

Synthesis of 2-Aryl-5-oxo-4-[2-(phenylmethylidene)hydrazino]-2,5-dihydro-1H-pyrrole-3-carboxylates by the Reaction between Hydrazones, Acetylenedicarboxylates, and 1-Aryl-*N,N'*-bis(arylmethylidene)methanediamines

by **Abdolali Alizadeh***, **Vahid Saberi**, and **Javad Mokhtari**

Department of Chemistry, Tarbiat Modares University, P.O. Box 14115-175, Tehran, Iran
(phone: +98-21-88006631; fax: +98-21-88006544; e-mail: abdol_alizad@yahoo.com, aalizadeh@Modares.ac.ir)

An efficient approach for the preparation of functionalized 2-aryl-2,5-dihydro-5-oxo-4-[2-(phenylmethylidene)hydrazino]-1H-pyrroles is described. The four-component reaction between aldehydes, $\text{NH}_2\text{NH}_2 \cdot \text{H}_2\text{O}$, dialkyl acetylenedicarboxylates, and 1-aryl-*N,N'*-bis(arylmethylidene)methanediamines proceeds in EtOH under reflux in good-to-excellent yields (*Scheme 1*). The structures of **4** were corroborated spectroscopically (IR, ^1H - and ^{13}C -NMR, and EI-MS, and, in the case of **4f**, by X-ray crystallography). A plausible mechanism for this type of reaction is proposed (*Scheme 2*).

Introduction. – Multicomponent reactions (MCRs) are excellent strategies, employed in the synthesis of many natural products. These MCRs are generally defined as reactions where more than two starting materials react to form a product, incorporating more or less atoms of all the starting materials [1].

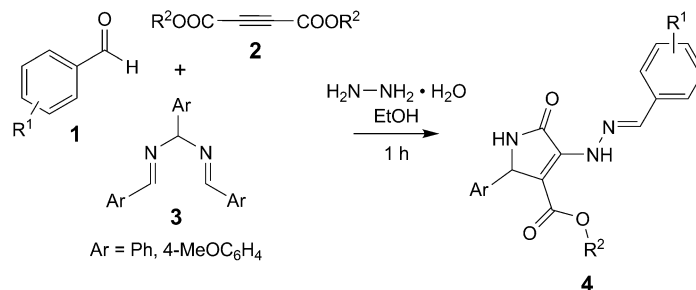
Pyrrole and its derivatives such as dihydro-2-oxopyrroles and pyrrolidines are important structural motifs that are found in natural and unnatural products [2]. 2-Oxopyrroles show high versatility, and they are important substructures in a variety of pharmaceutical drugs, including products active against viral infections (HIV, influenza, cytomegalovirus), anticancer agents, and products active against microbiological diseases (bacterial or fungal) [3].

Hydrazones have also been demonstrated to possess, among others, antimicrobial, anticonvulsant, analgesic, anti-inflammatory, antiplatelet, antitubercular, and antitumor activities [4]. Also hydrazone-based coupling methods are used in medical biotechnology to couple drugs to targeted antibodies, *e.g.*, antibodies against a certain type of cancer cell. The hydrazone-based bond is stable at neutral pH (in the blood), but is rapidly destroyed in the acidic environment of lysosomes of the cell. The drug is thereby released in the cell, where it exerts its function [5]. Inspired by the above findings and in continuation of our ongoing research program in the field of synthesis of medicinally relevant compounds [6], we herein report a synthesis of novel hydrazone derivatives with 2-oxopyrrole building blocks.

We previously investigated the reactions of 1-aryl-*N,N'*-bis(arylmethylidene)methanediamine **3** with heterocyclic ketene amins and isocyanides in *Ugi* reaction, respectively [7], for the synthesis of new heterocyclic compounds. Now, we have

developed a novel, one-pot synthesis of 2-aryl-2,5-dihydro-5-oxo-4-[2-(phenylmethylenidene)hydrazino]-1H-pyrroles using $\text{NH}_2\text{NH}_2 \cdot \text{H}_2\text{O}$, different aldehydes **1**, dialkyl acetylenedicarboxylates **2**, and 1-aryl-*N,N'*-bis(arylmethylidene)methanediamines **3** (Scheme 1).

