Isocyanide-Based Multicomponent Reaction: One-Pot Synthesis of New Derivatives of Iminofuranone

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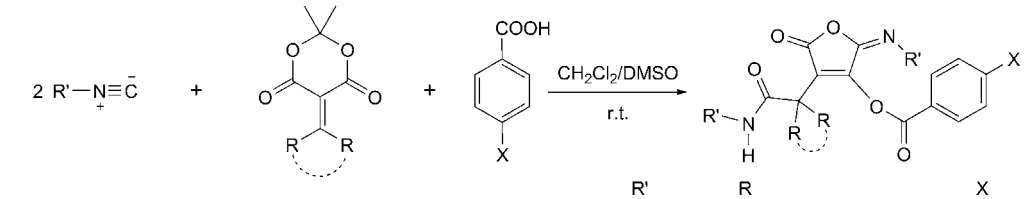
The one-pot multicomponent reaction of alkyl isocyanide, alkylidene-substituted *Meldrum*'s acid, and arylcarboxylic acids affords new derivatives of iminofuranone in fair yields. The structure of the products was deduced from their spectroscopic data. Two equivalents of the respective isocyanides participate in this reaction.

Introduction. – Multicomponent reactions (MCRs) have been used as a versatile synthetic method in the preparation of complex molecules, in which multiple new bonds can be created in a single reaction from readily available starting materials. MCRs have unique features such as high convergence, atom efficiency, simple and short procedure, and they also reduce the environmental burden [1–4]. To accomplish the synthesis of highly complex molecules, particularly natural products, great efforts have been made to develop new multicomponent reactions. Among these reactions, isocyanide-based multicomponent reactions (IMCRs) are very powerful condensations in organic synthesis [1][2]. The *Passerini* and *Ugi* reactions are classical examples. In the organic synthesis, only a few MCRs are well-known, and each reaction affords compounds with a similar framework and a few different substituents, whereas, in the chemistry of the isocyanides, a much greater variation of MCRs is known. In the *Ugi* four component reactions (U-4CRs) and related reactions, the skeletons and the substituents can differ. Thus, IMCRs have achieved an extensive application, because starting materials and products with a greater variety than in other reactions can participate. To expand their utility and gaining access also to drug-like heterocyclic compounds, several research groups are now developing modifications of these reactions [1–8].

Meldrum's acid and its various derivatives have been widely used for heterocycle and drug synthesis [9–11]. We were interested in developing isocyanide-based multicomponent reaction using these derivatives. We have already studied the reactions between isocyanides and alkylidene-substituted *Meldrum*'s acid in the presence of SH-, OH-, and NH-containing compounds [11–16]. In this article, we now describe a facile and convenient one-pot reaction of alkyl isocyanide, alkylidene-substituted *Meldrum*'s acid, and arylcarboxylic acid.

Results and Discussion. – The one-pot reaction of alkyl isocyanide **1**, alkylidene-substituted *Meldrum*'s acid **2**, and arylcarboxylic acid **3** in CH_2Cl_2/DMSO leads to new derivatives of (2*E*)-4-{1-[(*tert*-butyl)amino]-2-methyl-1-oxopropan-2-yl}-2-[(*tert*-butyl)-imino]-2,5-dihydro-5-oxofuran-3-yl 4-bromobenzoate (**4a**; *Scheme 1*). An interesting aspect of this reaction is the participation of two molecules of isocyanide in a 2:1:1 multicomponent reaction. The reaction occurred smoothly at room temperature and was completed within 48 h. As far as iminofuranones have been of interest for chemists (the synthesis of new derivatives of iminofuranone and the investigation of their pharmaceutical activities have been reported recently [17–20]), this protocol can be used as a simple one-pot method to synthesize these derivatives.

