Monatsh Chem 139, 821–824 (2008)
DOI 10.1007/s00706-007-0829-5
Printed in The Netherlands

Monatshefte für Chemie
Chemical Monthly

A facile and convenient approach to the synthesis of 3,5-diaryl-1*H*-pyrazoles

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Received 11 October 2007; Accepted 18 October 2007; Published online 19 May 2008

Abstract A simple and convenient one-pot synthesis route is described for the synthesis of 3,5-diaryl-1*H*-pyrazoles in short reaction times from the reaction of α-epoxyketones with semicarbazide hydrochloride under mild conditions.

Keywords 3,5-Diaryl-1*H*-pyrazoles; α-Epoxyketones; Semicarbazide hydrochloride; Heterocycles; One-pot synthesis.

Introduction

The pyrazole ring is one of the fundamental heterocycles. Its derivatives have certainly been shown to exhibit various pharmaceuticals and biological activities [1]. In recent years, there have been enhanced interests in the synthesis of pyrazole derivatives due to their wide applications [2]. The reaction between hydrazine and β-difunctional compounds [3] and 1,3-dipolar cycloaddition of diazo compounds to triple bonds [4] are more common strategies for pyrazoles synthesis. It is important that general effective methods to synthesize or to modify such compounds are improved and exploitation of non-toxic molecules and simple reagents with different functionalities is a worthwhile effort among organic synthesis chemists.

Results and discussion

The synthesis and biological evaluation of 3,5-diarylpyrazoles as the most interesting pyrazoles has been reported already. In some of them the α-epoxyketones are first reacted with an acidic solution of hydrazine hydrate under reflux in xylene or *Et*OH for about 3–6 h; then, in the second step, the produced hydroxypyrazoles were dehydrated in acidic solution to obtain the desired 3,5-diarylpyrazoles [5]. However, in the present article we wish to report a facile and convenient synthesis of the 3,5-diaryl-1*H*-pyrazoles **2** from the reaction of the α-epoxyketones **1** with semicarbazide hydrochloride salt under simple and mild conditions (Scheme 1). The synthesis strategy reported in this article improves on times and reaction steps under mild conditions as compared with the previous ones. All reactions were carried out in one reaction vessel without separation and purification of the intermediates. Furthermore, the use of semicarbazide hydrochloride as the reagent in place of hydrazine has advantages for this transformation. Semicarbazide hydrochloride is significantly easier to handle and safe to use in organic synthesis in comparison with the highly toxic hydrazine hydrate. Also, it is convenient to use this route for various aromatic substituents. The results are summarized in Table 1.

Two plausible mechanisms are proposed in Scheme 2. In the first way (Path A) the α-epoxyketone derivatives **1** are condensed with semicarbazide hydrochloride salt to produce the corresponding semicarbazones **3**. These semicarbazones are cyclized to the intermediates **4** through the ring opening of the epoxide in the presence of released HCl. Dehydration of **4** following with hydrolysis of **5** under the reaction condition employed gives the pyr-

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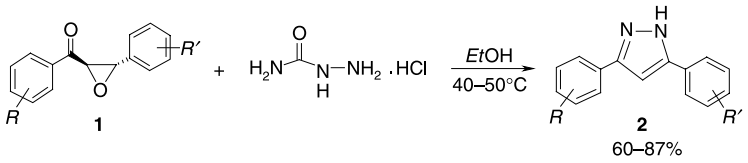


Scheme 1

Table 1 Reaction of the α-epoxyketones **1a**–**1k** with semicarbazide hydrochloride in *Et*OH