Scheme 1. Synthesis of 2-Aryl-2,5-dihydro-5-oxo-4-[2-(phenylmethylenidene)hydrazino]-1H-pyrroles



Results and Discussion. – For this purpose, 1 equiv. of **1** was reacted with 1 equiv. of **2** and 1 equiv. **3** in presence of hydrazine hydrate in refluxing EtOH to yield 2-aryl-2,5-dihydro-5-oxo-4-[2-(phenylmethylenidene)hydrazino]-1H-pyrroles **4** in *ca.* 80% yield. We have shown that the use of various substituted aldehydes **1** in this reaction makes it possible the synthesis of libraries of **4** under the same conditions. The results are compiled in the Table. Irrespective of the presence of a MeO substituent in the *para*-positions of **3**, the reactions proceeded fairly well and afforded the desired products in good-to-excellent yields (Entries 4 and 5, Table). An electron withdrawing substituent in *meta*-position of the aldehyde (3- NO_2) afforded the desired products in a lower yield (Entry 7, Table), and electron-releasing substituents in *para*-position afforded the desired products in high yields (Entries 3 and 5, Table).

The structures of compounds **4a–4h** were deduced from their elemental analyses, IR, and high-field ^1H - and ^{13}C -NMR spectra. The structure of product **4f** was further confirmed by X-ray crystallographic analysis (Fig.). The mass spectrum of **4a** displayed the molecular-ion peak at m/z 335, which is in agreement with the proposed structure. The IR spectrum of this compound showed absorption bands due to the NH group at

Table. Synthesis of Functionalized 2-Aryl-2,5-dihydro-5-oxo-4-[2-(phenylmethylenidene)hydrazino]-1H-pyrroles **4**. Time, 1 h.

Entry	4	R ¹	R ²	Ar	Yield [%]
1	4a	H	Me	Ph	81
2	4b	4-Cl	Me	Ph	82
3	4c	4-MeO	Me	Ph	85
4	4d	H	Me	4-MeO-C ₆ H ₄	82
5	4e	4-MeO	Me	4-MeO-C ₆ H ₄	84
6	4f	4-Me	Me	Ph	83
7	4g	3-NO ₂	Me	Ph	74
8	4h	H	Et	Ph	80

3301 and 3036, COOMe group at 1709, C=N group at 1650, and the Ph group at 1561 and 1445 cm^{-1} . The ^1H -NMR spectrum of **4a** showed three *singlet* signals for the MeO, CH-NH, and N=CH groups at $\delta(\text{H})$ 3.64, 5.30, and 7.85, respectively, and of two NH groups at 6.44 and 9.90 ppm, and the aromatic moieties gave rise to *multiplets* in the aromatic region of the spectrum (7.26–7.73 ppm). The ^1H -decoupled ^{13}C -NMR spectrum of **4a** displayed 15 distinct resonances in agreement with the suggested structure.

