Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron 63 (2007) 4730–4736
Tetrahedron

A novel ambident reactivity of azolylacroleins

Ildikó Nagy, György Hajós,* Zsuzsanna Riedl, Orsolya Egyed and Imre Pápai

Chemical Research Center, H-1025 Budapest, Pusztaszeri út 59, Hungary

Received 8 December 2006; revised 27 February 2007; accepted 15 March 2007
Available online 18 March 2007

Abstract—Reaction of azolylacroleins with phosphoranes bearing a conjugated double bond was found to yield either azolyltrienes in a Wittig reaction, or to undergo cyclization to a dihydrobenzene containing the azole substituent. Transformation with an aza-Wittig reagent gave tetrazolylpyridines. The ambident reactivity was found to be dependent on the substituent of the phosphorane, which was rationalized by ab initio (DFT) calculation of the atomic charges of the reaction centres.

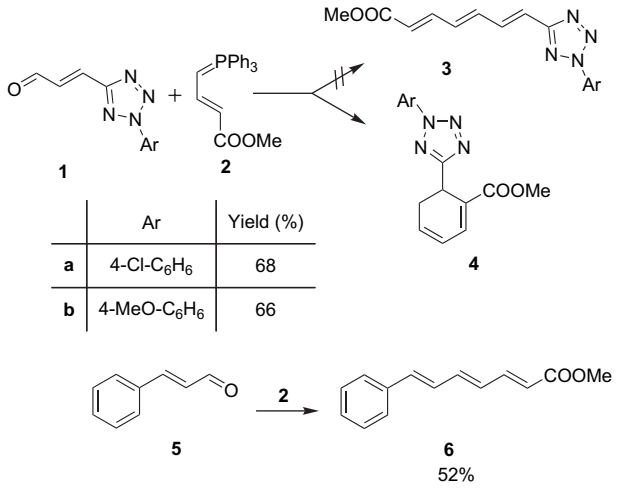
1. Introduction

Conjugated polyene building blocks are present in several biologically important compounds such as leukotrienes, fatty acids, arachidonic acid, as well as in important natural substances, e.g., in β-carotene or vitamin A.[1] Furthermore, some drugs like polyene antibiotics, amphotericin B, candicidin, nystatin, etc. contain such structural units.[2] Because of the biological importance of conjugated polyene systems, we have extended our earlier research activity[3,4] on tetrazolyldienes for trienes.

Recently we have described that tetrazolylacroleins (**1**) can be prepared via a relatively easy pathway (a four-step synthesis starting from 2-aminopyridine),[3] and these compounds easily undergo condensation reactions with *C*-nucleophiles (e.g., with ethyl nitroacetate or acetylacetone) and participate in Wittig reactions.[4] The synthetic possibility that phosphoranes bearing a conjugating double bond (e.g., **2**) could also be used in such reactions giving azolyltrienes (**3**), prompted us to explore this reactivity and to seek a synthesis of such derivatives. To the best of our knowledge, only very few azolyltrienes have been reported earlier.[13–16]

2. Results and discussion

When tetrazolylacrolein **1** was reacted with methyl (2*E*)-4-(triphenylphosphoranylidene)but-2-enoate (**2**) (synthesized from methyl 4-bromocrotonate in two steps according to a literature procedure[5]), a substituted dihydrophenyltetrazole **4** was obtained instead of the expected triene (**3**) (Scheme 1). Interestingly, when a similar transformation was carried out with the related cinnamaldehyde (**5**), the fully *trans* triene **6** was formed and no product reminiscent of **4** was detected.



	Ar	Yield (%)
a	4-Cl-C_6H_6	68
b	4-MeO-C_6H_6	66

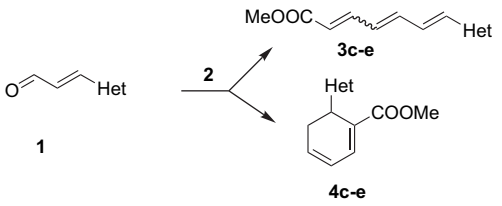
Scheme 1.

In order to decide if the unexpected formation of the dihydrobenzene (**4**) is due specifically to the presence of the tetrazole moiety, the behaviour of three additional azolylacroleins (triazolyl **1c**,**d** and pyrazolyl **1e** compounds) has been studied. All these acroleins were synthesized according to literature procedures.[6,7] In each of these reactions, in contrast to the tetrazolylacroleins **1a**,**b**, simultaneous formation of a triene (**3c–e**) and a dihydrobenzene (**4c–e**) was experienced (Scheme 2).

The outcome of the transformations with phosphorane **2** is summarized in Table 1. Comparison of these data reveals that with a decrease of the nitrogen atoms in the azole ring

Keywords: Azolyltriene; Wittig reaction; Phosphorane; Ab initio calculation.
* Corresponding author. Fax: +36 14381145; e-mail: ghajos@chemres.hu

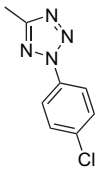
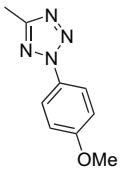
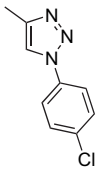
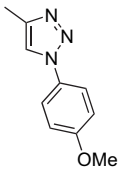
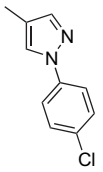
0040–4020/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2007.03.098



	Het
c	1-(4-chlorophenyl[1,2,3]triazol)-4-yl
d	1-(4-methoxyphenyl[1,2,3]triazol)-4-yl
e	1-(4-chlorophenylpyrazol-4-yl)

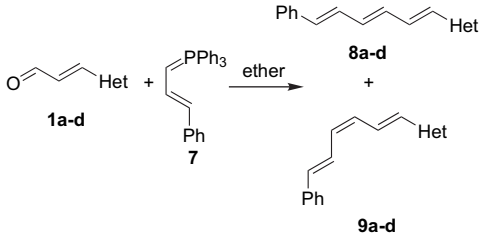
Scheme 2.

Table 1. Products obtained from reaction of azolylacroleins (**1a**–**e**) with phosphorane (**2**)

1	**a**	**b**	**c**	**d**	**e**
Het					
Product **3**	—	—	7%	Not isolated	24%
Product **4**	68%	66%	78%	71%	29%

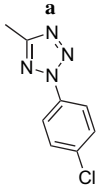
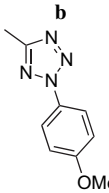
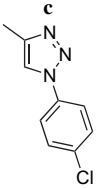
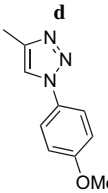
(i.e., with triazole and pyrazole rings), formation of the expected triene **3** took place to increasing extent. Moreover, with the pyrazolylacrolein derivative (**1e**), the relative amount of **3** substantially increased, and the two types of products **3e** and **4e** were obtained in comparable amounts.