Scheme 1. *Synthesis of Iminofuranone Derivatives*



1a R' = ^{t}Bu
1b R' = Cyclohexyl

2a R = Me
2b R··R = $(CH_2)_2$–CH(Me)–$(CH_2)_2$
2c R··R = $(CH_2)_5$
2d R··R = $(CH_2)_4$

3a X = Br
3b X = Cl
3c X = NO_2

	R'	R	X
4a	^{t}Bu	Me, Me	Br
4b	^{t}Bu	Me, Me	Cl
4c	^{t}Bu	Me, Me	NO_2
4d	^{t}Bu	–$(CH_2)_2$–CH(Me)–$(CH_2)_2$–	NO_2
4e	^{t}Bu	–$(CH_2)_5$–	NO_2
4f	^{t}Bu	–$(CH_2)_4$–	Br
4g	Cyclohexyl	Me, Me	Cl
4h	^{t}Bu	–$(CH_2)_2$–CH(Me)–$(CH_2)_2$–	Cl
4i	Cyclohexyl	–$(CH_2)_4$–	NO_2
4j	^{t}Bu	–$(CH_2)_5$–	Br

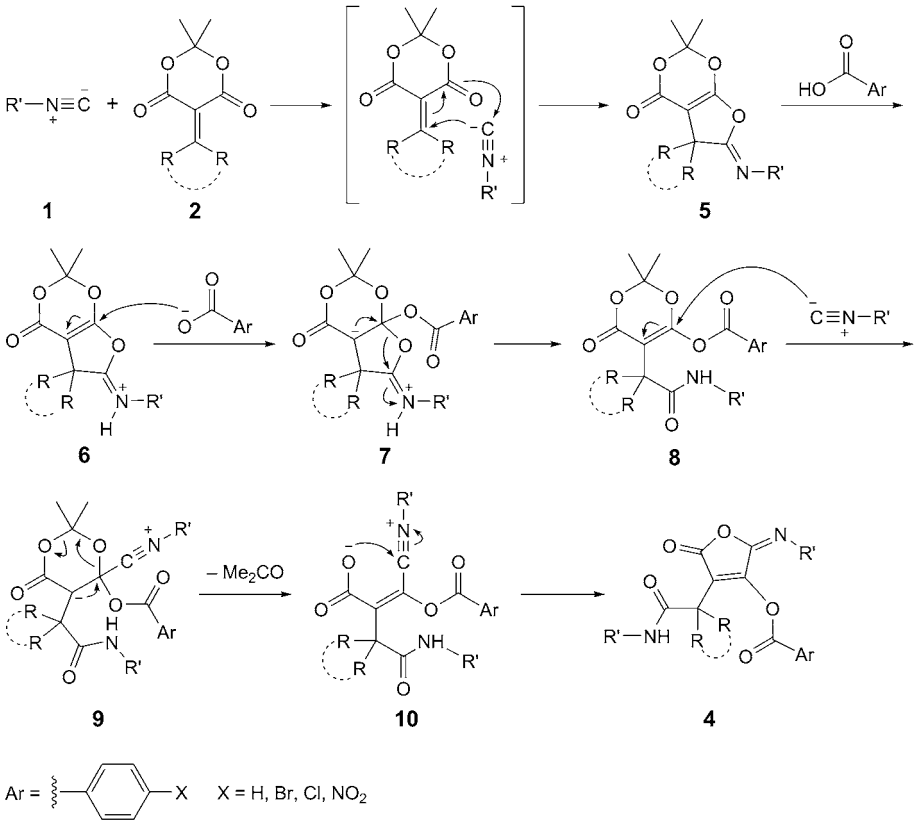
Alike to our previous work, we expected equimolar amounts of starting materials to react. But spectroscopic data of the products showed that two equivalents of isocyanide participated in the reaction. The IR spectrum of **4a** clearly exhibited an NH stretching band at 3216 cm^{-1}, and three C=O bands at 1769, 1744, and 1693 cm^{-1}. The ^{1}H-NMR spectrum of **4a** exhibited three sharp *singlet*s arising from Me_2C (δ(H) 1.39) and two Me_3C (δ(H) 1.41 and 1.62) groups. An *AA′BB′* signal for the aromatic-H-atoms was indicative for a *para*-substituted phenyl group, and a signal at 9.59 ppm for the amide NH. The ^{13}C-NMR spectrum of **4a** showed 16 distinct resonances in agreement with the proposed structure. The signals at δ(C) 28.3 and 28.4 relate to two Me_3C moieties from two *t*-butyl isocyanide molecules. The two signals at δ(C) 52.1 and 59.6 belong to Me_3C. All other signals were consistent with the core-structure of compound **4a**.