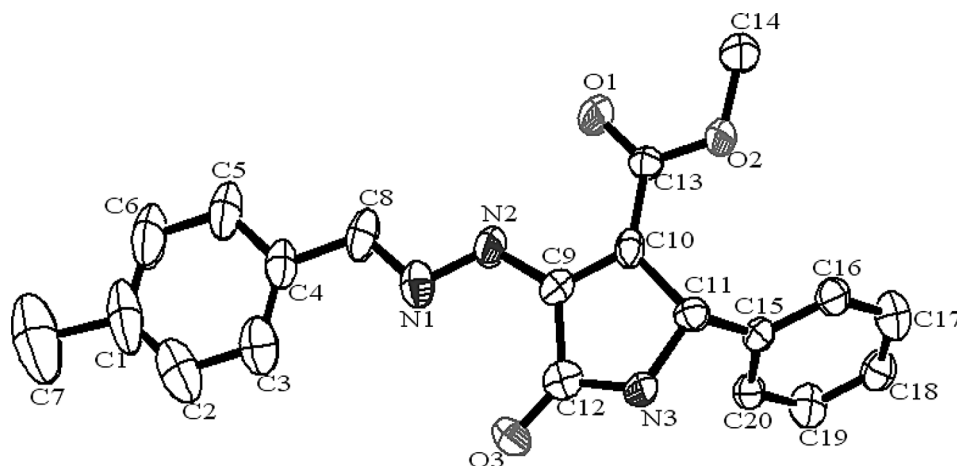
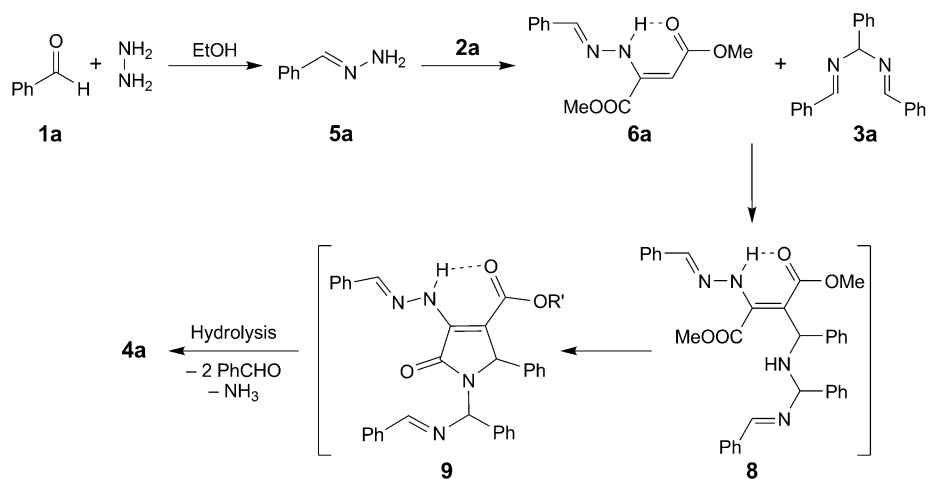


Figure. X-Ray crystal structure of compound **4f**

Although we have not established the mechanism of the reaction experimentally, a proposal is outlined in *Scheme 2*.

Scheme 2. Proposed Mechanism for the Formation of Compound **4** (exemplified for **4a**)



Compound **4a** could result from the initial formation of hydrazone **5a** and subsequent attack on dimethyl acetylenedicarboxylate (**2a**) to yield hydrazino-carboxylate **6a**. Then, the reaction between **6a** and compound **3a**, which was obtained from the reaction of aldehyde **1a** with NH_3 solution [8], gives the intermediate **8**, which undergoes successive intramolecular cyclization, followed by hydrolysis, to give compound **4a**. The solvent has an important effect on the configuration of compound **6**. In a protic solvent, the (*Z*)/(*E*) ratio is 95 : 5, and in an aprotic solvent, this ratio is 2 : 98 [9].

In conclusion, we have developed a novel four-component reaction leading to 2-aryl-2,5-dihydro-5-oxo-4-[2-(phenylmethylidene)hydrazino]-1*H*-pyrroles **4** from the simple synthons $\text{NH}_2\text{NH}_2 \cdot \text{H}_2\text{O}$, aldehydes, NH_3 , and acetylenedicarboxylates. The high yields, mild reaction conditions, the ease of purification, and commercial availability of the synthons render this an ecologically friendly procedure for the synthesis of **4**. This protocol does not only provide a novel and effective methodology for synthesis but also opens a new way for employing hydrazone intermediates to design other similar multicomponent reactions. Further extension of the scope and synthetic applications of this methodology are in progress in our laboratory.

Financial support of this work by the Tarbiat Modares University, Iran, is gratefully acknowledged.

Experimental Part

General. The reagents and solvents were obtained from *Fluka* (CH-Buchs) and used without further purification. M.p.: *Electrothermal 9100* apparatus. IR Spectra: *Shimadzu IR-460* spectrometer. ^1H - and ^{13}C -NMR spectra: at 500.1 and 125.7 MHz, resp., on a *BRUKER DRX 500-AVANCE* FT-NMR instrument in CDCl_3 as solvent. MS: *FINNIGAN-MAT 8430* mass spectrometer, operating at an ionization potential of 70 eV.