Besides the study on the effect of the aryl or heteroaryl substituent on the ambident reactivity, a change of the terminal moiety in the Wittig reagent also seemed of interest. To this end, the phenyl substituted reagent (**7**) liberated in situ from the appropriate phosphonium salt[8] has also been investigated. The results are summarized in Scheme 3 and Table 2.

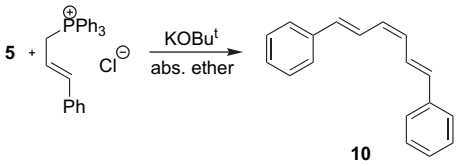


Scheme 3.

Table 2. Products obtained from reaction of azolylacroleins (**1a**–**d**) with non-stabilized phosphorane (**7**)

1	**a**	**b**	**c**	**d**
Het				
Product **8**	38%	25%	24%	14%
Product **9**	Not isolated	20%	24%	15%

Inspection of Scheme 3 and Table 2 reveals that, in contrast to the results obtained with phosphorane **2**, every reaction carried out with the phenyl substituted phosphorane **7** yielded only triene compounds in the form of the geometrical isomers **8** and **9**. Reaction of cinnamaldehyde (**5**) with the phosphonium salt precursor of phosphorane (**7**), resulted exclusively in only one isomer: the symmetrical trans–cis–trans product (**10**) (Scheme 4).



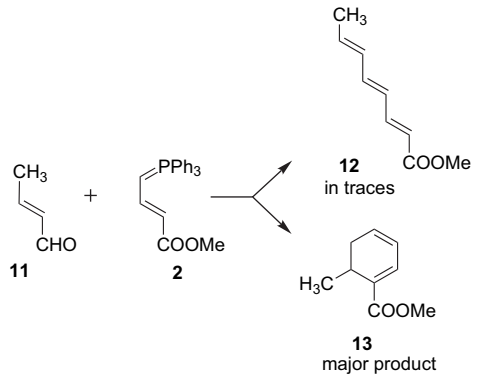
Scheme 4.

Comparison of the above results shows that the two extreme cases are the tetrazolylacroleins (e.g., their reaction with phosphorane **2** yields dihydrobenzene **4** only) and the phenylacrolein (i.e., cinnamaldehyde yielding only triene **6**), whereas in all other cases dihydrobenzene and triene compounds were formed simultaneously. At first sight, one could assume that in the course of the cyclization to **4**, the triene **3** could have been formed first, followed by electrocyclisation to the dihydrobenzene **4** and, thus, **3** could be an intermediate along the pathway to **4**. This supposition, however, seems rather unlikely for three reasons:

(a) such an electrocyclisation can only take place if the triene has a trans–cis–trans geometry like **9** and **10**. Even if isomerization of a triene of another geometry could occur, the electrocyclisation would result in a product containing the two double bonds in different locations (i.e., also the ester group should be attached to a saturated ring-carbon atom);
(b) literature data reveal that such electrocyclisations need fairly drastic reaction conditions (e.g., heating the triene in pentane or heptane at 130–200 °C in a sealed tube for 6–24 h[17]);
(c) transformation of **1a** to **4a** was also carried out successfully under very mild conditions (at −20 °C), which clearly contradicts the above-mentioned literature data.

All these results suggest that **3** and **4** were formed by two independent pathways. A literature search led us to an earlier finding similar to the formation of **4**.[9] These authors reported the transformation of crotonaldehyde (**11**) with **2** yielding a dihydrobenzene (**13**) derivative as the main product, whereas the triene product **12** was also observed in trace amounts (Scheme 5).

These authors supposed that it is the conjugate carbon atom in the Wittig reagent that attacks the β-carbon atom in acrolein to form an intermediate in which an internal Wittig reaction yields the product (Fig. 1). Thus, movement of electrons as shown in (a) can be anticipated to result in a Michael addition to (b). In this species a hydrogen shift as shown, followed by tautomerism can occur to give (c) and, finally, an intramolecular Wittig reaction leads to the ring closure to (d).



Scheme 5.

Upon inspection of the data in Tables 1 and 2, the following conclusion can be made. In the cases of the ester substituted phosphorane, the outcome of the reaction essentially depended on the structure of the starting heteroarylacrolein. This indicates that formation of a cyclohexadiene is basically favoured by the presence of an electron withdrawing (e.g., COOR) group in the phosphorane reagent, and also by high number of nitrogen atoms in the heteroaryl ring.

This ambident behaviour can be rationalized schematically as represented in Figure 2. Thus, the investigated acroleins can react in two different ways: (i) if the first step is the attack of the phosphorane on the β-carbon atom of the acrolein (route A), a Michael addition occurs followed by an intramolecular Wittig reaction with participation of the oxophosphorane intermediate resulting in ring closure to the cyclohexadiene product; (ii) an alternative pathway is route B, which is a simple Wittig reaction between the formyl group of the acrolein and the phosphorane moiety to yield a triene.

A recent publication of Palacios and Rubiales[10] called to our attention the possibility of a further extension of our studies. These authors described that treatment of cinnamaldehyde or acrolein with the phosphazane **14** results in an aza-Wittig reaction followed by electrocyclization of the intermediate azatriene to yield pyridine derivatives.

Treatment of the tetrazolylacroleines **1a**,**b** with **14** (prepared from propiolic acid according to literature procedure[11a–d] in four steps) resulted in a similar course of transformations: the Wittig reaction to **15**-trans took place at room temperature, which compound is in equilibrium with the **15**-cis isomer in accordance with other literature observation, and the reaction mixture—without isolation of this intermediate—was heated at reflux in order to accomplish the cyclization reaction to **16**. This second intermediate underwent spontaneous oxidation during this transformation to yield azolylpyridine **17** in moderate yield (Scheme 6).

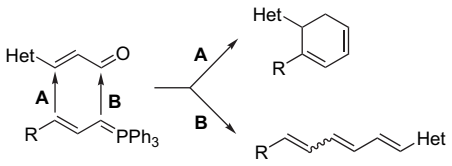


Figure 2. Rationalization of the ambident behaviour of heteroarylacroleins in their transformations with phosphoranes.

In an attempt to rationalize our observations in the context of the above mechanistic picture, DFT calculations for selected aldehydes (**1a** and **5**) and for the two Wittig reagents (**2** and **7**) have been carried out. The calculated net charges of the carbon atoms relevant to reaction routes A and B are collected in Table 3.

