A Novel One-Pot Rearrangement Reaction of 2,3-Epoxydiaryl Ketones: Synthesis of (±)-5,5-Disubstituted Imidazolones and 5,5-Disubstituted Hydantoins

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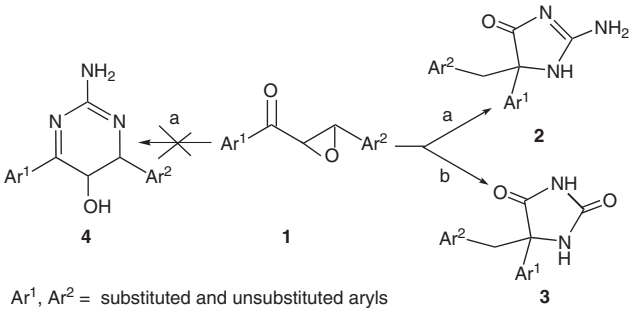
Abstract: A novel one-pot rearrangement reaction, involving sequential epoxide rearrangement, condensation, cyclization and phenyl migration took place when 2,3-epoxydiphenyl ketones were treated with guanidine hydrochloride or urea in the presence of a base like sodium hydride and new type of imidazolone derivatives were obtained in good to excellent yields.

Key words: one-pot, epoxydiphenyl ketones, rearrangement, guanidine, imidazolone

With the emphasis on the search for atom-efficient transformations of easily available starting materials into complex organic molecules,[1] reactions that provide maximum diversity are especially desirable. In this context one-pot synthesis of heterocycles is a powerful tool in the modern drug-discovery process in terms of lead finding and lead optimization.[2] The range of easily accessible and functionalized small heterocycles like 5,5-disubstituted imidazolones and 5,5-disubstituted hydantoins is rather limited. Over the last few decades there has been considerable interest in the synthesis of these scaffolds as an important class of heterocyclic chemistry. The imidazolone scaffold is found in a large number of natural products and pharmacologically active compounds.[3] Substituted imidazolones have received significant attention as a result of their diverse medicinal uses.[4] On the other hand, hydantoin derivatives find application in pharmaceuticals,[5] chemical industry[6] and polymer chemistry.[7] Only a few general methodologies exist for the assembly of such substituted imidazolones and hydantoins.[8] Therefore, the development of new, rapid, and robust routes towards focused libraries of such compounds is of great importance.

As part of our research program directed towards the design and synthesis of lead compounds for potentially interesting drugs, 2,3-epoxydiphenyl ketones[9] were taken into consideration as a possible starting point to obtain new substances with pharmacological and medicinal applications. Previously we reacted **1** with hydrazine hydrate to form the corresponding 4-hydroxypyrazole derivatives, which are of pharmacological interest.[10] In our recent efforts aiming at synthesizing compound **4**, we treated **1** with guanidine hydrochloride in the presence of sodium hydride in tetrahydrofuran (Scheme 1). It was interesting to note that instead of compound **4**, or its dehydrated analogue, a new compound, 2-amino-5-benzyl-5-phenyl-3,5-dihydro-4*H*-imidazol-4-one (**2**) was obtained in good yield.



Scheme 1 *Reagents and conditions*: (a) Guanidine hydrochloride, NaH/THF; (b) urea, NaH/THF.

In the first step, we subjected a heterogeneous solution of 2,3-epoxydiphenyl ketone (**1**) and guanidine hydrochloride to heating at reflux temperature, and no reaction was observed. However, when sodium hydride was added to the reaction mixture, it was found to effect a novel rearrangement reaction, involving sequential epoxide rearrangement to a 1,2-diketone, condensation, cyclization, phenyl migration and double bond repositioning in a one-pot procedure. To test the efficacy of the reaction under different conditions, we examined the effect of various bases like sodium methoxide, potassium *tert*-butoxide besides sodium hydride. It was found that all these bases mediate this rearrangement, but sodium hydride was found to be the best in terms of yield of desired compound. Reaction was also carried out with different ratios of sodium hydride and guanidine hydrochloride. The best result was achieved by carrying out the reaction with 2:1 equivalents of sodium hydride–guanidine hydrochloride in tetrahydrofuran for 6 hours. One mole of the base is utilized for the generation of guanidine from its hydrochloride salt and the next mole effects the reaction. It is noteworthy that the reaction went to completion even at room temperature, but this procedure required longer reaction time. It may also be noted that when the reaction was carried out between 2,3-epoxydiphenyl ketone and sodium hydride alone, it formed 1,2-diketone, which when treated with guanidine reduced the reaction time considerably. This confirmed the formation of 1,2-diketone as the first intermediate during the reaction.

