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Synthesis and NMR spectral assignments of novel 1,4-benzothiazepine-5-one derivatives

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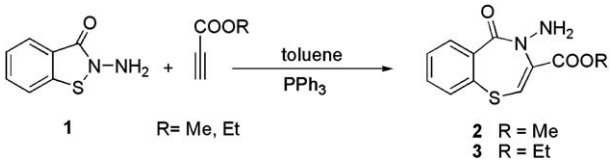
Heterocyclic ring expansion
One-pot reaction

ABSTRACT

The one-pot reaction between 2-aminobenzo[*d*]isothiazol-3-one and alkyl propiolates in presence of triphenylphosphine leads to the corresponding alkyl 4-amino-5-oxobenzo[*f*][1,4]thiazepine-3-carboxylates. A plausible mechanism of the reaction is proposed and unambiguous evidence for the structures is obtained from a detailed magnetic resonance spectral analysis. 1D and 2D NMR spectra such as COSY, ^{1}H–^{13}C and ^{1}H–^{15}N HSQC and HMBC heteronuclear correlations and an INADEQUATE experiment are reported and discussed.

1. Introduction

The chemical modification of heterocyclic systems offers a continuous challenge for the medicinal chemists in search of compounds with bio-pharmacological activity. It is known that benzo[*d*]isothiazole-3-ones are a class of compounds with a wide spectrum of biological activity but they can be also considered relatively unexplored with respect to both their chemical reactivity and biological activity.[1,2] Pursuing our research on benzisothiazoles we have synthesized a variety of novel 2-aminobenzo[*d*]isothiazole-3-one derivatives which were demonstrated to be endowed with significant biological properties.[3–5] In this context, recently, we have explored the one-pot reaction between 2-aminobenzo[*d*]isothiazol-3-one (ABO) **1** and dimethyl acetylenedicarboxylate in the presence of triphenylphosphine (PPh_3) that afforded a new functionalized tricyclic compound, namely 3-*H*-benzo[*d*]pyrazolo[1,5-*b*]isothiazole-2,3a-dicarboxylic acid dimethyl ester.[6] In our efforts to further exploit PPh_3 promoted reactions between 2-aminobenzo[*d*]isothiazol-3-one and activated acetylenes, we herein report a new synthesis of alkyl 4-amino-5-oxo-4,5-dihydrobenzo[*f*][1,4]thiazepine-3-carboxylates **2** and **3** obtained, through heterocyclic ring expansion, from ABO and alkyl propiolates (Fig. 1).



1 R= Me, Et

2 R = Me
3 R = Et

Figure 1. Synthesis of **2** and **3**.

In this paper we also present the detailed NMR spectral characterisation of the new heterocyclic compounds. Additional ^{1}H NMR and ^{13}C NMR data on the previously reported starting compound **1**[7] and on methyl 4-amino-5-oxo-2,3,4,5-tetrahydrobenzo[*f*][1,4]thiazepine-3-carboxylate **4** are given and were used for comparison purposes.

2. Results and discussion

2.1. Synthesis

Reactions are known in which highly reactive alkylidenephosphoranes undergo Michael addition to produce stabilised phosphorus ylides, which can give a variety of final products interesting for their synthetic and biological value.[6,8–12]

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The reaction of both methyl and ethyl propiolate with 2-aminobenzo[*d*]isothiazol-3-one (**1**) in presence of PPh_3 in toluene, at room temperature, was completed within one hour. The TLC of the crude reaction mixture clearly indicated the complete consumption of **1**, the formation of product **2** or **3** and the presence of PPh_3. Products other than **2** or **3** could not be detected. These compounds were separated by column cromatography and their structures were deduced from their elemental analysis and from IR and NMR spectroscopic data. The mass spectra displayed molecular ion peaks at appropriate *m*/*z* values. The IR spectrum indicated the presence of unreacted NH_2 and C=O groups. The ^1H–^{15}N NMR spectra confirmed the presence of the NH_2 group and of a nitrogen atom linked to a C=O group.