Although the mechanism of the reaction between isocyanide and alkylidene-substituted *Meldrum*'s acid in the presence of aryl carboxylic acid has not been established in an experimental manner, a plausible mechanism for the formation of the product is presented in *Scheme 2*. The first step of this mechanism involves the formal [4 + 1] cycloaddition reaction of the electron-deficient heterodiene moiety of alkylidene-substituted *Meldrum*'s acid **2** with the isocyanide **1** affording the inter-

mediate imino lactone **5**. Then, protonation of **5** by the arylcarboxylic acid occurs to give intermediate **6**. *Michael* addition of the carboxylate anion to the iminium enone moiety of **6** leads to intermediate **7** and subsequently to compound **8**. Then, a second molecule of **1** attacks the enone in a second *Michael* addition to give intermediate **9**. Next, ring opening of *Meldrum*'s acid core in intermediate **9** *via* elimination of acetone occurs to form intermediate **10**. Finally, the latter intermediate undergoes 5-*exo-dig* cyclization to form the highly substituted iminofuranone **4** as the product.

In summary, the multicomponent reaction between two molecules of isocyanide, alkylidene-substituted *Meldrum*'s acid and arylcarboxylic acids provide a simple one-pot entry to the synthesis of furanones. The advantages of this route are that the reaction can be performed under neutral conditions at room temperature, and that no activation or modification of the starting materials is needed. The simplicity of this protocol makes it a suitable alternative to complex multistep approaches.

Scheme 2. *Proposed Mechanism for the Reaction*



Experimental Part

General. *Meldrum*'s acid and isocyanides were obtained from *Fluka* (Buchs, Switzerland) and used without further purification. M.p.: *Electrothermal 9100* apparatus; uncorrected. IR Spectra: *FT-IR 102MB BOMEM* spectrometer; $\tilde{\nu}$ in cm^{-1}. ^1H- and ^{13}C-NMR spectra: *Bruker DRX-300 Avance* instrument; in $CDCl_3$ at 300.1 and 75.47 MHz, resp.; δ in ppm, J in Hz. MS: *Finnigan-MAT-8430* mass spectrometer at 70 eV; in m/z (rel. %). Elemental analyses (C, H, N): *Heraeus CHN-S-O-Rapid* analyzer.

*(2*E*)-4-{1-[(*tert*-Butyl)amino]-2-methyl-1-oxopropan-2-yl}-2-[(*tert*-butyl)imino]-2,5-dihydro-5-oxofuran-3-yl 4-Bromobenzoate* (**4a**). *Typical Procedure.* To a magnetically stirred soln. of isopropylidene-substituted *Meldrum*'s acid **2a** (0.18 g, 1 mmol) and 4-bromobenzoic acid (0.20 g, 1 mmol) in CH_2Cl_2 (10 ml) and a few drops of DMSO was added dropwise a soln. of *tert*-butyl isocyanide (0.22 ml, 2 mmol) in CH_2Cl_2 at r.t. within 5 min. The mixture was kept at r.t. for 48 h. The solvent was removed under reduced pressure, and the residue was extracted with AcOEt and cold MeOH and filtered. The solvent was evaporated at reduced pressure, and **4a** was obtained. Yield: 320 mg (65%). White powder. M.p. 174–176°. IR (KBr): 3216, 3065, 2873, 1769, 1744, 1693, 1670, 1582, 1460, 1346, 1253, 1165, 1138, 1041, 838, 740. ^1H-NMR: 1.39 (*s*, 2 Me); 1.41 (*s*, ^{t}Bu); 1.62 (*s*, ^{t}Bu); 7.63, 7.97 (*AA′BB′*, $J = 9$, 4 CH); 9.59 (*s*, NH). ^{13}C-NMR: 22.8; 28.3; 28.4; 44.5; 52.1; 59.6; 127.0; 128.5; 129.5; 131.9; 132.2; 150.0; 157.3; 164.0; 169.4; 180.0. EI-MS: 495 (4, M^+), 493 (4, M^+), 394 (5), 392 (5), 364 (3), 292 (9), 236 (10), 185 (88), 183 (100), 157 (11), 154 (16), 57 (20), 41 (12). Anal. calc. for $C_{23}H_{29}BrN_2O_5$ (493.39): C 55.99, H 5.92, N 5.68; found: C 55.87, H 6.01, N 5.59.