General Procedure (exemplified for **4a**). A soln. of benzaldehyde (**1a**; 0.106 g, 1 mmol) and $\text{NH}_2\text{NH}_2 \cdot \text{H}_2\text{O}$ (0.32 g, 1 mmol) was magnetically stirred in 5 ml of EtOH for 10 min. Then, a soln. of dimethyl acetylenedicarboxylate (**2a**; 0.142 g, 1 mmol) was added, and the mixture was stirred for 30 min at r.t. Finally, 1-phenyl-*N,N'*-bis(phenylmethylidene)methanedianiline (**3a**; 0.298 g, 1 mmol) was added, and the mixture was stirred for 1 h under reflux, and the progress of the reaction was followed by TLC. After completion, the mixture was cooled to r.t., and a pale-yellow solid precipitated. The precipitate was filtered and washed with Et_2O to give **4a** in 81% yield. All products gave satisfactory spectroscopic data in accordance with the assigned structures.

Methyl 4-[(2*E*)-2-Benzylidenehydrazinyl]-2,5-dihydro-5-oxo-2-phenyl-1*H*-pyrrole-3-carboxylate (4a**).** Yield: 0.32 g (81%). Pale-yellow powder. M.p. 179–182°. IR: 3301 (NH), 3063 (NH), 1709 (COOMe), 1650 (C=N), 1620 (NC=O), 1260 (C–O of ester). ^1H -NMR: 3.64 (s, 3 H); 5.30 (s, 1 H); 6.44 (s, 1 H); 7.26–7.34 (m, 5 H); 7.36–7.40 (m, 3 H); 7.73 (d, *J* = 6.8, 2 H); 7.85 (s, 1 H); 9.90 (s, 1 H). ^{13}C -NMR: 51.4; 57.8; 108.6; 127.2; 127.3; 128.4; 128.6; 128.69; 129.8; 134.0; 137.8; 142.6; 144.8; 165.3; 165.3. EI-MS (70 eV): 335 (36, M^+), 276 (71), 232 (47), 173 (81), 129 (39), 104 (100), 77 (90), 55 (53). Anal. calc. for $\text{C}_{19}\text{H}_{17}\text{N}_3\text{O}_3$ (335.36): C 68.05, H 5.11, N 12.53; found: C 68.10, H 5.19, N 12.59.

Methyl 4-[(2*E*)-2-(4-Chlorobenzylidene)hydrazinyl]-2,5-dihydro-5-oxo-2-phenyl-1*H*-pyrrole-3-carboxylate (4b**).** Yield: 0.33 g (79%). Pale-yellow powder. M.p. 178–181°. IR: 3182 (NH), 3030 (NH), 1720 (COOMe), 1612 (NC=O), 1224 (C–O of ester). ^1H -NMR: 3.69 (s, 3 H); 4.35 (s, 1 H); 6.58 (s, 1 H); 7.08–7.55 (m, 9 H); 7.86 (s, 1 H); 11.68 (s, 1 H). ^{13}C -NMR: 51.1; 56.5; 105.6; 124.9; 127.7; 127.8; 128.1; 128.2; 129.6; 130.5; 133.8; 142.9; 147.3; 160.3; 164.0. EI-MS (70 eV): 369 (20, M^+), 368 (50), 313 (16), 236 (32), 142 (20), 123 (27), 97 (65), 69 (100). Anal. calc. for $\text{C}_{19}\text{H}_{16}\text{ClN}_3\text{O}_3$ (369.80): C 61.71, H 4.36, N 11.36; found: C 61.75, H 4.39, N 11.40.