The calculations reveal that the partial charges associated with the reacting carbon atoms on route B (C_B) are invariant with respect to the nature of the Het and R substituents of the molecules, whereas those values calculated for the C_A atoms show a noticeable variation. Namely, the electron density on the C_A atom of **7** is calculated to be lower as compared to that in **2** pointing to a reduced nucleophilic character of C_A in **7**, which may explain that all the reactions with the non-stabilized phosphorane proceeded via route B yielding exclusively triene products. On the other hand, the variation of C_A atomic charges in aldehydes does not account for the observed reactivities, because one expects an enhanced electrophilicity for the C_A atom in the aldehyde to drive the reaction towards route A, but the calculated charges show the opposite trend. It seems, therefore, that a more detailed mechanistic study involving the identification of key elementary steps along the two reaction channels is required to provide a satisfactory explanation for the observed reactivities.

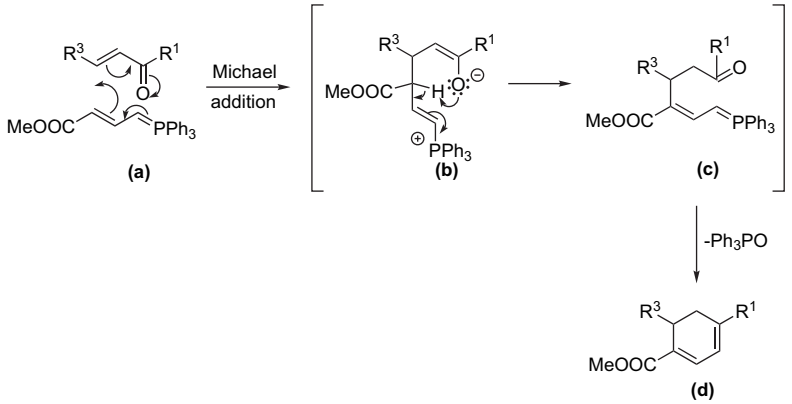
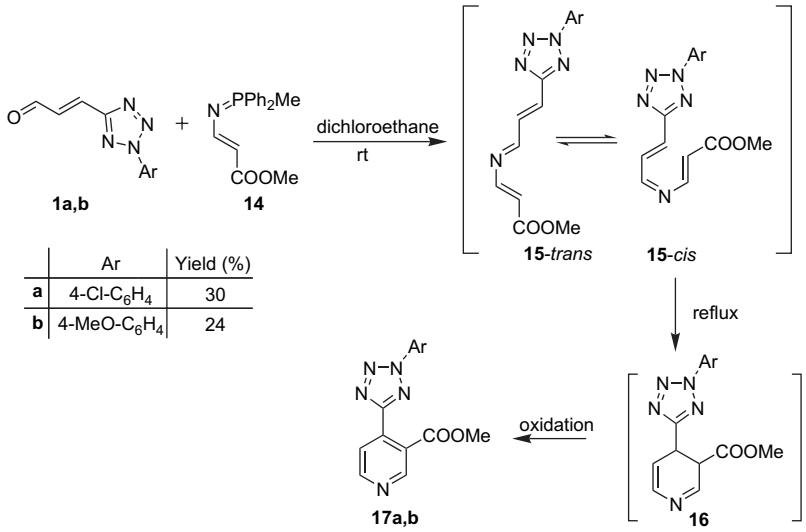


Figure 1. Rationalization of the reaction of an acrolein derivative and a viniloguous phosphorane.



	Ar	Yield (%)
a	4-Cl-C_6H_4	30
b	4-MeO-C_6H_4	24

Scheme 6.

Table 3. Net NPA atomic charges for carbon atoms relevant to reaction routes A and B as obtained from B3LYP/6-31G** calculations

		C_A	C_B
Aldehyde	**1a**	−0.21	+0.36
	5	−0.16	+0.36
Phosphorane	**2**	−0.43	−0.89
	7	−0.31	−0.89

3. Conclusion

From these results one can conclude that by selection of an appropriate reagent, the ambident reactivity can be directed to the desired pathway and, thus, valuable azolyltrienes or azolyldihydrobenzene derivatives can be synthesized in acceptable yields. The DFT calculations provided satisfactory rationalization for the sensitivity of the reaction on the change of substituents.

4. Experimental part

4.1. General methods

Melting points were determined by a Büchi apparatus and are uncorrected. The IR spectra were recorded on a Thermo Nicolet Avatar 320 FTIR spectrometer, the NMR spectra were determined on a Varian Unity Inova spectrometer (200 MHz and 400 MHz for ^{1}H and 100 MHz for ^{13}C), and the elemental analysis has been carried out with an Elementar Vario EL III apparatus.

Computational details: Density functional calculations have been carried out at the B3LYP/6-31G** level to describe the charge distribution in selected aldehydes (**1a** and **5**) and in Wittig reagents **2** and **7**. For the latter two compounds, the bulky PPh_3 groups were replaced by PH_3 moieties. The reported net atomic charges were obtained for the geometry optimized structures using the NPA (natural population analysis) procedure as implemented in the Gaussian03 program.[12]

4.1.1. (2*E*)-3-[2-(4-Methoxyphenyl)-2*H*-tetrazol-5-yl]-acrylaldehyde (1b). This compound was prepared according to the literature process.[3] Yield: 36%. Yellow crystals. Mp 105–106 °C (CH_3CN). IR (KBr) ν_{max}: 1682, 1511, 1254, 1166, 1109, 1027, 1009, 993, 839 cm^{-1}. δ_H (200 MHz, $CDCl_3$) 9.84 (1H, d, *J* 8.0 Hz, C*H*O), 8.06 (2H, m, 2″+6″-H), 7.62 (1H, d, *J* 16.0 Hz, 3-H), 7.25 (1H, dd, *J* 8.0, 16.0 Hz, 2-H), 7.06 (2H, m, 3′+5′-H), 3.90 (3H, s, O*Me*); δ_C ($CDCl_3$) 192.9, 161.9, 161.3, 135.8, 134.8, 130.2, 121.8, 115.2, 56.0. Anal. Calcd for $C_{11}H_{10}N_4O_2$: C, 57.39; H, 4.38; N, 24.34. Found: C, 57.68; H, 4.30; N, 24.33.

4.2. General procedure for the reaction of acroleins with methyl (2*E*)-4-(triphenylphosphoranylidene)but-2-enoate

A solution of acrolein (1.0 mmol) and phosphorane (**2**) (1.1 mmol) in dichloromethane (15 mL) was stirred at room tempetarure for periods specified below. The reaction was monitored by TLC. The reaction mixture was separated by flash chromatography on Kieselgel 60H, using dichloromethane as an eluent.