On the basis of the chemistry of trivalent phosphorus nucleophiles, a plausible mechanism might be advanced to rationalise products formation with ring expansion. Presumably the dipolar intermediate, formed by a Michael addition of triphenylphosphine to alkyl propiolate, reacts with the nitrogen atom of the isothiazole ring that is susceptible to nucleophilic attack when activated as for the adjacent carbonyl group. The nucleophilic attack to nitrogen is accompanied by the cleavage of the N–S bond to give an open-chain adduct which further reacts with a nucleophilic attack of the sulphur to the electrophilic centre (C-2 carbon) of the betainic intermediate. Thus, an intramolecular cyclocondensation with ring expansion occurs and, with the elimination of PPh_3, leads to the stable seven-membered benzofused ring, namely a benzothiazepine system (Fig. 2).

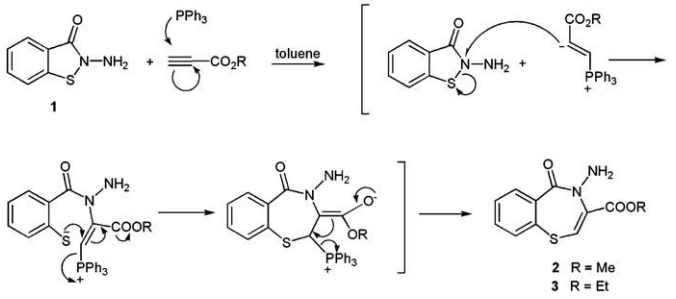


Figure 2. Mechanistic pathway for compounds **2** and **3**.

The above mechanism is supported by many examples, in the literature, of reactions of isothiazole derivatives that result in S–N bond breaking and/or isothiazole ring conversion to other heterocycles.[2,13–17]

Although the chemical data and of a lot of spectral analyses were consistent with the obtained structures, the novelty of the reaction which produced **2** and **3** suggested us further synthetic and spectral experiments for additional structural confirmation. With regard to the synthesis, chemical reduction of the methyl 4-amino-5-oxo-4,5-dihydrobenzo[*f*][1,4]thiazepine-3-carboxylate (**2**) with $NaBH_4$, was carried out to obtain the corresponding saturated derivative **4** (Fig. 3).

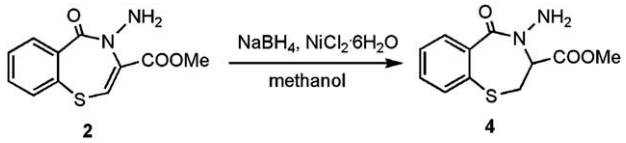
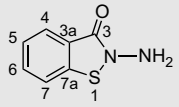


Figure 3. Chemical reduction of **2** to **4**.

2.2. NMR Spectroscopy

The structure of compounds **1**–**4** was assigned through detailed analysis by one- and two-dimensional NMR experiments. All the ^1H and ^{13}C chemical shifts and coupling constants for compounds **1**–**4** are given in Tables 1 and 2, along with the HMBC ^1H–^{13}C correlations.

Table 1
^1H and ^{13}C chemical shifts[a] and HMBC[b] correlations of compound **1**



Position	^1H	^{13}C	HMBC
3	—	165.2	—
3a	—	123.0	—
4	7.99 (d, $J_{4,5}$=7.9)	126.4	3,3a,5,6,7,7a
5	7.36 (t, $J_{5,6}$=7.9)	125.5	3,3a,4,6,7,7a
6	7.58 (t, $J_{6,7}$=7.9)	132.1	3a,4,5,7,7a
7	7.46 (d, $J_{7,6}$=7.9)	120.2	3,3a,4,5,6
7a	—	139.1	—
NH_2	4.65 (s)	—	3

[a] Chemical shifts in ppm (multiplicity, *J* in Hz).
[b] Carbons coupled to the corresponding H atom.