*(2*E*)-4-[1-(*tert*-Butylamino)-2-methyl-1-oxopropan-2-yl]-2-(*tert*-butylimino)-2,5-dihydro-5-oxofuran-3-yl 4-Chlorobenzoate* (**4b**). Yield: 269 mg (60%). White powder. M.p. 167–169°. IR (KBr): 3291, 3087, 2932, 1747, 1742, 1707, 1642, 1599, 1488, 1335, 1255, 1160, 1116, 1014, 845, 756. ^1H-NMR: 1.39 (*s*, 2 Me); 1.42 (*s*, ^{t}Bu); 1.62 (*s*, ^{t}Bu); 7.47, 8.05 (*AA′BB′*, $J = 9$, 4 CH); 9.58 (*s*, NH). ^{13}C-NMR: 22.8; 28.3; 28.4; 44.5; 52.1; 59.6; 126.7; 126.8; 129.2; 131.9; 132.0; 150.1; 157.4; 163.9; 169.4; 180.0. EI-MS: 449 (5, M^+), 376 (2), 350 (3), 348 (3), 320 (3), 292 (4), 236 (5), 155 (6), 141 (29), 139 (100), 113 (4), 111 (15), 57 (16), 41 (9). Anal. calc. for $C_{23}H_{29}ClN_2O_5$ (448.94): C 61.53, H 6.51, N 6.24; found: C 61.42, H 6.45, N 6.07.

*(2*E*)-4-{1-[(*tert*-Butyl)amino]-2-methyl-1-oxopropan-2-yl}-2-[(*tert*-butyl)imino]-2,5-dihydro-5-oxofuran-3-yl 4-Nitrobenzoate* (**4c**). Yield: 363 mg (79%). White powder. M.p. 176–178°. IR (KBr): 3216, 3060, 2997, 1777, 1748, 1693, 1667, 1624, 1567, 1531, 1461, 1363, 1347, 1219, 1162, 1136, 1042, 846, 701. ^1H-NMR: 1.41 (*s*, 2 Me); 1.42 (*s*, ^{t}Bu); 1.64 (*s*, ^{t}Bu); 8.28–8.36 (*m*, 4 CH); 9.87 (*s*, NH). ^{13}C-NMR: 22.9; 28.3; 28.4; 44.6; 52.2; 59.8; 123.9; 127.0; 128.5; 129.6; 133.8; 151.1; 156.8; 163.0; 169.3; 179.8. EI-MS: 459 (8, M^+), 387 (4), 361 (2), 359 (20), 331 (21), 303 (40), 292 (6), 236 (12), 155 (13), 150 (100), 104 (24), 92 (12), 76 (15), 57 (39), 56 (15), 41 (22). Anal. calc. for $C_{23}H_{29}N_3O_7$ (459.49): C 60.12, H 6.36, N 9.14; found: C 60.62, H 6.77, N 8.81.

*(2*E*)-4-{1-[(*tert*-Butyl)carbamoyl]-4-methylcyclohexyl}-2-[(*tert*-butyl)imino]-2,5-dihydro-5-oxofuran-3-yl 4-Nitrobenzoate* (**4d**). Yield: 329 mg (64%). White powder. M.p. 187–189°. IR (KBr): 3305, 2956, 2921, 1750, 1744, 1706, 1646, 1605, 1559, 1535, 1524, 1458, 1336, 1260, 1181, 1117, 851, 718. ^1H-NMR: 0.88 (*d*, $J = 6.5$, Me); 1.42 (*s*, ^{t}Bu); 1.61 (*s*, ^{t}Bu); 1.10–2.09 (*m*, cyclohexyl); 8.29–8.39 (*m*, 4 CH); 9.48 (*s*, NH). ^{13}C-NMR: 22.2; 24.7; 28.2; 28.4; 29.9; 31.4; 46.1; 52.2; 59.3; 124.0; 128.7; 131.8; 133.7; 149.5; 151.2; 157.5; 162.9; 169.0; 178.3. EI-MS: 513 (7, M^+), 414 (3), 385 (5), 357 (12), 290 (5), 234 (7), 208 (12), 150 (100), 104 (19), 92 (11), 76 (7), 57 (29), 41 (8). Anal. calc. for $C_{27}H_{35}N_3O_7$ (513.58): C 63.14, H 6.87, N 8.18; found: C 62.99, H 7.02, N 8.02.

