CDCl_3$): 1.04-1.95 (m, 20H), 2.30 (s, 6H), 3.80 (m, 2H), 5.39 (brs, 2H), 5.77 (s, 2H), 6.5-7.47(m, 12H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ= 21.2, 24.6, 25.4, 32.7, 48.9, 66.3, 114.2, 118.1, 127.5, 129.7, 130.7, 133.7, 139.2, 157.4, 166.5 ppm; Anal. Calcd (%) for $C_{42}H_{46}F_6N_2O_4$: C, 63.31; H, 5.84; N, 7.38. Found: C, 63.50; H, 5.81; N, 7.35.

(l) 1,4-Bis[benzyl (4-nitrophenyl) carboxamido (*t*-butyl carbamoyl) methyl] benzene (5l)

white powder; mp 256-258 ^oC. IR (KBr): ν_{max}= 3411, 3337, 3067, 2968, 1679, 1633, 1524, 1347; ^1H NMR (300.1 MHz, $CDCl_3$): 1.32 (s, 18H), 4.37 (d, *J*= 15.8 Hz, 2H), 4.55 (d, *J*= 16.7 Hz, 2H), 5.55 (s, 2H), 5.72 (s, 2H), 6.68-7.52 (m, 18H), 8.12 (d, *J*= 8.2 Hz, 4H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ= 28.5, 51.9, 63.5, 123.6, 126.5, 127.3, 127.5, 128.4, 130.3, 135.4, 136.8, 142.2, 167.5, 171.2 ppm. ; Anal. Calcd (%) for $C_{46}H_{48}N_6O_8$: C, 67.96; H, 5.95; N, 10.34. Found: C, 67.80; H, 5.81; N, 10.35.

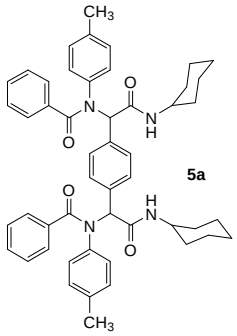
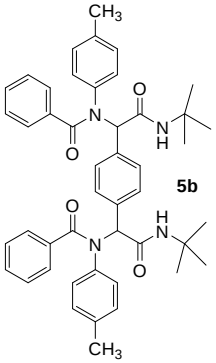
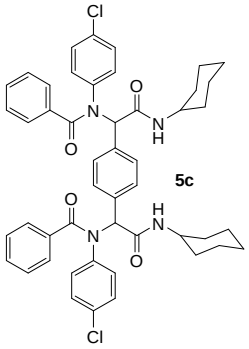
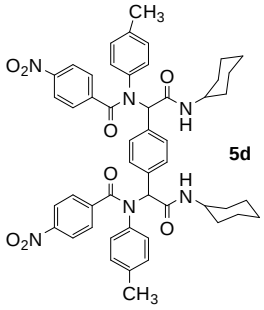
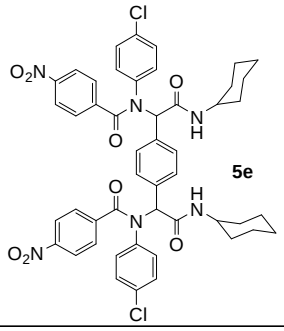
RESULTS AND DISCUSSION

As part of our study on the isocyanide based multicomponent reactions[6], and encourage by the work of Charton *et al.* on the using of squaric acid in Ugi reaction,[7] herein we report the first use of



Scheme 1 : Synthesis of *bis* (α-amino acyl amides) with terephthaldehyde

TABLE 1 : Diversity in the synthesis of *bis* (α-amino acyl amides)

Entry	R^1	R^2	R^3	Product	Yield (%)[a]
1	4-CH_3-Ph	Ph	cyclohexyl-	 **5a**	55
2	4-CH_3-Ph	Ph	*t*-butyl	 **5b**	33
3	4-Cl-Ph	Ph	cyclohexyl-	 **5c**	35
4	4-CH_3-Ph	4-NO_2-Ph	cyclohexyl-	 **5d**	71
5	4-Cl-Ph	4-NO_2-Ph	cyclohexyl-	 **5e**	68