Methyl 2,5-Dihydro-4-[(2E)-2-(4-methoxybenzylidene)hydrazinyl]-5-oxo-2-phenyl-1H-pyrrole-3-carboxylate (4c). Yield: 0.32 g (75%). Pale-yellow powder. M.p. 178–181°. IR (KBr): 3304 (NH), 1707 (COOMe), 1649 (C=N), 1613 (NC=O), 1254 (C–O of ester). ¹H-NMR: 3.62 (s, 3 H); 3.83 (s, 3 H); 5.26 (s, 1 H); 6.60 (s, 1 H); 6.90 (d, *J* = 8.0, 2 H); 7.25–7.28 (m, 5 H); 7.66 (d, *J* = 8.0, 2 H); 7.85 (s, 1 H); 9.91 (s, 1 H). ¹³C-NMR: 51.4; 55.4; 57.8; 107.6; 114.2; 127.3; 128.4; 128.6; 128.8; 129.9; 133.9; 137.9; 144.9; 161.1; 165.4; 165.4. EI-MS (70 eV): 365 (1, *M*⁺), 349 (61), 335 (19), 290 (100), 276 (36), 231 (32), 199 (22), 173 (86), 128 (32), 118 (49), 104 (77), 91 (45), 77 (45), 65 (20), 51 (16). Anal. calc. for C₂₀H₁₉N₃O₄ (365.38): C 65.74, H 5.24, N 11.50; found: C 65.80, H 5.32, N 11.62.

Methyl 4-[(2E)-2-Benzylidenehydrazinyl]-2,5-dihydro-2-(4-methoxyphenyl)-5-oxo-1H-pyrrole-3-carboxylate (4d). Yield: 0.33 g (82%). Yellow powder. M.p. 167–179°. IR (KBr): 3340 (NH), 1708 (COOMe), 1640 (C=N), 1621 (NC=O), 1248 (C–O of ester). ¹H-NMR: 3.64 (s, 3 H); 3.78 (s, 3 H); 5.23 (s, 1 H); 6.76 (s, 1 H); 6.83 (d, *J* = 8.0, 2 H); 6.90 (d, *J* = 8.3, 1 H); 7.19 (d, *J* = 8.0, 2 H); 7.37 (d, *J* = 7.0, 2 H); 7.66 (d, *J* = 8.3, 1 H); 7.71 (d, *J* = 7.0, 1 H); 7.85 (s, 1 H); 9.88 (s, 1 H). ¹³C-NMR: 51.3; 55.4; 57.44; 108.0; 114.2; 127.2; 128.4; 128.7; 128.9; 129.8; 134.0; 142.4; 144.7; 159.5; 165.4; 165.6. EI-MS (70 eV): 365 (1, *M*⁺), 257 (12), 149 (24), 137 (23), 123 (20), 109 (20), 95 (37), 81 (77), 69 (100), 55 (57). Anal. calc. for C₂₀H₁₉N₃O₄ (365.38): C 65.74, H 5.24, N 11.50; found: C 65.81, H 5.32, N 11.58.

Methyl 2,5-Dihydro-4-[(2E)-2-(4-methoxybenzylidene)hydrazinyl]-2-(4-methoxyphenyl)-5-oxo-1H-pyrrole-3-carboxylate (4e). Yield: 0.36 g (76%). Pale-yellow powder. M.p. 177–179°. IR: 3338 (NH), 1706 (COOMe), 1650 (C=N), 1616 (C=O), 1251 (C–O of ester). ¹H-NMR: 3.63 (s, 3 H); 3.79 (s, 3 H); 3.83 (s, 3 H); 5.23 (s, 1 H); 6.32 (s, 1 H); 6.84 (d, *J* = 8.4, 2 H); 6.90 (d, *J* = 8.4, 2 H); 7.19 (d, *J* = 8.4, 2 H); 7.66 (d, *J* = 8.4, 2 H); 7.79 (s, 1 H); 9.79 (s, 1 H). ¹³C-NMR: 51.3; 55.3; 55.4; 57.3; 107.8; 114.0; 114.2; 126.7; 128.4; 128.8; 129.7; 137.9; 144.7; 159.5; 161.1; 161.1; 165.3. EI-MS (70 eV): 395 (16, *M*⁺), 368 (16), 336 (24), 303 (20), 288 (40), 268 (32), 203 (53), 161 (38), 134 (89), 97 (53), 83 (57), 69 (73), 57 (100). Anal. calc. for C₂₁H₂₁N₃O₅ (395.40): C 63.79, H 5.35, N 10.63; found: C 63.85, H 5.39, N 10.68.