The ^1H and ^{13}C chemical shifts assignments and coupling constants for all of the compounds were found through the combined use of proton and carbon 1D and 2D NMR experiments such as gCOSY[18] and gHSQC.[19] For compound **1** (ABO)[7] ^{13}C–^1H long range correlation's confirmed the structure, nevertheless the gHMBC[20] spectra showed a number of $^4J_{CH}$ correlations (see Table 1). For methyl 4-amino-5-oxo-4,5-dihydrobenzo[*f*][1,4]thiazepine-3-carboxylate (**2**) the protons on carbons 2, 6, 7, 8, 9 and 11, which were easily assigned at the different residues on the basis of chemical shift and multiplicity, allowed the assignment of carbons to which they are directly attached by C–H correlation (gHSQC). The ^{13}C spectra showed two carbon atoms with chemical shifts higher than δ=160 ppm indicating the presence of two carbonyl groups (see Table 2). The gCOSY spectra allowed assigning the aromatic spin system pattern H6–H7–H8–H9 but the two couples H6–H9 and H7–H8 may be interchanged because of the symmetric-like shaped molecule. H6 and H9 can be discriminated on the basis of chemical shift (H6 should be more deshielded than H9 because of the neighbouring CO group). In fact, supposing H6 at δ=7.81 ppm, we found, for H6, the correlations with two quaternary carbons at δ=169.3 and 139.8 and with C8 at 131.6 ppm; for H9 we found a correlation with C8, C7 and two quaternary carbons at δ=136.2 and 139.8 ppm. This suggests that C5, C5a and C9a should be at δ=169.3, 136.2 and 139.8 ppm, respectively. H7 shows correlations with C5a, C6, C8 and C9 and H8 with H5a, C6, C7, C9, and C9a. All these evidences strongly confirm the proposed structure, but the presence of some $^4J_{CH}$ correlations in every spectrum, nevertheless the different transfer delays, such as H9–C5, H9–C6 or H8–C5a, and the lacking of some $^2J_{CH}$ correlations, such as H6–C5a or H6–C7, induced us to search other evidences.

The carbon skeleton of compound **2** was further confirmed by means of a ^{13}C–^{13}C INADEQUATE[21] experiment. The INADEQUATE spectrum of **2** reveals a very clear pattern showing two distinct spin systems. Starting from the unambiguous C6 at δ=132.4 ppm, it is easy to trace the aromatic ring correlation net. C6 correlates with C7 at 128.8 ppm and with C5a at δ=136.2 ppm that has a second correlation with a carbon at δ=169.3 ppm: it cannot be other than C5. From C7 we can correlate C8; C8 and C9 are strongly overlapped giving a distorted signal correlated with C9a. Finally C9a correlates with C5a. Starting from C10 at 162.4 ppm we can recognise C3 and C2 at 140.4 and 128.6 ppm, respectively. This spectrum not only allows discrimination of C5a and C9a, but also separates the C7 and C2 resonance which were strongly overlapped in HSQC spectrum.

Table 2
^{1}H and ^{13}C chemical shifts[a] and HMBC[b] correlations of compounds **2**, **3** and **4**