4.2.1. Methyl 6-[2-(4-chlorophenyl)-2*H*-tetrazol-5-yl]-cyclohexa-1,3-diene-1-carboxylate (4a). This compound was obtained from **1a**, reaction time: 2 h. Yield: 0.215 g, 68%, yellow oil. IR (KBr) ν_{max}: 1702, 1492, 1272, 1233, 1089, 1002, 830 cm^{-1}. δ_H (400 MHz, $CDCl_3$) 8.02 (2H, m, 2″+6″-H), 7.44 (2H, m, 3″+5″-H), 7.31 (1H, dd, *J* 2.0, 5.0 Hz, 2-H), 6.17 (1H, ddd, *J* 3.0, 5.5, 9.5 Hz, 4-H), 6.12 (1H, dddd, *J* 1.0, 2.7, 5.0, 9.5 Hz, 3-H), 4.46 (1H, dd, *J* 2.0, 9.2 Hz, 6-H), 3.80 (3H, s, COO*Me*), 3.03 (1H, ddd, *J* 2.7, 5.5, 18.0 Hz, 5-H), 2.83 (1H, dddd, *J* 1.0, 3.0, 9.2, 18.0 Hz, 5-H); δ_C ($CDCl_3$) 168.0, 167.2, 135.6, 135.5, 135.2, 131.8, 129.9 (2C), 126.1, 124.3, 121.3 (2C), 52.1, 28.8, 28.6. HRMS (EI): M(-N_2)$^+$, found 288.0663. $C_{15}H_{13}ClN_2O_2$ requires 288.0666.

4.2.2. Methyl-6-[2-(4-methoxyphenyl)-2*H*-tetrazol-5-yl]-cyclohexa-1,3-diene-1-carboxylate (4b). This compound was obtained from **1b**, reaction time: 2 h. Yield: 0.205 g,

66%, yellow oil. IR (KBr) ν_{max}: 2955, 2835, 1708, 1609, 1573, 1513, 1435, 1275, 1251, 1170, 1092, 1068, 998, 833 cm^{-1}. δ_H (200 MHz, $CDCl_3$) 7.97 (2H, m, 2″+6″-H), 7.31 (1H, dd, *J* 1.1, 4.8 Hz, 2-H), 6.99 (2H, m, 3″+5″-H), 6.15 (2H, m, 3+4-H), 4.43 (1H, dd, *J* 1.1, 9.2 Hz, 6-H), 3.86 (3H, s, COO*Me*), 3.79 (3H, s, O*Me*), 3.04 (1H, ddd, *J* 2.2, 5.2, 18.3 Hz, 5-H), 2.81 (1H, dddd, *J* 2.2, 4.0, 9.2, 18.3 Hz, 5-H); δ_C ($CDCl_3$) 167.6, 167.3, 160.6, 135.2, 132.0, 130.8, 126.4, 124.3, 121.7 (2C), 114.8 (2C), 55.9, 52.2, 29.0, 28.6. HRMS (EI): $M(-N_2)^+$, found 284.1161. $C_{16}H_{16}N_2O_3$ requires 284.1146.

4.2.3. Methyl-(2*E*,4*Z*,6*E*)-7-[1-(4-chlorophenyl)-1*H*-1,2,3-triazol-4-yl]hepta-2,4,6-trienoate (3c). This compound was obtained from **1c**, reaction time: 4 h. Yield: 0.021 g, 7%, white crystals. Mp 166–168 °C (CH_3CN). IR (KBr) ν_{max}: 3129, 1696, 1606, 1498, 1435, 1311, 1260, 1209, 1134, 1092, 1047, 1014, 980, 830 cm^{-1}. δ_H (400 MHz, $CDCl_3$+DMSO-d_6) 8.30 (1H, s, 5′-H), 7.87 (1H, dd, *J* 12.0, 15.1 Hz, 3-H), 7.78 (2H, m, 2″+6″-H), 7.62 (1H, dd, *J* 11.7, 15.4 Hz, 6-H), 7.53 (2H, m, 3″+5″-H), 6.79 (1H, d, *J* 15.4 Hz, 7-H), 6.50 (1H, dd, *J* 10.3, 11.7 Hz, 5-H), 6.23 (1H, dd, *J* 10.3, 12.0 Hz, 4-H), 5.96 (1H, d, *J* 15.1 Hz, 2-H), 3.80 (3H, s, COO*Me*); δ_C ($CDCl_3$+DMSO-d_6) 167.4 (C=O), 146.5 (4′-C), 139.0 (3-C), 136.6 (5-C), 135.5 (1″-C), 134.5 (4″-C), 130.0 (3″+5″-C), 127.9 (6-C), 126.0 (2-C+4-C), 124.1 (2-C+4-C), 122.0 (7-C), 121.6 (2″+6″-C), 119.4 (5′-C), 51.7. Anal. Calcd for $C_{16}H_{14}N_3O_2Cl$: C, 60.86; H, 4.47; N, 13.31. Found: C, 60.92; H, 4.29; N, 13.24.

4.2.4. Methyl-6-[1-(4-chlorophenyl)-1*H*-1,2,3-triazol-4-yl]cyclohexa-1,3-diene-1-carboxylate (4c). This compound was obtained from **1c**, reaction time: 4 h. Yield: 0.246 g, 78%, beige crystals. Mp 70–72 °C (CH_3CN). IR (KBr) ν_{max}: 2949, 1705, 1573, 1501, 1435, 1398, 1272, 1236, 1095, 1044, 1026, 992, 833, 770, 734 cm^{-1}. δ_H (200 MHz, $CDCl_3$) 7.65 (2H, m, 2″+6″-H), 7.62 (1H, s, 5′-H), 7.45 (2H, m, 3″+5″-H), 7.24 (1H, dd, *J* 1.8, 4.4 Hz, 2-H), 6.15 (2H, m, 3+4-H), 4.29 (1H, dd, *J* 1.8, 9.0 Hz, 6-H), 3.77 (3H, s, COO*Me*), 2.98 (1H, ddd, *J* 1.8, 5.2, 18.0 Hz, 5-H), 2.80 (1H, ddd, *J* 1.8, 9.0, 18.0 Hz, 5-H); δ_C ($CDCl_3$) 167.6, 149.9, 136.0, 134.7, 134.4, 133.1, 130.1 (2C), 128.0, 123.8, 121.8 (2C), 119.4, 52.2, 29.7, 28.3. Anal. Calcd for $C_{16}H_{14}N_3O_2Cl$: C, 60.86; H, 4.47; N, 13.31. Found: C, 60.84; H, 4.61; N, 13.09.