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To test this procedure, the scope of the reaction was then investigated with various substituted 2,3-epoxydiphenyl ketones and guanidine hydrochloride under the established protocol. All reactions proceeded smoothly to give the corresponding 2-amino-5-benzyl-5-phenyl-3,5-dihydro-4*H*-imidazol-4-ones in good to excellent yields (Table 1). Encouraged by the results obtained with guanidine hydrochloride, we turned our attention to urea. It followed the same general rule as guanidine hydrochloride. However, it is interesting to note that under the similar conditions, the product formed was 5-benzyl-5-phenylimidazolidine-2,4-diones. All these products were characterized by ^{1}H NMR, ^{13}C NMR, IR, ESI–MS and elemental analysis.[11] Compounds **2a** and **3a** were additionally confirmed by 2D NMR techniques like HMBC and HSQC and the structure of one of the derivatives, **2a**, was also confirmed by X-ray crystal structure analysis (Figure 1).

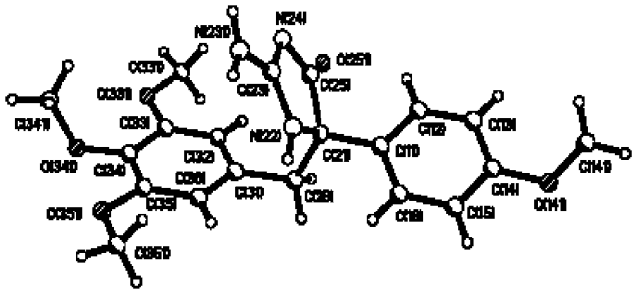
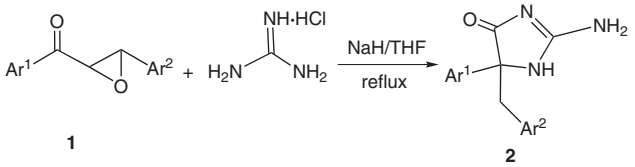


Figure 1 X-ray crystal structure of **2a**

For 2,3-epoxydiphenyl ketones, the presence of electron-withdrawing groups and electron-releasing groups on the aromatic ring Ar^2, did not exhibit significant effects on yields or rates of reaction while as on ring Ar^1, electron-withdrawing groups like chloro and nitro slightly slows down the reaction kinetics and yields are also low (Tables 1 and 2).

A proposed reaction mechanism that accounts for this rearrangement reaction is shown in Scheme 2. As in numerous classical base-catalyzed reactions of 2,3-epoxydiphenyl ketones,[12] the initial event in this reaction is the formation of 1,2-diketones **II**, followed by condensation of guanidine or urea with 2-ketone to generate the relatively more resonance-stabilized intermediate **III**. Subsequently, the resulting intermediate **III** undergoes cyclization by the second nucleophilic attack of the NH_2 on the other carbonyl carbon to generate the intermediates **V** and **VII** with guanidine and urea, respectively. The intermediate **V** undergoes the phenyl migration and double-bond repositioning because of the electron-withdrawing carbonyl group to give the product **2**. However, in case with urea the more stable, hydantoin derivative **3**, is the final product.

Table 1 Reaction Time and Yields of Some Representative Examples of 2-Amino-5-benzyl-5-phenyl-3,5-dihydro-4*H*-imidazol-4-ones

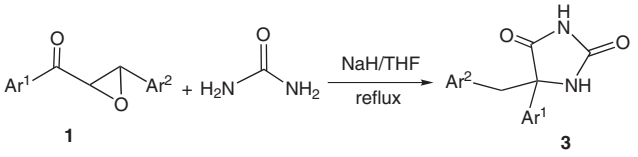


1 2

Entry	Ar^1	Ar^2	Product	Time (h)	Yield (%)[a]
1	4-$OMeC_6H_4$	3,4,5-$(OMe)_3C_6H_2$	**2a**	5	72
2	4-$OMeC_6H_4$	4-$OMeC_6H_4$	**2b**	5	77
3	4-$OMeC_6H_4$	4-FC_6H_4	**2c**	6	71
4	3,4,5-$(OMe)_3C_6H_2$	4-$OMeC_6H_4$	**2d**	5	75
5	Ph	4-ClC_6H_4	**2e**	6	72
6	4-$OMeC_6H_4$	4-ClC_6H_4	**2f**	6	74
7	4-$OMeC_6H_4$	3,4-$(OMe)_2C_6H_3$	**2g**	5	83
8	3,4,5-$(OMe)_3C_6H_2$	4-FC_6H_4	**2h**	6	79
9	3,4,5-$(OMe)_3C_6H_2$	3,4-$OMeC_6H_3$	**2i**	5	81
10	4-$OMeC_6H_4$	Ph	**2j**	6	82
11	4-ClC_6H_4	Ph	**2k**	8	53
12	2-$NO_2C_6H_4$	Ph	**2l**	12	40
13	2-MeC_6H_4	4-FC_6H_4	**2m**	6	79
14	4-$OMeC_6H_4$	4-MeC_6H_4	**2n**	4	80

[a] Isolated yield.