	2				**3**				**4**		
Position	^{1}H	^{13}C	^{15}N	HMBC	Position	^{1}H	^{13}C	HMBC	Position	^{1}H	^{13}C	HMBC
2	7.27 (s)	128.6		3,9a,10	2	7.18 (s)	128.0	3,9a,10	2a	3.48 (dd, $J_{2a,2b}$=12.6, J_{2a3}=4.8)	35.5	3,5a,10
									2b	3.61 (dd, $J_{2b,2a}$=12.6, $J_{2b,3}$=10.7)		
3	—	140.4		—	3	—	140.5	—	3	4.45 (dd, $J_{3,2b}$=10.7, $J_{3,2a}$=4.8)	62.3	2,5,10
4			148.7									
4′	4.81 (b)	—	77.9		4′	4.75 (br)	—	3,5	4′	4.53 (s)	—	3,5
5	—	169.3		—	5	—	169.1	—	5	—	169.4	
5a	—	136.2		—	5a	—	136.2	—	5a	—	129.1	
6	7.81 (dd, $J_{6,7}$=7.2, $J_{6,8}$=1.8)	132.4		5,8,9a	6	7.73 (dd, $J_{6,7}$=7.1, $J_{6,8}$=2.0)	132.3	5,5a,7,8,9a	6	7.61 (dd, $J_{6,7}$=7.5, $J_{6,8}$=1.7)	129.2	5,5a,7,8
7	7.37 (td, $J_{7,8}$=7.2, $J_{7,9}$=2.1)	128.8		5a,6,8,9	7	7.28 (td, $J_{7,8}$=7.1, $J_{7,9}$=2.0)	128.6	5a,6,9,9a	7	7,39 (td, $J_{7,8}$=7.5, $J_{7,9}$=1.5)	129.3	5,6,8,9,9a
8	7.35 (td, $J_{8,9}$=7.2, $J_{8,6}$=1.8)	131.6		5a,6,7,9,9a	8	7.26 (td, $J_{8,9}$=7.1, $J_{8,6}$=2.0)	131.4	5a,6,7,9,9a	8	7,35 (td, $J_{8,9}$=7.5, $J_{8,6}$=1.7)	131.6	5a,6,7,9,9a
9	7.33 (dd, $J_{9,8}$=7.2, $J_{9,7}$=2.1)	131.5		5,5a,6,7,8,9a	9	7.23 (dd, $J_{9,8}$=7.1, $J_{9,7}$=2.0)	131.4	5,5a,6,7,8,9a	9	7.47 (dd, $J_{9,8}$=7.5, $J_{9,7}$=1.5)	134.3	5,7,8,9a
9a	—	139.8		—	9a		139.6	—	9a	—		—
10	—	162.4		—	10	—	161.7	—	10	—	167.7	—
11	3.78 (s)	52.7		3,10	11	4.14 (q, $J_{11,12}$=7.2)	61.9	10,12	11	3.66 (s)	52.8	3,10
					12	1.19 (t, $J_{12,11}$=7.2)	14.0	11				

[a] Chemical shifts in ppm (multiplicity, *J* in Hz).
[b] Carbons coupled to the corresponding H atom.

Finally the presence and nature of the two nitrogen atoms was detected running ^{1}H–^{15}N HSQC and HMBC correlation spectra in DMSO solution where we found a NH_2 group at 77.9 ppm (referred to the external NH_3 signal) with a one-bond coupling of 69.7 Hz and an amide type nitrogen at δ=148.7 ppm. The latter shows correlations to the olefinic proton (three-bond) at δ=7.18 ppm and to the NH_2 pair (two-bonds) at δ=5.41 ppm.

In the ^{1}H and ^{13}C spectra of compound **3** the same behaviour for chemical shifts, with respect to **2**, was found (see Table 2).

Table 2 also reports the ^{1}H and ^{13}C spectral values of compound **4**, obtained by reduction of **2**, to get a deeper insight in the feature of the NMR spectroscopic information. In particular it is evidenced the presence of an AMX spin system attributable to two diastereotopic protons near to a stereogenic centre.

3. Conclusion

We have described a novel transformation involving 2-aminobenzo[*d*]isothiazole-3-one, alkyl propiolates and triphenylphosphine, in a one-pot reaction, leading to 4-amino-5-oxo-4,5-dihydrobenzo[*f*]-[1,4]thiazepine-3-carboxylates, that were unambiguously characterised through a detailed ^{1}H, ^{13}C and ^{15}N NMR spectral investigation. Functionalized 1,5-benzothiazepine-4-ones may be considered potentially useful biologically active compounds. Their derivatives have been much less studied than their pharmacologically active isomers 1,4-benzothiazepine-5-ones[22,23] and obviously much less than their isosteric psychoactive 1,4-benzodiazepine-2-ones. This is also due to the difficulties of their chemical synthesis that rarely gives pure isomers.[24–26]

We have therefore discovered an unprecedented reaction of 2-aminobenzo[*d*]isothiazole-3-one, involving alkyl propiolates and Ph_3P, that proceeds through an isothiazole ring expansion affording novel functionalized 1,4-benzothiazepine-5-ones. The simplicity of the procedure makes it an interesting approach to novel heterocyclic compounds of biological interest. In the future research, taking advantage from the present results, the synthetic approach through the chemistry of trivalent phosphorus nucleophiles, using the 2-aminobenzo[*d*]isothiazole-3-one as privileged starting structure, will be extended to new functionalised heterocycles.