4.2.5. Methyl-6-[1-(4-methoxyphenyl)-1*H*-1,2,3-triazol-4-yl]cyclohexa-1,3-diene-1-carboxylate (4d). This compound was obtained from **1d**, reaction time: 4 h. Yield: 0.223 g, 71%, white crystals. Mp 79–81 °C (CH_3CN). IR (KBr) ν_{max}: 3141, 1693, 1519, 1426, 1280, 1244, 1223, 1186, 1095, 1047, 1038, 947, 828, 777, 744 cm^{-1}. δ_H (200 MHz, $CDCl_3$) 7.57 (2H, m, 2″+6″-H), 7.55 (1H, s, 5′-H), 7.23 (1H, dd, *J* 1.8, 4.4 Hz, 2-H), 6.96 (2H, m, 3″+5″-H), 6.15 (2H, m, 3+4-H), 4.29 (1H, dd, *J* 1.8, 9.2 Hz, 6-H), 3.84 (3H, s, COO*Me*), 3.76 (3H, s, O*Me*), 2.98 (1H, ddd, *J* 1.8, 5.0, 18.2 Hz, 5-H), 2.78 (1H, ddd, *J* 1.8, 9.2, 18.2 Hz, 5-H); δ_C ($CDCl_3$) 167.6, 159.9, 149.4, 134.6, 133.1, 131.0, 128.2, 123.8, 122.3 (2C), 119.7, 114.9 (2C), 55.9, 52.1, 29.8, 28.3. Anal. Calcd for $C_{17}H_{17}N_3O_3$: C, 65.58; H, 5.50; N, 13.50. Found: C, 65.41; H, 5.74; N, 13.23.

4.2.6. Methyl-(2*E*,4*E*,6*E*)-7-[1-(4-chlorophenyl)-1*H*-pyrazol-4-yl]hepta-2,4,6-trienoate (3e). This compound was obtained from **1e**, reaction time: 4 h. Yield: 0.076 g, 24%, yellow needles. Mp 192–195 °C (CH_3CN). IR (KBr) ν_{max}: 3117, 1705, 1594, 1543, 1498, 1432, 1405, 1335, 1293, 1254, 1212, 1131, 1092, 998, 944, 827 cm^{-1}. δ_H (400 MHz, DMSO-d_6) 8.71 (1H, s, 5′-H), 8.04 (1H, s, 3′-H), 7.82 (2H, m, 2″+6″-H), 7.54 (2H, m, 3″+5″-H), 7.31 (1H, dd, *J* 11.2, 15.1 Hz, 3-H), 6.88 (1H, dd, *J* 10.9, 14.6 Hz, 6-H), 6.82 (1H, dd, *J* 10.9, 14.0 Hz, 5-H), 6.72 (1H, d, *J* 14.6 Hz, 7-H), 6.45 (1H, dd, *J* 11.2, 14.0 Hz, 4-H), 5.96 (1H, d, *J* 15.1 Hz, 2-H), 3.64 (3H, s, COO*Me*); δ_C (DMSO-d_6) 167.6, 145.7, 142.7, 140.9, 139.0, 131.4, 130.4 (2C), 129.6, 128.5, 127.6, 127.1, 123.2, 120.8 (2C), 120.4, 52.1. Anal. Calcd for $C_{17}H_{15}N_2O_2Cl$: C, 64.87; H, 4.80; N, 8.90. Found: C, 64.86; H, 4.63; N, 8.73.

4.2.7. Methyl-6-[1-(4-chlorophenyl)-1*H*-pyrazol-4-yl]-cyclohexa-1,3-diene-1-carboxylate (4e). This compound was obtained from **1e**, reaction time: 4 h. Yield: 0.091 g, 29%, pale yellow oil. IR (KBr) ν_{max}: 2943, 1702, 1594, 1573, 1498, 1435, 1395, 1272, 1236, 1089, 1065, 1023, 950, 830, 773, 731 cm^{-1}. δ_H (200 MHz, $CDCl_3$) 7.70 (1H, s, 5′-H), 7.59 (1H, s, 3′-H), 7.56 (2H, m, 2″+6″-H), 7.36 (2H, m, 3″+5″-H), 7.14 (1H, dd, *J* 2.2, 4.8 Hz), 6.15 (2H, m), 4.00 (1H, d, *J* 9.2 Hz), 3.76 (3H, s, COO*Me*), 2.80 (1H, ddd, *J* 1.8, 9.2, 18.3 Hz), 2.59 (1H, ddd, *J* 1.8, 5.1, 18.3 Hz); δ_C ($CDCl_3$) 167.7, 140.8, 134.4, 133.0, 132.3, 131.8, 129.9, 129.7 (2C), 125.6, 124.9, 124.2, 120.3 (2C), 52.1, 31.1, 26.8. HRMS (EI): M^+, found 314.0832. $C_{17}H_{15}ClN_2O_2$ requires 314.0822.

4.2.8. Methyl-(2*E*,4*E*,6*E*)-7-phenylhepta-2,4,6-trienoate (6). This compound is known from the literature.[18] This compound was obtained from **5**, reaction time: 1.5 h. Yield: 0.112 g, 52%, yellow crystals. δ_H (400 MHz, $CDCl_3$) 7.42 (2H, m, H-2Ph), 7.38 (1H, dd, *J* 11.5, 15.0 Hz, 3-H), 7.33 (2H, m, H-3Ph), 7.26 (1H, m, H-4Ph), 6.86 (1H, dd, *J* 10.5, 15.0 Hz, 6-H), 6.73 (1H, d, *J* 15.0 Hz, 7-H), 6.71 (1H, dd, *J* 10.5, 15.0 Hz, 5-H), 6.42 (1H, dd, *J* 11.5, 15.0 Hz, 4-H), 5.93 (1H, d, *J* 15.0 Hz, 2-H), 3.78 (3H, s, COO*Me*); δ_C ($CDCl_3$) 167.7, 144.8, 141.1, 137.0, 136.9, 130.4, 129.0 (2C), 128.6, 128.2, 127.0 (2C), 120.6, 51.7.

4.3. General procedure for the reaction of acroleins with triphenylcinnamylphosphonium chloride

To a stirred suspension of triphenylcinnamylphosphonium chloride (0.456 g, 1.1 mmol) in abs ether (10 mL) was added potassium *tert*-butoxide (0.118 g, 1.05 mmol) and the mixture was stirred for 30 min under an argon atmosphere. To the resulting red coloured mixture was added dropwise the solution or suspension of the acrolein (1 mmol) in dichloromethane (5 mL) and the reaction mixture was stirred for additional 1 h. The reaction mixture was poured into water (30 mL) and was extracted with dichloromethane (15 mL) three times. The combined organic layer was washed with water (30 mL) and dried over sodium sulfate. The solvent was evaporated in vacuo and the two isomers were separated by flash chromatography on Kieselgel 60H or neutral aluminium oxide (as indicated below) by using dichloromethane/hexane (2:1) as an eluent.