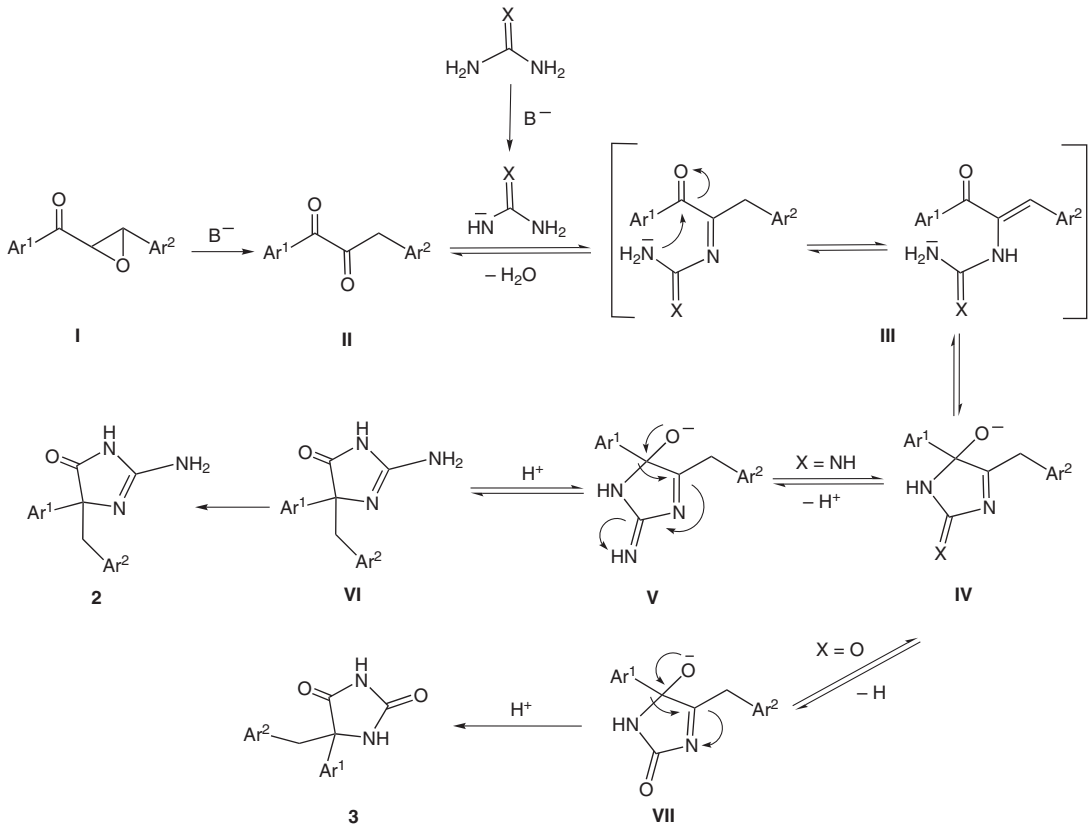
Table 2 Reaction Time and Yields of Some Representative Examples of 5-Benzyl-5-phenylimidazolidine 2,4-diones



1 **3**

Entry	Ar^1	Ar^2	Product	Time (h)	Yield (%)[a]
1	4-$OMeC_6H_4$	3,4,5-$(OMe)_3C_6H_2$	**3a**	5	79
2	4-$OMeC_6H_4$	4-FC_6H_4	**3b**	7	73
3	4-$OMeC_6H_4$	4-$OMeC_6H_4$	**3c**	5	76
4	4-$OMeC_6H_4$	3,4-$(OMe)_2C_6H_3$	**3d**	5	77
5	4-$OMeC_6H_4$	Ph	**3e**	5	81
6	4-$OMeC_6H_4$	4-ClC_6H_4	**3f**	7	70
7	Ph	4-ClC_6H_4	**3g**	6	78
8	2-$NO_2C_6H_4$	3,4-$OMeC_6H_3$	**3h**	12	44
9	4-ClC_6H_4	4-$OMeC_6H_4$	**3i**	12	58
10	2-MeC_6H_4	Ph	**3j**	5	76
11	4-$OMeC_6H_4$	2-MeC_6H_4	**3k**	5	72

[a] Isolated yield.