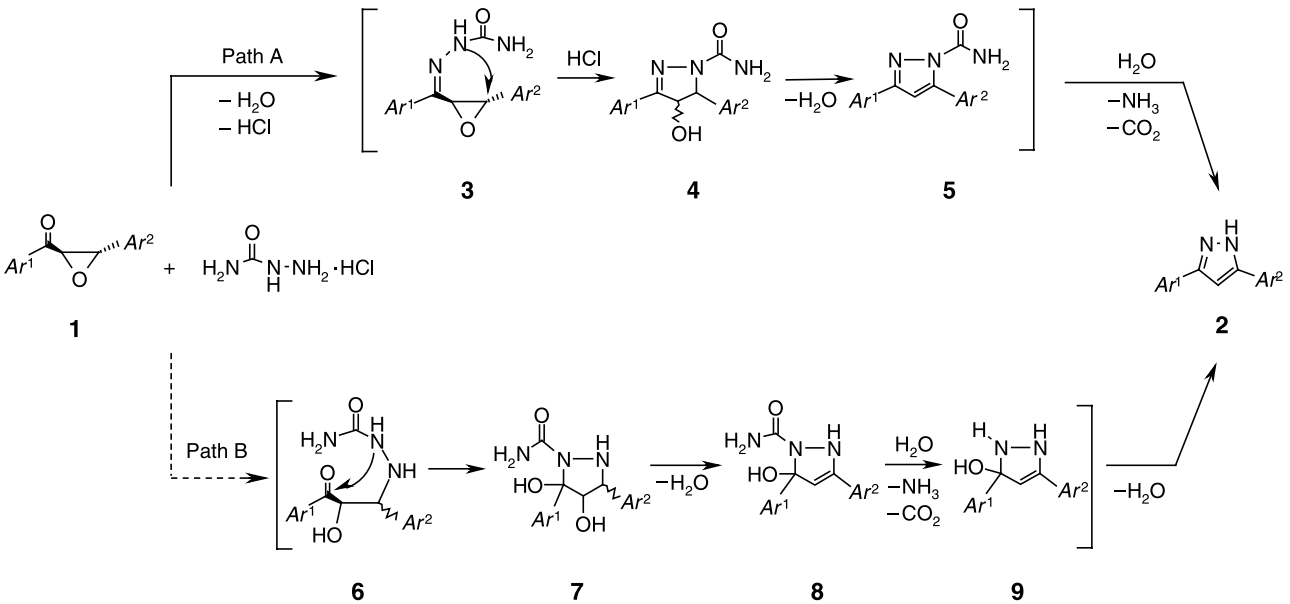
	1		Time/ min	Yield **2**/ %[a,b]	M.p./°C	Ref.
	R	*R′*				
a	H	H	20	80	199–200	[5d]
b	4-Cl	H	30	87	215–217	[2e]
c	H	4-Cl	30	85	216–217	[2e]
d	H	2-Cl	30	83	124–126	[2e]
e	H	4-*Me*	20	83	175–177	
f	4-*Me*	H	20	79	174–176	
g	4-*Me*	4-*Me*	15	70	221–223	
h	4-*Me*O	H	20	63	167–169	[5d]
i	H	4-*Me*O	20	65	167–169	[5d]
j	4-*Me*O	4-*Me*O	15	60	153–154	[5d]
k	H	3-NO_2	45	85	196–198	

[a] Products were identified and characterized by their physical and spectral data and comparison of them with those of authentic samples. [b] Isolated yields

azoles **2**. In the second pathway (Path B), ring opening of the α-epoxyketones **1** gives the intermediates **6**, which are first cyclized and then dehydrated to produce the intermediates **8**. Hydrolysis of **8** in the same reaction conditions and then, aromatization of **9** with removal of water proceeds to **2**. Since the epoxide ring, in particular in conjugate forms as in the α-epoxyketones is stable against non-anionic nucleophiles in neutral solutions, and their ring opening is carried out in acidic solution or in the presence of suitable *Lewis* acids, the pathway A is more probable for beginning and progression of the reaction.

We wish to report that *Et*OH is an eco-friendly solvent for this reaction procedure; however, it was found that the reaction yields were increased about 10–15% by using of *DMF* instead of *Et*OH, because semicarbazide hydrochloride is more soluble in *DMF* than in *Et*OH.