4.3.1. 2-(4-Chlorophenyl)-5-[(1*E*,3*E*,5*E*)-6-phenylhexa-1,3,5-trien-1-yl]-2*H*-tetrazole (8a). This compound was obtained from **1a**, and the crude product was purified on neutral aluminium oxide. Yield: 0.128 g, 38%, yellow crystals. Mp 152–153 °C (CH_3CN). IR (KBr) ν_{max}: 1603, 1492, 1218, 1089, 1002, 992, 830, 752, 686 cm^{-1}. δ_H (400 MHz, $CDCl_3$) 8.06 (2H, m, 2′+6′-H), 7.54 (1H, dd, *J* 11.0, 15.8 Hz, 2″-H), 7.51 (2H, m, 3′+5′-H), 7.42 (2H, m, H-2Ph), 7.32 (2H, m, H-3Ph), 7.26 (1H, m, H-4Ph), 6.90 (1H, dd, *J* 10.5, 15.8 Hz, 5″-H), 6.69 (1H, d, *J* 15.8 Hz, 6″-H), 6.68 (1H, d, *J* 15.8 Hz, 1″-H), 6.67 (1H, dd, *J* 10.5, 15.5 Hz, 4″-H), 6.55 (1H, dd, *J* 11.0, 15.5 Hz, 3″-H); δ_C ($CDCl_3$) 164.8, 138.0, 137.6, 137.1, 137.0, 135.6, 135.5, 131.8, 130.1 (2C), 128.9 (2C), 128.6, 128.3, 126.9 (2C), 121.1 (2C), 116.1. Anal. Calcd for $C_{19}H_{15}N_4Cl$: C, 68.16; H, 4.52; N, 16.73. Found: C, 68.47; H, 4.48; N, 16.78.

4.3.2. 2-(4-Methoxyphenyl)-5-[(1*E*,3*E*,5*E*)-6-phenylhexa-1,3,5-trien-1-yl]-2*H*-tetrazole (8b). This compound was obtained from **1b**. The crude product was purified on neutral aluminium oxide. Yield: 0.083 g, 25%, yellow crystals. Mp 145–148 °C (CH_3CN). IR (KBr) ν_{max}: 1609, 1594, 1516, 1471, 1254, 1218, 1167, 1107, 995, 833, 749, 689 cm^{-1}. δ_H (400 MHz, C_6D_6) 7.91 (2H, m, 2′+6′-H), 7.70 (1H, dd, *J* 10.9, 15.7 Hz, 2″-H), 7.20 (2H, m, H-2Ph), 7.09 (2H, m, H-3Ph), 7.00 (1H, m, H-4Ph), 6.73 (1H, d, *J* 15.7 Hz, 1″-H), 6.62 (1H, dd, *J* 10.4, 15.4 Hz, 5″-H), 6.54 (2H, m, 3′+5′-H), 6.35 (1H, d, *J* 15.4 Hz, 6″-H), 6.29 (1H, dd, *J* 10.4, 14.9 Hz, 4″-H), 6.18 (1H, dd, *J* 10.8, 14.9 Hz, 3″-H), 3.14 (3H, s, O*Me*); NOE: 6.73 (irrad.)/6.18; 6.62 (irrad.)/7.20; 7.70 (irrad.)/6.29; 7.20 (irrad.)/6.35, 6.62, 7.09; δ_C ($CDCl_3$) 164.4, 160.7, 137.6 (2″-C), 137.2, 137.0 (4″-C), 135.2 (6″-C), 132.0 (5″-C), 130.6, 128.9 (C-3Ph), 128.7 (C-4Ph), 128.2 (3″-C), 126.8 (C-2Ph), 121.5 (2′+6′-C), 116.6 (1″-C), 114.9 (3′+5′-C), 55.9 (OCH_3). Anal. Calcd for $C_{20}H_{18}N_4O$: C, 72.71; H, 5.49; N, 16.96. Found: C, 72.57; H, 5.39; N, 16.89.

4.3.3. 2-(4-Methoxyphenyl)-5-[(1*E*,3*Z*,5*E*)-6-phenylhexa-1,3,5-trien-1-yl]-2*H*-tetrazole (9b). This compound was obtained from **1b**. The crude product was purified on neutral aluminium oxide. Yield: 0.067 g, 20%, yellow crystals. Mp 104–106 °C (CH_3CN). IR (KBr) ν_{max}: 1630, 1609, 1597, 1513, 1468, 1444, 1374, 1254, 1167, 1023, 998, 965, 824, 755, 731, 689 cm^{-1}. δ_H (400 MHz, $CDCl_3$) 8.06 (2H, m, 2′+6′-H), 8.00 (1H, dd, *J* 12.0, 15.8 Hz, 2″-H), 7.52 (2H, m, H-2Ph), 7.42 (1H, dd, *J* 11.5, 15.5 Hz, 5″-H), 7.37 (2H, m, H-3Ph), 7.26 (1H, m, H-4Ph), 7.04 (2H, m, 3′+5′-H), 6.72 (1H, d, *J* 15.8 Hz, 1″-H), 6.69 (1H, d, *J* 15.5 Hz, 6″-H), 6.42 (1H, dd, *J* 10.5, 11.5 Hz, 4″-H), 6.28 (1H, dd, *J* 10.5, 12.0 Hz, 3″-H), 3.88 (3H, s, O*Me*); δ_C ($CDCl_3$) 164.4, 160.7, 137.2, 135.8, 134.1, 132.0, 130.6, 128.9 (2C), 128.5, 128.4, 127.1 (2C), 124.0, 121.6 (2C), 117.4, 114.9 (2C), 55.9. Anal. Calcd for $C_{20}H_{18}N_4O$: C, 72.71; H, 5.49; N, 16.96. Found: C, 72.53; H, 5.16; N, 16.85.

4.3.4. 1-(4-Chlorophenyl)-4-[(1*E*,3*E*,5*E*)-6-phenylhexa-1,3,5-trien-1-yl]-1*H*-1,2,3-triazole (8c). This compound was obtained from **1c**. The product was precipitated from the reaction mixture. This was filtered off, washed with water and ether. Yield: 0.080 g, 24%, pale yellow crystals, insoluble in $CDCl_3$ and DMSO-d_6. Mp 208–210 °C. IR (KBr) ν_{max}: 3117, 3015, 1495, 1447, 1233, 1092, 1038, 989, 833, 752, 692 cm^{-1}. δ_H (200 MHz, $CDCl_3$+TFA) 8.35 (1H, s, 5-H), 7.60–7.74 (3H, m), 7.42 (2H, m, 2′+6′-H), 7.32 (2H, m, 3′+5′-H), 7.27 (2H, m), 7.20 (1H, dd, *J* 10.0, 14.3 Hz), 6.86 (1H, dd, *J* 11.0, 14.8 Hz), 6.74 (2H, d, *J* 15.4 Hz, 1″+6″-H), 6.48 (2H, m). Anal. Calcd for $C_{20}H_{16}N_3Cl$: C, 71.96; H, 4.83; N, 12.59. Found: C, 71.97; H, 4.81; N, 12.41.