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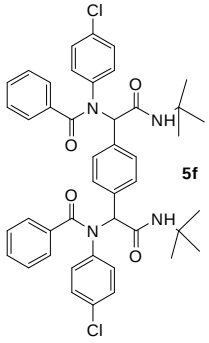
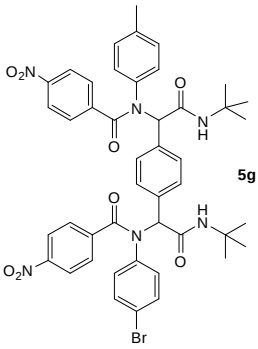
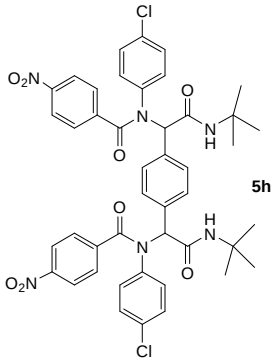
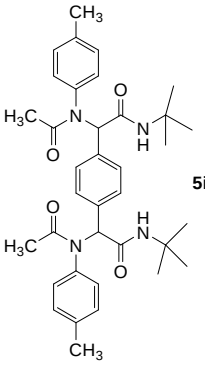
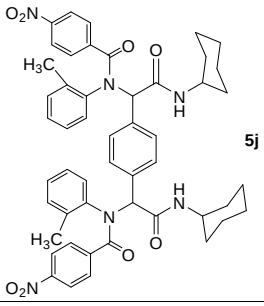
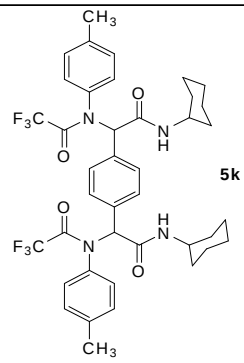
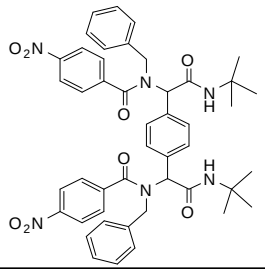
Entry	R^1	R^2	R^3	Product	Yield (%)[a]
6	4-Cl-Ph	Ph	*t*-butyl	 **5f**	32
7	4-Br-Ph	4-NO_2-Ph	*t*-butyl	 **5g**	59
8	4-Cl-Ph	4-NO_2-Ph	*t*-butyl	 **5h**	63
9	4-CH_3-Ph	CH_3	*t*-butyl	 **5i**	21
10	2-CH_3-Ph	4-NO_2-Ph	cyclohexyl-	 **5j**	49

Entry	R^1	R^2	R^3	Product	Yield (%)[a]
11	4-CH_3-Ph	CF_3	cyclohexyl-	 **5k**	45
12	$PhCH_2$	4-NO_2-Ph	*t*-butyl	 **5l**	48

[a] **Isolated yield**

terephthaldehyde as carbonyl component in the 4C-Ugi reaction. This allows rapid access to a variety of original symmetrical product in moderate to good yields. The reaction is a double 4C-Ugi reaction or pseudo-seven-component reaction that uses two carbonyl functions of terephthaldehyde to give *bis* (α-amino acyl amides) derivatives of general formula 5 (Scheme 1).

The 4C-Ugi reaction with terephthaldehyde was examined with cyclohexyl isocyanide, *p*-methylaniline, and benzoic acid (TABLE 1) to optimize the reaction conditions. Amine, terephthaldehyde, acid and isocyanide were used in 1:0.5:1:1 proportions with a one-pot sequential procedure. Pre-formation of the *bis*-imine was performed by mixing the amine and the terephthaldehyde for 25 min. that react with acid to form the iminium intermediate. Isocyanide was finally added and the mixture was reacted overnight to give the desired product in good yields in methanol without any catalyst at 50 °C. The products were collected by a simple work-up as it precipitates and was purified by recrystallization in mixture of ethanol and diethyl ether. Under these conditions, the synthesized *bis* compound 5 is a mixture of diastereomers that was evidenced by NMR. After optimization of the reaction conditions, the generality of these conditions was examined by using various components as shown in TABLE 1. It was found that with using *p*-nitrobenzoic acid the products were obtained in high yields (entries 4, 5, 7 and 8, TABLE 1). Acetic acid gave poor yields (21%) in this reaction (entry 9, TABLE 1). Also, the reactions gave good to high yields with moderate electron-donating and electron-withdrawing groups on aniline. Aliphatic amine such as benzyl amine gave good yields. Furthermore, reaction with *p*-nitro aniline did not lead to any results because of the electron-withdrawing character of nitro group. In addition, the reaction is favorable with both *tert*-butyl isocyanide and cyclohexyl isocyanide. Reaction with tosylmethyl isocyanide was not successful. Reaction with triflouroacetic acid gave moderate yields of product (entry 11, TABLE 1). Reaction with equimolar of an amine, terephthaldehyde, an acid and an isocyanide gave mixture of *bis* and mono Ugi adducts. The structure of products was fully characterized by ^{1}H-NMR and ^{13}C-NMR, IR spectra and elemental analysis. The representative peak at 5.5-6.5 ppm in ^{1}H NMR spectra was assigned for the benzylic hydrogen, while the two peaks at 160-170 ppm in ^{13}C NMR was assigned for the two amide groups. Also the NH group was observed at 5-6 ppm.

In summary, we have described herein a novel

and highly efficient double Ugi-four component reaction (pseudo-seven-component) with terephthaldehyde as oxo component that allows the rapid access to a variety of originally symmetrical products in moderate to good yields.

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