*(2*E*)-4-{1-[(*tert*-Butyl)carbamoyl]cyclohexyl}-2-[(*tert*-butyl)imino]-2,5-dihydro-5-oxofuran-3-yl 4-Nitrobenzoate* (**4e**). Yield: 364 mg (73%). White powder. M.p. 173–175°. IR (KBr): 3218, 3063, 2975, 2935, 1761, 1742, 1694, 1668, 1619, 1566, 1529, 1459, 1362, 1260, 1183, 1118, 1050, 1010, 865, 847, 708. ^1H-NMR: 1.42 (*s*, ^{t}Bu); 1.63 (*s*, ^{t}Bu); 1.56–1.95 (*m*, cyclohexyl); 8.30–8.39 (*m*, 4 CH); 9.48 (*s*, NH). ^{13}C-NMR: 21.4; 24.8; 29.6; 28.4; 28.6; 46.5; 52.1; 59.3; 123.9; 128.8; 131.6; 133.7; 149.5; 151.1; 157.5; 162.8; 169.0; 178.3. EI-MS: 499 (5, M^+), 427 (8), 399 (8), 371 (5), 343 (18), 276 (7), 220 (7), 194 (14), 150 (100), 120 (5), 104 (19), 92 (6), 76 (6), 57 (29), 41 (13). Anal. calc. for $C_{26}H_{33}N_3O_7$ (499.56): C 62.51, H 6.66, N 8.41; found: C 63.07, H 7.00, N 8.09.

*(2*E*)-4-{1-[(*tert*-Butyl)carbamoyl]cyclopentyl}-2-[(*tert*-butyl)imino]-2,5-dihydro-5-oxofuran-3-yl 4-Bromobenzoate* (**4f**). Yield: 390 mg (75%). White powder. M.p. 201–203°. IR (KBr): 3222, 3060, 2974, 1759, 1741 1690, 1667, 1589, 1579, 1485, 1361, 1261, 1219, 1167, 1124, 1068, 997, 848, 739. ^{1}H-NMR: 1.42 (*s*, ^{t}Bu); 1.65 (*s*, ^{t}Bu); 1.46–2.06 (*m*, cyclopentyl); 7.64, 7.97 (*AA′BB′*, *J* = 9.2, 4 CH), 9.78 (*s*, NH). ^{13}C-NMR: 28.0; 28.3; 28.4; 28.7; 37.4; 53.0; 59.4; 127.3; 129.5; 129.7; 132.0; 132.2; 149.2; 157.3; 164.1; 169.9; 181.6. EI-MS: 520 (2, M^+), 518 (2, M^+), 518 (2), 420 (8), 418 (8), 318 (10), 262 (16), 206 (10), 185 (100), 183 (97), 180 (15), 157 (11), 153 (10), 76 (7), 57 (18), 41 (10). Anal. calc. for $C_{25}H_{31}BrN_2O_5$ (519.43): C 57.81, H 6.02, N 5.39; found: C 57.73, H 6.05, N 5.33.