4.3.5. 1-(4-Chlorophenyl)-4-[(1*E*,3*Z*,5*E*)-6-phenylhexa-1,3,5-trien-1-yl]-1*H*-1,2,3-triazole (9c). This compound was obtained from **1c**. The crude product was purified on Kieselgel 60H. Yield: 0.079 g, 24%, pale yellow crystals. Mp 128–130 °C (CH_3CN). IR (KBr) ν_{max}: 3141, 3027, 1495, 1447, 1233, 1089, 1044, 986, 959, 842, 815, 740, 683 cm^{-1}. δ_H (400 MHz, $CDCl_3$) 7.92 (1H, s, 5-H), 7.70 (2H, m, 2″+6″-H), 7.68 (1H, dd, *J* 11.0, 15.5 Hz, 2′-H), 7.50 (2H, m, 3″+5″-H), 7.47 (2H, m, H-2Ph), 7.39 (1H, dd, *J* 11.0, 15.1 Hz, 5′-H), 7.33 (2H, m, H-3Ph), 7.24 (1H, m, H-4Ph), 6.64 (1H, d, *J* 15.1 Hz, 6′-H), 6.61 (1H, d, *J* 15.5 Hz, 1′-H), 6.29 (1H, dd, *J* 10.8, 11.0 Hz, 4′-H), 6.22 (1H, dd, *J* 10.8, 11.0 Hz, 3′-H); δ_C ($CDCl_3$) 147.2 (4-C), 137.4, 135.6, 134.7, 134.6 (6′-C), 131.7 (5′-C), 130.2 (C-3Ph), 129.3 (2′-C), 128.9 (C-2Ph), 128.1 (C-4Ph), 127.3 (4′-C), 126.9 (3″+5″-C), 124.3 (3′-C), 121.7 (2″+6″-C), 120.3 (1′-C), 118.4 (5-C). Anal. Calcd for $C_{20}H_{16}N_3Cl$: C, 71.96; H, 4.83; N, 12.59. Found: C, 71.93; H, 4.89; N, 12.35.

4.3.6. 1-(4-Methoxyphenyl)-4-[(1*E*,3*E*,5*E*)-6-phenylhexa-1,3,5-trien-1-yl]-1*H*-1,2,3-triazole (8d). This compound was obtained from **1d**. The crude product was purified on Kieselgel 60H. Yield: 0.047 g, 14%, white crystals. Mp 185–186 °C (CH_3CN). IR (KBr) ν_{max}: 1525, 1510, 1302, 1248, 1179, 1167, 1041, 1008, 995, 833, 788, 749, 689 cm^{-1}. δ_H (400 MHz, DMSO-d_6) 8.77 (1H, s, 5-H), 7.79 (2H, m, 2′+6′-H), 7.49 (2H, m, H-2Ph), 7.35 (2H, m, H-3Ph), 7.24 (1H, m, H-4Ph), 7.14 (2H, m, 3′+5′-H), 7.12 (1H, dd, *J* 10.0, 15.8 Hz, 5″-H), 7.04 (1H, dd, *J* 10.0, 15.8 Hz, 2″-H), 6.70 (2H, d, *J* 15.8 Hz, 1″+6″-H), 6.60–6.65 (2H, m, 3″+4″-H), 3.85 (3H, s, O*Me*); δ_C (DMSO-d_6) 160.0, 146.8, 137.7, 134.7, 133.8, 133.5, 131.5, 130.7, 129.8, 129.4 (2C), 128.3, 127.0 (2C), 122.4 (2C), 121.3, 120.6, 115.6 (2C), 56.3. Anal. Calcd for $C_{21}H_{19}N_3O$: C, 76.57; H, 5.81; N, 12.76. Found: C, 76.55; H, 5.82; N, 12.39.

4.3.7. 1-(4-Methoxyphenyl)-4-[(1*E*,3*Z*,5*E*)-6-phenylhexa-1,3,5-trien-1-yl]-1*H*-1,2,3-triazole (9d). This compound was obtained from **1d**. The crude product was purified on Kieselgel 60H. Yield: 0.050 g, 15%, pale yellow crystals. Mp 133–135 °C (CH_3CN). IR (KBr) ν_{max}: 1525, 1510, 1444, 1299, 1251, 1170, 1110, 1038, 965, 830, 782, 749, 695 cm^{-1}. δ_H (400 MHz, $CDCl_3$+DMSO-d_6) 7.96 (1H, s, 5-H), 7.66 (1H, dd, *J* 10.5, 15.8 Hz), 7.65 (2H, m, 2′+6′-H), 7.48 (2H, m, H-2Ph), 7.40 (1H, m), 7.34 (2H, m, H-3Ph), 7.24 (1H, m, H-4Ph), 7.02 (2H, m, 3′+5′-H), 6.63 (2H, d, *J* 16.0 Hz, 1″+6″-H), 6.25 (2H, m), 3.79 (3H, s, O*Me*); δ_C ($CDCl_3$+DMSO-d_6) 160.0, 146.7, 137.4, 134.6, 134.5, 131.2, 129.5 (2C), 128.8, 128.0, 126.8 (2C), 126.6, 124.3, 122.2 (2C), 120.8, 119.0, 115.0 (2C), 55.8. Anal. Calcd for $C_{21}H_{19}N_3O$: C, 76.57; H, 5.81; N, 12.76. Found: C, 76.21; H, 5.78; N, 12.64.

4.3.8. 1,1′-(1*E*,3*Z*,5*E*)-Hexa-1,3,5-triene-1,6-diyldibenzene (10). This compound is known from the literature.[19]

The crude product was purified on Kieselgel 60H using dichloromethane/hexane (1:1) as an eluent. Yield: 0.121 g, 52%, yellow crystals. Mp 122–124 °C (EtOH). IR (KBr) ν_{max}: 3015, 1483, 1444, 995, 911, 854, 743, 689 cm^{-1}. δ_H (400 MHz, $CDCl_3$+DMSO-d_6) 7.42 (4H, m, H-2Ph), 7.31 (4H, m, H-3Ph), 7.22 (2H, m, H-4Ph), 6.85–6.92 (2H, m), 6.60 (2H, d, *J* 15.6 Hz), 6.54 (2H, m).

