Synthesis of Bis(aminofuryl)bicinchoninic Amides by a One-Pot Three-Component Reaction of Isocyanides, Acetylenic Esters, and Bicinchoninic Acid

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Abstract: A simple synthesis of dialkyl 2-(alkylamino)-5-[alkyl[2-[4-{(alkyl[5-(alkylamino)-3,4-bis(alkoxycarbonyl)-2-furyl]amino}carbonyl]-2-quinolyl]-4-quinolyl]carbonyl]amino]-3,4-furandicarboxylate derivatives is described. This involves reaction of isocyanides, dialkyl acetylenedicarboxylates, and bicinchoninic acid (BCA) in MeCN–THF at 25 °C for 36 hours.

Key words: dialkyl acetylenedicarboxylate, isocyanide, bicinchoninic acid, multicomponent reaction, bicinchoninic amide

A general way to improve synthetic efficiency and also to address other criteria is the development of new types of multicomponent reactions.1 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 combinatorial chemistry.1–6 Of pivotal importance in multicomponent area are the isocyanide-based MCRs such as the versatile Ugi and Passerini reactions.2,3,5

Passerini’s three-component reactions of isocyanides, aldehydes, and carboxylic acids produce α-amido esters that can be used in the synthesis of a variety of drugs such as euristatin6 and hydrastine.7 Also the production of many drugs such as benzodiazepine8 and carbacefem9 using Ugi reaction was reported.

We recently reported a new class of isocyanide based multicomponent reaction (IMCRs/DMAD) mediated by zwiterionic intermediates and Dimroth-type rearrangement.10–14 Treatment of nicotinic or isonicotinic acid with dialkyl acetylenedicarboxylate and alkyl isocyanide at 25 °C led to the formation of the nicotinamide and isonicotinamide derivatives (Scheme 1).11

Although we have not established the mechanism of this reaction, a possible explanation is proposed in Scheme 2. On the basis of the well-established chemistry of isocyanides,2,3,5,10–15 it is reasonable to assume that the functionalized diaminofuran 4 apparently results from the initial addition of the isocyanide to the acetylenic system and subsequent protonation of the 1:1 adduct 5 by compound 3, followed by the attack of the carboxylate anion on the positively charged ion of 6 to form imidoyl carboxylate 7 as an intermediate. This intermediate rearranges10–13 under the reaction conditions employed to produce the intermediate 8, followed by its trapping with an isocyanide, to give the intermediate 9, which leads to compound 4 (Scheme 2) by a 1,5-H-shift.11,13

In view of the success of the above reaction, we have explored the use of the biochemically interesting bicinchoninic acid (BCA) as the third component in this reaction. Herein, we report the results of an extended investigation of the reactivity of the intermediate zwiterions with a bifunctional heteroaromatic acid in MeCN–THF. The products are bis(aminofuryl)bicinchoninic amide derivatives.

We prepared the bicinchoninic acid by the reaction of the sodium salt of bicinchoninic acid with hydrochloric acid. The reaction of alkyl isocyanides and dialkyl acetylenedicarboxylates in the presence of bicinchoninic acid proceeded spontaneously at 25 °C in MeCN–THF and was completed within 36 hours, to produce dialkyl 2-(alkylamino)-5-[alkyl[2-[4-{(alkyl[5-(alkylamino)-3,4-bis(alkoxycarbonyl)-2-furyl]amino}carbonyl]-2-quinolyl]amino]carbonyl)-2-quinolyl]carbonyl]amino]-3,4-furandicarboxylate derivatives in 37–52% yields (Table 1).
The structures of compounds 12a–d were deduced from their elemental analyses, IR, and high-field 1H and 13C NMR spectra. The mass spectrum of 12a displayed the molecular ion peak at \( m/z = 961 \), which is consistent with the 2:4:1 adduct of dimethyl acetylenedicarboxylate, tert-butyl isocyanide, and bicinchoninic acid. The IR spectrum of 12a exhibited absorption bands due to the carbonyl groups of ester and amide at 1722, 1710, and 1665 cm\(^{-1}\), respectively, and NH groups at 3325 cm\(^{-1}\). The 1H NMR spectrum of 12a exhibited six single sharp lines readily recognized as arising from tert-butyl groups (1.65 and 1.66) and methoxy groups (3.47 and 3.48) along with two NH groups (6.51 and 6.59). The quinoline moiety gave rise to characteristic signals in the aromatic region of the spectrum. The 1H and 13C NMR spectra of compounds 12b–d are similar to those of 12a, except for the ester and alkyl groups, which exhibit characteristic signals with appropriate chemical shifts.

In summary, the reaction between isocyanides and dialkyl acetylenedicarboxylates in the presence of bicinchoninic acid provides a simple one-pot three-component reaction entry into the synthesis of bis(aminofuran)bicinchoninic amide derivatives,\(^1\) which may be of interest in the pharmaceutical chemistry. The present method carries the advantage of being performed under neutral conditions and requires no activation or modification of the adducts.

The sodium salt of bicinchoninic acid, dimethyl and diethyl acetylenedicarboxylates, tert-butyl and cyclohexyl isocyanides were obtained from Merck (Germany) and Fluka (Switzerland), and were used without further purification. Melting points were measured on an Electrothermal 9100 apparatus. Mass spectra were recorded on a
Maldi mass spectrometer: MALDI-TOF spectra were measured on a Bruker Biflex III with a 19 kV acceleration voltage. trans-2-[[3-(4-tert-Butylphenyl)-2-methyl-2-propenylidene]malononitrile was used as the matrix, as a saturated solution in CH2Cl2. Ionization was effected with a nitrogen laser at 337 nm, detecting of molecules by molecular weight about 1000. Elemental analyses were performed using a Heraeus CHN–O–Rapid analyzer. 1H and 13C NMR spectra were measured (CDCl3 solution) with a Bruker DRX-500 Avance spectrometer at 500.13 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).