Methyl 2,5-Dihydro-4-[(2E)-2-(4-methylbenzylidene)hydrazinyl]-5-oxo-2-phenyl-1H-pyrrole-3-carboxylate (4f). Yield: 0.32 g (80%). Pale-yellow powder. M.p. 179–182°. IR: 3301 (NH), 1708 (COOMe), 1649 (C=N), 1617 (C=O), 1258 (C–O of ester). ¹H-NMR: 2.37 (s, 3 H); 3.63 (s, 3 H); 5.26 (s, 1 H); 6.32 (s, 1 H); 7.20–7.37 (m, 9 H); 7.85 (s, 1 H); 9.89 (s, 1 H). ¹³C-NMR: 21.5; 51.4; 57.8; 106.0; 127.3; 128.6; 128.7; 129.4; 131.2; 137.7; 140.2; 144.9; 145.1; 165.0; 167.5. EI-MS (70 eV): 349 (8, *M*⁺), 335 (8), 290 (12), 276 (12), 232 (20), 173 (100), 118 (53), 104 (88), 91 (32), 77 (46), 57 (40). Anal. calc. for C₂₀H₁₉N₃O₃ (349.38): C 68.75, H 5.48, N 12.03; found: C 68.87, H 5.57, N 12.12. Crystal data for **4f** C₂₀H₁₉N₃O₃ (CCDC-927914): *M*_r 349.38, *a* = 6.1557(6) Å, *b* = 7.3821(7) Å, *c* = 19.4275(19) Å, *α* = 90.00° = 89.971(8), *γ* = 90.00°, *V* = 882.82(15) Å³, *Z* = 2, *F*(000) = 368, radiation, MoK_α (*λ* = 0.71073 Å), 3.15 ≤ 2 θ ≤ 25.05, intensity data were collected at 295(2) K with a Bruker APEX area-detector diffractometer, and employing $\omega/2\theta$ scanning technique, in the range of $-7 \leq h \leq 6$, $-8 \leq k \leq 8$, $-23 \leq l \leq 22$; the structure was solved by a direct method, all non-H-atoms were positioned, and anisotropic thermal parameters were refined from 3831 observed reflections with *R*(into) = 0.1055 by a full-matrix least-squares technique converged to *R* = 0.0752 and *R*_w = 0.1834 [*I* > 2 σ (*I*)].

Methyl 2,5-Dihydro-4-[(2E)-2-(3-nitrobenzylidene)hydrazinyl]-5-oxo-2-phenyl-1H-pyrrole-3-carboxylate (4g). Yield: 0.32 g (83%). Pale-yellow powder. M.p. 170–173°. IR: 3419 (NH), 1719 (COOMe), 1626 (C=O), 1529 (NO₂), 1267 (C–O of ester). ¹H-NMR: 3.68 (s, 3 H); 5.72 (s, 1 H); 6.57 (s, 1 H); 6.70–7.17 (m, 7 H); 7.79 (m, 1 H); 8.31 (m, 1 H); 8.69 (s, 1 H); 11.61 (s, 1 H). ¹³C-NMR: 51.1; 56.5; 105.6; 123.1; 124.8; 126.3; 127.7; 128.1; 128.8; 131.1; 134.9; 135.7; 147.3; 148.7; 161.0; 164.3; 164.3. EI-MS (70 eV): 368 (5), 298 (81), 281 (32), 252 (44), 234 (28), 176 (100), 149 (26), 130 (61), 103 (69), 89 (67), 76 (90), 63 (40), 50 (35). Anal. calc. for C₁₉H₁₆N₄O₅ (380.35): C 60.00, H 4.24, N 14.73; found: C 60.12, H 4.33, N 14.84.

Ethyl 4-[(2E)-2-Benzylidenehydrazinyl]-2,5-dihydro-5-oxo-2-phenyl-1H-pyrrole-3-carboxylate (4h). Yield: 0.33 g (80%). Pale-yellow powder. M.p. 190–193°. IR: 3413 (NH), 3309 (NH), 1702 (CO₂Et), 1635 (C=N), 1620 (NC=O), 1253 (C–O of ester). ¹H-NMR: 1.07 (t, *J* = 7.2, 3 H); 4.06 (q, *J* = 7.2, 2 H); 5.26 (s, 1 H); 6.70 (s, 1 H); 7.28–7.38 (m, 8 H); 7.71 (d, *J* = 7.5, 2 H); 7.83 (s, 1 H); 9.99 (s, 1 H). ¹³C-NMR: 14.0; 57.8; 60.3; 108.8; 127.3; 127.4; 128.3; 128.5; 128.7; 129.8; 134.0; 137.8; 142.9; 144.7; 165.1; 165.5. EI-MS (70 eV): 349 (31, *M*⁺), 276 (72), 256 (15), 236 (23), 173 (43), 149 (65), 137 (32), 123 (32),