4. Experimental

4.1. Synthetic procedure

4.1.1. General methods

Unless otherwise noted, reagents and starting materials were obtained from commercial suppliers and were used without purification. Anhydrous THF was distilled over Na/benzophenone. Anhydrous toluene and dioxane were obtained by distillation from Na. Anhydrous dichloromethane was obtained by distillation from dried granular calcium chloride. All reactions were carried out using flame-dried glassware under atmosphere of nitrogen.

Melting points were measured on a Buchi 512 apparatus and are uncorrected. The progress of the reactions was monitored by thin layer chromatography with F_{254} silica-gel precoated sheets (Merck, Darmstadt, Germany). UV light was used for detection. Flash chromatography was performed using Merck silica gel 60 (Si 60, 40–63 μm, 230–400 mesh ASTM).

Elemental analyses for C, H, N and S were performed using a ThermoQuest Flash 1112 Elemental Analyzer in the analytical laboratory of Dipartimento Farmaceutico, Università di Parma. IR spectra were recorded on a Jasco FT-IR 300E spectrometer. Mass spectra were recorded on an Applied Biosystem, API 150 EX LC/MS system spectrometer.

^{1}H and ^{13}C spectra were run on a Varian INOVA 600 spectrometer and ^{15}N spectra on a Varian VNMRS-400.

4.1.2. General procedure for the preparation of alkyl 4-amino-5-oxo-4,5-dihydrobenzo[f][1,4]thiazepine-3-carboxylates

To a magnetically stirred mixture of 2-aminobenzo[*d*]isothiazol-3-one **1** (0.5 g, 3.0 mmol) and triphenylphosphine (0.8 g, 3.0 mmol) in anhydrous toluene (7 mL), a solution of alkyl propiolate (3.0 mmol) in anhydrous toluene (2 mL) was added. The reaction mixture was stirred at room temperature for 5 h. The solvent was removed under reduced pressure and the oily residue was purified by silica gel flash chromatography (methylene chloride-ethanol: 98/2 v/v). The solid obtained was recrystallised from ethanol/water furnishing the product as a white solid.

*4.1.2.1. Methyl 4-amino-5-oxo-4,5-dihydrobenzo[f][1,4]thiazepine-3-carboxylate (**2**).* Yield 46%; mp 92–94 °C; IR (KBr) (ν_{max}/cm^{-1}): 3316, 3205 (NH_2), 3039 (CH Ar), 2960 and 2836 (CH_3), 1727 (C=O ester). MS (APCI) *m*/*z*: 251 (M+1). Anal. Calcd for $C_{11}H_{10}N_2O_3S$ (250.27): C, 52.79; H, 4.03; N, 11.19; S, 12.81. Found: C, 52.85; H, 4.17; N, 10.54, S, 12.59%. R_f (methylene chloride–ethanol: 95/5 v/v) 0.48.

*4.1.2.2. Ethyl 4-amino-5-oxo-4,5-dihydrobenzo[f][1,4]thiazepine-3-carboxylate (**3**).* Yield 44%; mp 94–96 °C; IR (KBr) (ν_{max}/cm^{-1}): 3359, 3293 (NH_2), 3058 (CH Ar), 2983 and 2825 (CH_3), 1731 (C=O ester). MS (APCI) *m*/*z*: 265 (M+1). Anal. Calcd for $C_{12}H_{12}N_2O_3S$ (264.30): C, 54.53; H, 4.58; N, 10.60; S, 12.13. Found: C, 54.45; H, 4.68; N, 10.26, S, 12.03%. R_f (methylene chloride–ethanol: 95/5 v/v) 0.44.