4.4. General procedure for the synthesis of 4-substituted methyl nicotinate (17a,b)

A solution of aldehyde **1** (1 mmol) and phosphazane (**14**) (1.2 mmol) in dichloroethane (20 mL) was stirred for 24 h under argon atmosphere and then heated at reflux for the period specified. The reaction was monitored by TLC. The solvent was removed in vacuo and the residue was purified by flash chromatography on Kieselgel 60H using dichloromethane as an eluent.

4.4.1. Methyl 4-[2-(4-chlorophenyl)-2*H*-tetrazol-5-yl]-nicotinate (17a). This compound was obtained from **1a**, reflux time: 62 h. Yield: 0.095 g, 30%, pale yellow crystals. Mp 168 °C (CH_3CN, decomp.). IR (KBr) ν_{max}: 1711, 1600, 1489, 1441, 1423, 1275, 1197, 1143, 1113, 1098, 998, 830, 746 cm^{-1}. δ_H (200 MHz, $CDCl_3$) 9.41 (1H, s, 6-H), 8.52 (1H, d, *J* 5.2 Hz, 2-H), 8.43 (1H, d, *J* 5.2 Hz, 3-H), 8.24 (2H, m, 2″+6″-H), 7.58 (2H, m, 3″+5″-H), 4.01 (3H, s, COO*Me*); δ_C ($CDCl_3$) 165.1, 163.6, 151.2, 149.5, 138.4, 136.1, 129.9 (2C), 127.0, 122.3, 121.3 (2C), 108.6, 52.6. Anal. Calcd for $C_{14}H_{10}N_5O_2Cl$: C, 53.26; H, 3.19; N, 22.18. Found: C, 53.46; H, 3.04; N, 22.02.

4.4.2. Methyl 4-[2-(4-methoxyphenyl)-2*H*-tetrazol-5-yl]-nicotinate (17b). This compound was obtained from **1b**, reflux time: 50 h. Yield: 0.075 g, 24%, white crystals. Mp 169–170 °C (CH_3CN). IR (KBr) ν_{max}: 1708, 1594, 1510, 1435, 1405, 1293, 1272, 1251, 1185, 1143, 1113, 1023, 827, 752 cm^{-1}. δ_H (200 MHz, $CDCl_3$) 9.41 (1H, d, *J* 2.2 Hz, 6-H), 8.51 (1H, dd, *J* 2.2, 5.4 Hz, 2-H), 8.42 (1H, d, *J* 5.4 Hz, 3-H), 8.18 (2H, m, 2″+6″-H), 7.07 (2H, m, 3″+5″-H), 4.01 (3H, s, COO*Me*), 3.90 (3H, s, O*Me*); δ_C ($CDCl_3$) 165.5, 164.3, 161.2, 151.8, 150.3, 138.6, 130.5 (2C), 127.1, 122.5 (2C), 122.1(2C), 115.1 (2C), 56.0, 52.9. Anal. Calcd for $C_{15}H_{13}N_5O_3$: C, 57.87; H, 4.21; N, 22.50. Found: C, 57.59; H, 4.24; N, 22.75.

Acknowledgements

Financial supports OTKA T047317, NKFP 1A/005/2004 and project (GVOP-3.2.1-2004-04-0311/3.0) for elemental analyzer are gratefully acknowledged.

References and notes

1. Wermuth, C. G. *The Practice of Medicinal Chemistry*; Academic: London, 1996; pp 29–39, 182–200, 827–840.
2. Kothler-Brajtburg, J.; Medoff, G.; Kobayashi, G. S.; Boggs, S.; Schlessinger, D.; Pandey, R. C.; Rinehart, K. L., Jr. *Antimicrob. Agents Chemother.* **1979**, *15*, 716–722.
3. Nagy, I.; Kónya, D.; Riedl, Zs.; Kotschy, A.; Timári, G.; Messmer, A.; Hajós, Gy *Tetrahedron* **2003**, *59*, 7485–7489.
4. Nagy, I.; Hajós, Gy.; Riedl, Zs *Heterocycles* **2004**, *63*, 2287–2307.
5. Buchta, A.; Andree, F. *Chem. Ber.* **1959**, *92*, 3111–3116.
6. Tanaka, S.; Wachi, K.; Terada, A. *Chem. Pharm. Bull.* **1980**, *28*, 2083–2088.
7. Tanaka, S.; Wachi, K.; Terada, A. *Chem. Pharm. Bull.* **1980**, *28*, 1265–1269.
8. McDonald, R. N.; Campbell, T. W. *Org. Synth. Coll. Vol.* **1973**, *5*, 499–501.
9. Bohlmann, F.; Zdero, C. *Chem. Ber.* **1973**, *106*, 3779–3787.
10. Palacios, F.; Rubiales, G. *Tetrahedron Lett.* **1996**, *37*, 6379–6382.
11. (a) Kurtz, A. N.; Billups, W. E.; Greenlee, R. B.; Hamil, H. F.; Pace, W. T. *J. Org. Chem.* **1965**, *30*, 3141–3146; (b) Truce, W. E.; Tichenor, G. J. W. *J. Org. Chem.* **1972**, *37*, 2391–2394; (c) Oikawa, T.; Kanomata, N.; Tada, M. *J. Org. Chem.* **1993**, *58*, 2046–2051; (d) Palacios, F.; Perez de Heredia, I.; Rubiales, G. *J. Org. Chem.* **1995**, *60*, 2384–2390.
12. Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, J. A., Jr.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Lyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Camml, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; Pople, J. A. *Gaussian 03, Revision C.02*; Gaussian: Pittsburgh, PA, 2004.
13. Pooranchand, D.; Satyanarayana, J.; Ila, H.; Junjappa, H. *Synthesis* **1993**, *2*, 241–244.
14. Purkayastha, M. L.; Patro, B.; Ila, H.; Junjappa, H. *J. Heterocycl. Chem.* **1991**, *28*, 1341–1350.
15. Thomas, A.; Chakaraborty, M.; Ila, H.; Junjappa, H. *Tetrahedron* **1990**, *46*, 577–586.
16. Tsuruta, H.; Kurabayashi, K.; Mukai, T. *Bull. Chem. Soc. Jpn.* **1972**, *45*, 2822–2828.
17. Marvell, E. N.; Caple, G.; Delphey, C.; Platt, J.; Polston, N.; Tashiro, J. *Tetrahedron* **1973**, *29*, 3797–3806.
18. Asokan, C. V.; Ila, H.; Junjappa, H. *Synthesis* **1985**, 163–165.
19. Sonoda, Y.; Suzuki, Y. *J. Chem. Soc., Perkin Trans. 2* **1996**, 401–404.