The identification and characterization of the products were carried out by their physical and spectroscopic data and comparison of them with those of authentic samples. In the IR spectra of the compounds **2** and comparing them with the α-epoxyketones **1**, the CO-stretching of the ketone carbonyl disappears completely and the NH-stretching of the



Scheme 2

pyrazol rings appears at about $\bar{\nu} = 3120\,cm^{-1}$. The NH-signal in ^1H NMR appears in about $\delta = 13.60$–13.15 ppm, probably because of its dislocation on the two nitrogen atoms of pyrazol ring. Also, the C^4-H appears as singlet in aromatic region. The C^3 and C^4-H peaks are observed in the ^{13}C NMR spectrum in about $\delta = 148$–139 and 103–99 ppm. Also, in all cases molecular ion-peaks were observed in the mass spectra.

In conclusion, a facile, safe, and convenient approach is reported for the synthesis of 3,5-1*H*-diarylpyrazoles involving the reaction of α-epoxyketones with semicarbazide hydrochloride under mild conditions. The reactions were carried out in a single reaction vessel without separation and purification of the intermediates. This strategy can be used for various aromatic substituents in short reaction times and good yields of the products of high purity are obtained.

Experimental

Melting points were measured with an Electrothermal 9100 apparatus. IR spectra were measured with a Shimadzu IR-460 spectrometer. NMR spectra were recorded with a Bruker DRX-250 AVANCE instrument (250.1 MHz for ^1H and 62.9 MHz for ^{13}C). Chemical shifts are given in ppm (δ) relative to internal *TMS*, and coupling constants *J* are reported in Hz. Mass spectra were recorded with a Finnigan-MAT 8430 mass spectrometer operating at an ionization potential of 70 eV. The synthesis of the α-epoxyketones was achieved by using the published methods [6].

Typical procedure for the example of ***2c***

To a solution of 0.258 g (1 mmol) of the α-epoxyketone **1c** in 1 cm^{-1} of *Et*OH, 0.123 g (1.1 mmol) of semicarbazide hydrochloride was added and the mixture was stirred at 40–50°C for about 30 min. After completion of the reaction, the reaction mixture was poured over crushed ice, filtered, and washed with water (three times) to remove the solvent and the residues of semicarbazide hydrochloride. The product **2c** was dried first in air and then in an oven at 50°C. For purification, it was crystallized from *Me*OH. It should be noted that in some cases the products were separated and purified by thin-layer chromatography on 20×20 plates of silicagel 60 GF_{254} with *n*-hexane/*Et*O*Ac* as eluent.

3-(4-Chlorophenyl)-5-phenylpyrazol (**2b** = **2c**, $C_{15}H_{11}ClN_2$)
IR (KBr): $\bar{\nu} = 3150$ (NH) cm^{-1}; ^1H NMR (250 MHz, *DMSO*-d_6): $\delta = 13.22$ (bs, 1H, NH), 7.91 (d, $^3J_{HH} = 8.5$ Hz, 2H–*Ar*), 7.86 (d, $^3J_{HH} = 7.5$ Hz, 2H–*Ar*), 7.46 (m, 3H–*Ar*), 7.36 (d, $^3J_{HH} = 7.5$ Hz, 2H–*Ar*), 7.15 (s, 1H, C^4-H) ppm; ^{13}C NMR (69.2 MHz, *DMSO*-d_6): $\delta = 146.7$, 132.8, 129.2, 128.8, 128.7, 128.0, 127.6, 127.5, 126.8, 125.3, 99.7 ppm; MS (EI): m/z (%) = 254 ($M^{+\bullet}$, 100), 256 [($M^{+\bullet} + 2$), 35].