*4.1.2.3. Methyl 4-amino-5-oxo-2,3,4,5-tetrahydrobenzo[f][1,4]thiazepine-3-carboxylate (**4**).* To a magnetically stirred solution of compound **2** (0.15 g, 0.6 mmol) and $NiCl_2 \cdot 6H_2O$ (0.02 g, 0.08 mmol) in methanol (20 mL), cooled at 0 °C, was added slowly $NaBH_4$ (0.2 g, 5 mmol). After stirring for 30 min at room temperature, the solvent was removed under reduced pressure and the excess of reagent was destroyed by the addition of saturated NH_4Cl aq solution, then the pH was adjusted to 7.0 adding 2 M HCl. The mixture was then extracted with CH_2Cl_2 (50 ml), dried over Na_2SO_4 and the solvent removed in vacuo. The white solid residue was purified by silica gel flash chromatography (methylene chloride–ethanol: 98/2 v/v) to afford the reduced benzothiazepine which was recrystallised from ethanol/water. Yield 43%; mp 79–81 °C; IR (KBr) (ν_{max}/cm^{-1}): 3320, 3215 (NH_2), 3042 (CH Ar), 2961 and 2837 (CH_3), 1730 (C=O ester). MS (APCI) *m*/*z*: 253 (M+1). Anal. Calcd $C_{11}H_{12}N_2O_3S$ (252.29): C, 52.37; H, 4.79; N, 11.10; S, 12.71. Found: C, 52.45; H, 4.77; N, 10.94, S, 12.59%. R_f (methylene chloride–ethanol: 95/5 v/v) 0.40.

2-Amino-benzo[*d*]isothiazol-3(2*H*)-one (**1**) was obtained as previously described.[7]

4.2. NMR measurements

All spectra were acquired from samples as $CDCl_3$ solutions (50 mg mL^{-1}).

^{1}H and ^{13}C spectra (at 599.74 and 150.82 MHz respectively) were measured at 25 °C in 5 mm o.d. tubes. Chemical shifts are reported as δ (ppm); coupling constants (*J*) are expressed in Hz. ^{1}H and ^{13}C spectra were referred to residual $CHCl_3$ at δ=7.24 and 77.0 ppm respectively. For ^{1}H NMR analysis 16 transients were acquired with a pulse repetition time of 1.5 s and a spectral window of 5500 Hz ca., using 32 K data points and zero filled to a digital resolution of about 0.1 Hz. The ^{13}C NMR spectra were run operating typically with a 45° pulse flip angle, a relaxation delay time of 3–5 s and a spectral width of 37,000 Hz with 96 K data points end were zero filled to a digital resolution of about 3 Hz.

The gHSQC and gHMBC spectra were collected with 2 K data points for *F*2 and 128–256 increments for *F*1 with pulse sequences using gradient pulses; spectral windows were 2700–5500 and 27,894 Hz in the *F*2 (^{1}H) and *F*1 (^{13}C) dimensions, respectively. The relaxation delay was set to 1.5 s for 2D experiments. Once acquired, data were processed using π/2 shifted squared sine-bell weighting functions in both dimensions with 2 K data points zero-filled to 4 K in *F*2 and 256 data points zero-filled to 1 K and linear predicted to 768 data points in *F*1. In gHMBC the transfer delay varied between 60 and 125 ms.

The ^{13}C 2D INADEQUATE spectrum was performed from samples as $CDCl_3$ solutions at the concentration of 500 mg mL^{-1} added with $Cr(Acac)_3$ to reduce the longer *T*1 from ca. 5 to 0.5 s. The pulse sequence 90°–τ–180°–τ–90°–*t*1–90°–*t*2 was employed: τ (1/4 J) was 3.7 ms being *J* optimised to 66 Hz; 256 transients of 2 K data points for *F*2 and 64 increments for *F*1 were collected. Spectral windows were 7600 Hz in *F*2 and 15,200 in *F*1 dimensions. The recycle delay was 2.0 s. Spectra were processed with sine squared window functions in both dimensions followed by zero-filling to give 4 K×128 data matrix before Fourier transformation.

^{15}N spectra were run at 50.53 MHz in DMSO solution: ^{1}H and ^{15}N were referred to residual DMSO at δ=2.49 ppm and to external NH_3, respectively. The ^{15}N gHSQC and gHMBC spectra were collected with 1150 data points for *F*2 and 64–128 increments for *F*1 with pulse sequences that allowed gradient selection; spectral windows were 3834 and 5673 Hz in the *F*2 (^{1}H) and *F*1 (^{15}N) dimensions, respectively. The relaxation delay was set to 1–3 s. Data points zero-filled to 4 K in both directions. In gHMBC the transfer delay was 125 ms.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2009.07.003.