**Dimethyl 2-(tert-Butylamino)-5-(tert-buty1)-[2-[[4-[(4-tert-Butylamino)-3,4-bis(methyloxycarbonyl)-2-furyl]amino]carbonyl]-2-quinolyl]quinolyl]carbonyl]amino]-3,4-furandicarboxylate (12a): Typical Procedure**

To a magnetically stirred solution of dimethyl acetylenedicarboxylate (0.28 g, 2 mmol) and boric acid (0.34 g, 1 mmol) in MeCN–THF (5 mL) was added dropwise a solution of tert-butyl isocyanide (0.33 g, 4 mmol) in anhyd MeCN–THF (3 mL) at 25 °C over 15 min. Then the mixture was allowed to stir for 36 h. The solvent was removed under reduced pressure, and the residue was separated by silica gel (Merck 230–240 mesh) column chromatography using hexane–EtOAc mixture as eluent; yield: 0.41 g (42%); yellow powder; mp 117–119 °C.

**IR (KBr):** 3325 (NH), 1722, 1710 (CO–Me), 1665 (CON), 1596, 1537 (Ar), 1246, 1213 cm–1 (C–O).

1H NMR (CDCl3, 500 MHz): δ = 1.65, 1.66 (36 H, s, 4 × C(CH3)), 3.47, 3.48 (12 H, s, 4 × OCH3), 4.65, 4.69 (2 H, s, 2 × NH), 7.49 (2 H, s, J = 8.1 Hz), 7.66 (2 H, s, J = 7.1 Hz), 7.92 (2 H, s, J = 8.0 Hz). 8.08 (2 H, s, J = 8.2 Hz), 8.60 (2 H, s, J = 11.2 Hz).

13C NMR (CDCl3, 125 MHz): δ = 28.01 (2 × C(CH3)), 29.57, 29.74 (2 × C(CH3)), 50.75, 50.80, 51.69, 51.74 (4 × CMe2), 52.42, 62.08, 62.10 (4 × OCH3), 86.05 (2 × C furan), 115.06, 115.34 (2 × C furan), 124.43, 124.46 (2 × CMe2CON), 125.26 (2 × CH, Ar), 127.17, 127.22 (2 × C-4a), 128.18, 128.99, 129.38, 129.40, 130.17, 130.20 (8 × CH, Ar), 137.81, 137.95 (2 × C8a), 143.71, 147.73 (2 × C5 furan), 154.39, 154.46 (2 × C2 furan), 159.15, 159.25 (2 × C2 Ar), 162.56, 162.65, 164.47, 164.62 (4 × COMe), 169.62, 169.71 (2 × CON).

HRMS: m/z [M]+ calecd for C56H63N6O12: 961.37; found: 961.35.

Analy. Calcld for C56H63N6O12 (961): C, 64.99; H, 6.29; N, 8.74. Found: C, 65.10; H, 6.30; N, 8.71.

**Diethyl 2-(tert-Butylamino)-5-(tert-buty1)-[2-[[4-[(4-tert-Butylamino)-3,4-bis(methyloxycarbonyl)-2-furyl]amino]carbonyl]-2-quinolyl]quinolyl]carbonyl]amino]-3,4-furandicarboxylate (12b):**

Yield: 0.58 g (52%); yellow powder; mp 256–258 °C.

**IR (KBr):** 3335 (NH), 1716, 1743 (CO–Et), 1669 (CON), 1593, 1540 (Ar), 1248, 1210 cm–1 (C–O).

1H NMR (CDCl3, 500 MHz): δ = 0.82–0.86, 1.02–1.05 (12 H, m, 4 × OCH2CH3), 1.09, 1.14 (6.5), 1.66 (36 H, s, 4 × C(CH3)), 3.86–3.92, 3.96–4.00, 4.08–4.10 (8 H, m, 4 × OCH2CH3), 6.54, 6.59 (2 H, s, 2 × NH), 7.54 (2 H, s, J = 8.0 Hz), 7.67 (2 H, s, J = 7.1 Hz), 7.98 (2 H, s, J = 8.1 Hz), 8.12 (2 H, s, J = 8.3 Hz), 8.69 (2 H, s).

13C NMR (CDCl3, 125 MHz): δ = 13.49, 14.11 (4 × OCH2CH3), 28.02 [2 × C(CH3)], 29.66, 29.76 [2 × C(CH3)], 52.37 (2 × OCH2CH3), 59.42, 59.46, 61.01, 61.11 (4 × CMe2), 62.10, 62.16 (2 × OCH2CH3), 86.28 (2 × C furan), 115.40, 117.10 (2 × C furan), 124.50 (2 × CMe2CON), 125.25, 125.31 (2 × CH, Ar), 127.15 (2 × C4a), 127.26, 129.43, 130.10 (8 × CH, Ar), 137.72, 137.74 (2 × C8a), 143.90, 147.76 (2 × C5 furan), 154.47, 154.50 (2 × C2 furan), 159.10, 159.23 (2 × C2 Ar), 162.53, 162.57, 164.26, 164.38 (4 × COEt), 169.62, 169.72 (2 × CON).

HRMS: m/z [M]+ calecd for C64H74N10O12: 1017.18; found: 1017.39.


**References**