3-(2-Chlorophenyl)-5-phenylpyrazol (**2d**, $C_{15}H_{11}ClN_2$)
IR (KBr): $\bar{\nu} = 3135$ (NH) cm^{-1}; ^1H NMR (250 MHz, *DMSO*-d_6): $\delta = 13.52$ (bs, 1H, NH), 7.82 (d, $^3J_{HH} = 7.7$ Hz, 2H–*Ar*), 7.76 (m, 1H–*Ar*), 7.68 (d, $^3J_{HH} = 7.5$ Hz, 1H–*Ar*), 7.46–7.22 (m, 5H–*Ar*), 7.10 (s, 1H, C^4-H) ppm; ^{13}C NMR (250 MHz, *DMSO*-d_6): $\delta = 145.6$, 136.5, 131.5, 130.9, 130.7, 129.9, 129.3, 128.1, 128.4, 127.8, 125.6, 125.5, 103.6 ppm; MS (EI): m/z (%) = 254 ($M^{+\bullet}$, 100), 256 [($M^{+\bullet} + 2$), 35].

3-(4-Methylphenyl)-5-phenylpyrazol (**2e** = **2f**, $C_{16}H_{14}N_2$)
IR (KBr): $\bar{\nu} = 3115$ (NH) cm^{-1}; ^1H NMR (250 MHz, *DMSO*-d_6): $\delta = 13.27$ (bs, 1H, NH), 7.81 (d, $^3J_{HH} = 7.3$ Hz, 2H–*Ar*), 7.72 (d, $^3J_{HH} = 7.5$ Hz, 2H–*Ar*), 7.45–7.23 (m, 5H–*Ar*), 7.10 (s, 1H, C^4-H), 2.32 (s, 3H–CH_3) ppm; ^{13}C NMR (250 MHz, *DMSO*-d_6): $\delta = 139.1$, 138.2, 136.3, 129.8, 129.7, 129.2, 129.1, 125.5, 125.4, 125.3, 99.7, 21.3 ppm; MS (EI): m/z (%) = 234 ($M^{+\bullet}$, 100).

3-(4-Methylphenyl)-5-(4-methylphenyl)pyrazol
(**2g**, $C_{17}H_{16}N_2$)
IR (KBr): $\bar{\nu} = 3120$ (NH) cm^{-1}; ^1H NMR (250 MHz, *DMSO*-d_6): $\delta = 13.18$ (bs, 1H, NH), 7.69, 7.23 (2d, $^3J_{HH} = 7.2$ Hz, 8H–*Ar*), 7.05 (s, 1H, C^4-H), 2.31 (s, 6H-CH_3) ppm; ^{13}C NMR (250 MHz, *DMSO*-d_6): $\delta = 145.1$, 137.8, 132.5, 129.8, 125.4, 99.4, 21.3 ppm; MS (EI): m/z (%) = 248 ($M^{+\bullet}$, 100).

3-(3-Nitrophenyl)-5-phenylpyrazol (**2k**, $C_{15}H_{11}N_3O_2$)
IR (KBr): $\bar{\nu} = 3170$ (NH) cm^{-1}; ^1H NMR (250 MHz, *DMSO*-d_6): $\delta = 13.60$ (bs, 1H, NH), 8.64 (s, 1H–*Ar*), 8.27 (d, $^3J_{HH} = 7.5$ Hz, 1H–*Ar*), 8.14 (d, $^3J_{HH} = 7.2$ Hz, 1H–*Ar*), 7.82 (d, $^3J_{HH} = 6.2$ Hz, 2H–*Ar*), 7.69 (dd, $^3J_{HH} = 7.5$, 7.5 Hz, 1H–*Ar*), 7.49–7.40 (m, 3H–*Ar*), 7.39 (s, 1H, C^4-H) ppm; ^{13}C NMR (250 MHz, *DMSO*-d_6): $\delta = 149.8$, 148.8, 144.4, 135.8, 131.8, 130.7, 129.4, 129.1, 125.6, 125.7, 122.4, 119.6, 101.2 ppm; MS (EI): m/z (%) = 265 ($M^{+\bullet}$, 100).

Acknowledgements

We are thankful to the University of Kurdistan Research Council for the partial support of this work.

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