References and notes

1. Clerici, F.; Gelmi, M. L.; Pellegrino, S.; Pocar, D. *Top. Heterocycl. Chem.* **2007**, *9*, 179.
2. Siegemund, A.; Taubert, K.; Schulze, B. *Sulfur Rep.* **2002**, *23*, 279.
3. Vicini, P.; Zani, F.; Cozzini, P.; Doytchinova, I. *Eur. J. Med. Chem.* **2002**, *37*, 553.
4. Vicini, P.; Geronikaki, A.; Incerti, M.; Busonera, B.; Poni, C.; Cabras, C. A.; La Colla, P. *Bioorg. Med. Chem.* **2003**, *11*, 4785.
5. Zani, F.; Vicini, P.; Incerti, M. *Eur. J. Med. Chem.* **2004**, *39*, 135.
6. Vicini, P.; Incerti, M.; Ferretti, R.; Zanardi, F. *Mol. Diversity* **2006**, *10*, 251.
7. Vicini, P.; Manotti, C.; Caretta, A.; Amoretti, L. *Arzneim.-Forsch/Drug Res.* **1997**, *47*, 1218.
8. Hudson, H. R. In *The Chemistry of Organophosphorus Compounds: Primary, Secondary and Tertiary Phosphines and Heterocyclic Organophosphorus (III) Compounds*; Hantley, F. R., Ed.; Wiley: NewYork, NY, 1990; Vol. 1, pp 386–472.
9. Yavari, I.; Hosseini, N.; Moradi, L. *Monatsh. Chem.* **2008**, *139*, 133.
10. Yavari, I.; Moradi, L.; Mirzaei, A. *Helv. Chim. Acta* **2006**, *89*, 2918.
11. Yavari, I.; Hazeri, N.; Maghsoodlou, M. T.; Souri, S. *J. Mol. Catal. A: Chem.* **2007**, *264*, 313.
12. Yavari, I.; Souri, S.; Sirouspour, M.; Djahaniani, H.; Nasiri, F. *Synthesis* **2005**, *11*, 1761.
13. Abdel-Sattar, S. H. E. *Tetrahedron* **2003**, *59*, 7445.
14. Kaberdin, R. V.; Potin, V. I. *Russ. Chem. Rev.* **2002**, *71*, 673.
15. Grivas, J. C. *J. Org. Chem.* **1976**, *41*, 1325.
16. Ranganathan, S.; Muraleedharan, K. M.; Bharadwaj, P.; Chatterji, D.; Karle, I. *Tetrahedron* **2002**, *58*, 2861.
17. Abramovitch, R. A.; More, K. M.; Shinkai, I.; Srinivasan, P. C. *Heterocycles* **1976**, *5*, 95.
18. Hurd, R. E. *J. Magn. Reson.* **1990**, *87*, 422.
19. Palmer, A. G., III; Cavanagh, J.; Wright, P. E.; Rance, M. *J. Magn. Reson.* **1991**, *93*, 151.
20. Bax, A.; Summers, M. F. *J. Am. Chem. Soc.* **1986**, *108*, 2093.
21. Bax, A.; Freeman, R.; Frenkiel, T. A. *J. Am. Chem. Soc.* **1981**, *103*, 2102.
22. Levai, A.; Kiss-Szikszai, A. *ARKIVOC* **2008**, *1*, 65.
23. Bariwal, J. B.; Upadhyay, K. D.; Manvar, A. T.; Trivedi, J. C.; Singh, J. S.; Jain, K. S.; Shah, A. K. *Eur. J. Med. Chem.* **2008**, *43*, 2279.
24. Marcaccini, S.; Miguel, D.; Torroba, T.; Garcia-Valverde, M. *J. Org. Chem.* **2003**, *68*, 3315.
25. Kurz, T.; Geffken, D.; Mesaros, R. WO Patent 2005082873, 2005.
26. Wuensch, K. H.; Ehler, A.; Beyer, H. *Chem. Ber.* **1969**, *102*, 1618.