*(2*E*)-4-[1-(Cyclohexylamino)-2-methyl-1-oxopropan-2-yl]-2-(cyclohexylimino)-2,5-dihydro-5-oxofuran-3-yl 4-Chlorobenzoate* (**4g**). Yield: 375 mg (75%). White powder. M.p. 196–198°. IR (KBr): 3270, 3092, 2956, 2936, 1746, 1711, 1669, 1639, 1592, 1569, 1451, 1402, 1368, 1257, 1230, 1163, 1099, 863, 755. ^{1}H-NMR: 1.22–2.24 (*m*, 2 cyclohexyl); 1.43 (*s*, Me); 1.53 (*s*, Me); 3.85 (br., CH); 4.12 (*tt*, J_{aa} = 12.0, J_{ae} = 3.7, CH), 7.05, 7.94 (*AA′BB′*, *J* = 9.2, 4 CH); 9.95 (*d*, *J* = 6, NH). ^{13}C-NMR: 22.7; 24.7; 25.8; 28.6; 32.4; 44.6; 49.5; 52.4; 126.7; 126.8; 129.2; 131.8; 132.0; 157.3; 159.2; 164.0; 168.4; 179.2. EI-MS: 501 (4, M^+), 376 (16), 363 (19), 344 (33), 140 (24), 139 (100). Anal. calc. for $C_{27}H_{33}ClN_2O_5$ (501.01): C 64.73, H 6.64, N 5.59; found: C 64.64, H 6.74, N 5.57.

*(2*E*)-4-{1-[(*tert*-Butyl)carbamoyl]-4-methylcyclohexyl}-2-[(*tert*-butyl)imino]-2,5-dihydro-5-oxofuran-3-yl 4-Chlorobenzoate* (**4h**). Yield: 392 mg (78%). White powder. M.p. 192–194°. IR (KBr): 3304, 3086, 2956, 2927, 1748, 1742, 1707, 1646, 1592, 1560, 1486, 1444, 1365, 1336, 1258, 1202, 1170, 1047, 1013, 844, 749. ^{1}H-NMR: 0.89 (*d*, *J* = 6.4, Me); 1.4–2.02 (*m*, cyclohexyl); 1.43 (*s*, ^{t}Bu); 1.65 (*s*, ^{t}Bu); 7.49, 8.06 (*AA′BB′*, *J* = 9.2, 4 CH); 9.03 (*s*, NH). ^{13}C-NMR: 22.3; 24.9; 28.3; 28.4; 30.3; 31.3; 45.9; 52.0; 59.1; 126.7; 127.9; 129.1; 131.9; 149.5; 151.2; 158.2; 163.7; 168.9; 178.6. EI-MS: 503 (3, M^+), 402 (3), 346 (3), 290 (7), 234 (5), 207 (8), 141 (35), 139 (100), 113 (4), 111 (12), 57 (13), 41 (6). Anal. calc. for $C_{27}H_{35}ClN_2O_5$ (503.03): C 64.47, H 7.01, N 5.57; found: C 64.36, H 6.96, N 5.46.

*(2*E*)-4-[1-(Cyclohexylcarbamoyl)cyclopentyl]-2-(cyclohexylimino)-2,5-dihydro-5-oxofuran-3-yl 4-Nitrobenzoate* (**4i**). Yield: 402 mg (75%). White powder. M.p. 166–168°. IR (KBr): 3269, 3062, 2932, 2856, 1761, 1740, 1691, 1664, 1634, 1529, 1450, 1409, 1373, 1354, 1247, 1182, 1149, 1019, 1052, 1010, 847, 709. ^{1}H-NMR: 1.29–2.12 (*m*, 2 cyclohexyl, cyclopentyl); 3.81 (br., CH); 4.10 (br., CH); 8.28–8.37 (*m*, 4 CH); 10.43 (*d*, *J* = 6, NH). ^{13}C-NMR: 24.6; 24.9; 25.8; 28.0; 28.6; 32.3; 35.6; 49.6; 52.4; 123.9; 131.7; 133.7; 149.0; 151.1; 156.8; 163.2; 168.8; 180.4. EI-MS: 537 (5, M^+), 413 (14), 411 (57), 370 (32), 288 (13), 262 (11), 235 (13), 180 (41), 152 (12), 150 (100), 104 (11). Anal. calc. for $C_{29}H_{35}N_3O_7$ (537.60): C 64.79, H 6.56, N 7.82; found: C 64.71, H 6.68, N 7.65.