111 (32), 97 (57), 81 (97), 69 (100), 57 (73). Anal. calc. for $C_{20}H_{19}N_3O_3$ (349.39): C 68.75, H 5.48, N 12.03; found: C 68.86, H 5.56, N 12.14.

REFERENCES

- [1] A. Dömling, in 'Multicomponent Reactions', Eds. J. Zhu, H. Bienayme, Wiley-VCH, Weinheim, 2005.
- [2] E. Bellur, P. Langer, *Tetrahedron Lett.* **2006**, 47, 2151.
- [3] M. L. Barreca, A. Rao, L. De Luca, M. Zappalà, C. Gurnari, P. Monforte, E. De Clercq, B. Van Maele, Z. Debyser, M. Witvrouw, J. M. Briggs, A. J. Chimirri, *J. Chem. Inf. Comput. Sci.* **2004**, 44, 1450; Y. Ishihara, S. Imamura, S. Hashiguchi, O. Nishimura, N. Kanzaki, M. Baba, World Patent WO 2,000,066,551, 2000; N. Kolocouris, A. Kolocouris, G. B. Foscolos, G. Fytas, J. Neyts, E. Padalko, J. Balzarini, R. Snoeck, G. Andrei, E. De Clercq, *J. Med. Chem.* **1996**, 39, 3307; T. Wunberg, J. Baumeister, U. Betz, A. Jensen, S. Nikolic, J. Reefsclaeger, H. Zimmermann, F. Zumppe, R. Grosser, G. Kleymann, W. Bender, K. Henninger, G. Hewlett, J. Keldenich, World Patent WO 2,003,097,595, 2003; V. O. Koz'minykh, N. M. Igidov, S. S. Zykhova, V. E. Kolla, N. S. Shuklina, T. Odegova, *Pharm. Chem. J., Khim. Farm. Zh.* **2002**, 36, 188; T. A. Silina, V. L. Gein, L. F. Gein, E. V. Voronina, *Pharm. Chem. J., Khim. Farm. Zh.* **2003**, 37, 585; V. L. Gein, E. V. Voronina, T. E. Ryumina, G. N. Novoselova, K. D. Potemkin, Y. S. Andreichikov, *Khim. Farm. Zh.* **1996**, 30, 25; F. Lovren, I. D. Gaon, B. Bobarevic, *Arch. Pharm. (Weinheim, Ger.)* **1989**, 323, 901.
- [4] S. Rollas, N. Gulerman, H. Erdeniz, *Il Farmaco* **2002**, 57, 171.
- [5] A. M. Wu, P. D. Senter, *Nat. Biotechnol.* **2005**, 23, 1137.
- [6] A. Alizadeh, J. Mokhtari, *Tetrahedron* **2011**, 67, 3519; A. Alizadeh, J. Mokhtari, *Helv. Chim. Acta* **2011**, 94, 1315; A. Alizadeh, A. Rezvanian, J. Mokhtari, *Synthesis* **2011**, 3491; A. Alizadeh, A. Rezvanian, L.-G. Zhu, *Tetrahedron* **2010**, 66, 6924; A. Alizadeh, A. Rezvanian, L.-G. Zhu, *J. Org. Chem.* **2012**, 77, 4385.
- [7] A. Alizadeh, J. Mokhtari, *Synth. Commun.* **2012**, 42, 686; A. Alizadeh, J. Mokhtari, M. Ahmadi, *Tetrahedron* **2012**, 68, 319.
- [8] B. Kaboudin, T. Ghasemi, T. Yokomatsu, *Synthesis* **2009**, 3089.
- [9] Q. Zhu, H. Jiang, J. Li, M. Zhang, X. Wang, C. Qi, *Tetrahedron* **2009**, 65, 4604.

Received March 9, 2013