*(2*E*)-4-{1-[(*tert*-Butyl)carbamoyl]cyclohexyl}-2-[(*tert*-butyl)imino]-5-oxo-2,5-dihydrofuran-3-yl 4-Bromobenzoate* (**4j**). Yield: 299 mg (56%). White powder. M.p. 184–185°. IR (KBr): 3434, 3066, 2967, 2927, 2853, 1745, 1701, 1675, 1587, 1532, 1459, 1366, 1260, 1229, 1150, 1121, 1043, 1005, 845, 751. ^{1}H-NMR: 1.43 (*s*, ^{t}Bu); 1.62 (*s*, ^{t}Bu); 1.42–1.95 (*m*, cyclohexyl); 7.68, 8.02 (*AA′BB′*, *J* = 9.2, 4 CH); 9.04 (*s*, NH). ^{13}C-NMR: 21.4; 24.8; 30.0; 28.3; 28.4; 46.3; 52.0; 59.0; 127.1; 128.6; 129.7; 131.9; 132.4; 149.6; 158.2; 164.8; 168.9; 179.6. EI-MS: 535 (4, M^+), 533 (4, M^+), 435 (2), 433 (2), 332 (4), 276 (7), 220 (6), 194 (12), 184 (78), 182 (100), 157 (12), 155 (12), 104 (5), 76 (5), 57 (17), 41 (8). Anal. calc. for $C_{26}H_{33}BrN_2O_5$ (533.45): C 58.54, H 6.24, N 5.25; found: C 58.42, H 6.10, N 5.19.

REFERENCES

[1] A. Dömling, *Chem. Rev.* **2006**, *106*, 17.
[2] A. Dömling, I. Ugi, *Angew. Chem., Int. Ed.* **2000**, *39*, 3168.
[3] I. Ugi, 'Isonitrile Chemistry', Academic Press, London, 1971.
[4] J. Zhu, H. Bienaymé, 'Multicomponent Reactions', Wiley-VCH, Weinheim, 2005.
[5] V. Nair, R. S. Menon, V. Sreekumar, *Pure Appl. Chem.* **2005**, *77*, 1191.
[6] M. D. Burke, S. L. Schreiber, *Angew. Chem., Int. Ed.* **2004**, *43*, 46.
[7] C.-Y. Wu, C.-F. Chang, J. S.-Y. Chen, C.-H. Wong, C.-H. Lin, *Angew. Chem., Int. Ed.* **2003**, *42*, 4661.
[8] D. R. Spring, S. Krishnan, H. E. Blackwell, S. L. Schreiber, *J. Am. Chem. Soc.* **2002**, *124*, 1354.
[9] H. McNab, *Chem. Soc. Rev.* **1978**, *7*, 345.

[10] B.-C. Chen, *Heterocycles* **1991**, *32*, 529.
[11] A. S. Ivanov, *Chem. Soc. Rev.* **2008**, *37*, 789.
[12] I. Yavari, A. Habibi, M. R. Hosseini-Tabatabaei, H. R. Bijanzadeh, *Monatsh. Chem.* **2003**, *134*, 1651.
[13] I. Yavari, A. Habibi, *Synthesis* **2004**, *7*, 989.
[14] A. Habibi, E. Sheikhosseini-Lory, A. Shockravi, *Tetrahedron Lett.* **2009**, *50*, 1075.
[15] A. Habibi, L. Mousavifar, I. Yavari, M. R. Yazdanbakhsh, *Monatsh. Chem*. **2007**, *138*, 603.
[16] A. Habibi, L. Mousavifar, M. R. Yazdanbakhsh, I. Yavari, *Synth. Commun*. **2008**, *38*, 873.
[17] Q.-H. Chen, P. N. P. Rao, E. E. Knaus, *Bioorg. Med. Chem.* **2006**, *14*, 7898.
[18] A. E. Rubtsov, N. V. Kovylyaeva, V. V. Zalesov, *Pharm. Chem. J.* **2005**, *39*, 11.
[19] D. Matiadis, K. C. Prousis, O. Igglessi-Markopoulou, *Molecules* **2009**, *14*, 3914.
[20] D. Iannazzo, A. Piperno, G. Romeo, R. Romeo, U. Chiacchio, A. Rescifina, E. Balestrieri, B. Macchi, A. Mastino, R. Cortese, *Bioorg. Med. Chem*. **2008**, *16*, 9610.

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