Scheme 2 Plausible reaction mechanism

In conclusion, a novel and efficient one-pot rearrangement reaction of 2,3-epoxydiphenyl ketones to 2-amino-5-benzyl-5-phenyl-3,5-dihydro-4*H*-imidazol-4-ones and 5-benzyl-5-phenylhydantoins from guanidine hydrochloride and urea, respectively, has been developed. This method is a convenient and high-yielding procedure for the synthesis of synthetically and pharmacologically novel 5,5-disubstituted imidazolones and 5,5-disubstituted hydantoins.

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(11) **General Procedure for Preparation for 3,5-Disubstituted Imidazolones**: Typical experimental procedure for synthesis of 3,5-disubstituted imidazolones as exemplified for **2a**. Guanidine hydrochloride (95.5 mg, 1 mmol) was added to a solution of 2,3-epoxydiphenyl ketone (334 mg, 1 mmol) in anhyd THF (10 mL). To this was added NaH (48 mg, 2 mmol) at r.t. After 30 min, the reaction mixture was stirred at reflux temperature for 5 h; TLC analysis indicated that the reaction was complete. The reaction mixture was filtered, solvent was removed by rotatory evaporator and the residue passed through a silica gel column ($CHCl_3$–MeOH) afforded **2a** (315 mg, 72%) as a white solid; mp 281–284 °C. ^{1}H NMR (600 MHz, DMSO-d_6): δ = 2.97 (d, *J* = 13.2 Hz, 1 H), 3.11 (d, *J* = 13.2 Hz, 1 H), 3.57 (s, 3 H, OCH_3), 3.65 (s, 6 H, 2 × OCH_3), 3.72 (s, 3 H, OCH_3), 6.41 (s, 2 H), 6.89 (d, *J* = 9.0 Hz, 2 H), 7.42 (d, *J* = 9.0 Hz, 2 H), 8.34 (s, 1 H). ^{13}C NMR (125 MHz, DMSO-d_6): δ = 44.8, 55.8 56.3, 60.6, 70.6 108.2, 114.0, 127.4, 132.4, 33.8, 136.7, 152.6, 158.9, 171.2, 189.0. IR (KBr): 3346.2, 32.2, 1698.2, 1645.4, 1593.4, 1299.3, 1127.9, 828.4 cm^{-1}. MS (ESI): *m*/*z* = 386.2 [M + H], 408.0 [M + Na]. Anal. Calcd for $C_{20}H_{23}N_3O_5$: C, 62.32; H, 6.01; N, 10.90. Found: C, 62.13; H, 6.15; N, 11.20.
2b: White solid; mp 298–302 °C. ^{1}H NMR (200 MHz, DMSO-d_6): δ = 2.99 (d, *J* = 13.4 Hz, 1 H), 3.21 (d, *J* = 13.4 Hz, 1 H), 3.67 (s, 3 H, OCH_3), 3.72 (s, 3 H, OCH_3), 6.73 (d, *J* = 8.9 Hz, 2 H), 6.9 (d, *J* = 8.8 Hz, 2 H), 7.03 (d, *J* = 9.1 Hz, 2 H), 7.41 (d, *J* = 8.8 Hz, 2 H), 8.20 (s, 1 H). ^{13}C NMR (125 MHz, DMSO-d_6): δ = 42.6, 54.8, 70.5, 113.1, 125.5, 127.0, 127.9, 128.0, 131.2, 141.0, 157.9, 170.2, 187.9. IR (KBr): 3347.6, 1698.3, 1652.2, 1613.4, 1513.4, 1257.6, 1033.7, 837.6 cm^{-1}. MS (ESI): *m*/*z* = 325.2 [M + H]. Anal. Calcd for $C_{18}H_{19}N_3O_3$: C, 66.45; H, 5.89; N, 12.91. Found: C, 66.71; H, 6.05; N, 12.73.
3a: White solid; mp 238–241 °C. ^{1}H NMR (600 MHz, DMSO-d_6): δ = 2.88 (d, *J* = 13.5 Hz, 1 H), 3.35 (d, *J* = 13.5 Hz, 1 H), 3.59 (s, 3 H, OCH_3), 3.69 (s, 6 H, 2 × OCH_3), 3.73 (s, 3 H, OCH_3), 6.48 (s, 2 H), 6.95 (d, *J* = 8.9 Hz, 2 H), 7.51 (d, *J* = 8.9 Hz, 2 H), 8.51 (s, 1 H), 10.46 (s, 1 H). ^{13}C NMR (125 MHz, DMSO-d_6): δ = 44.9, 55.8, 56.4, 60.5, 68.6, 108.4, 114.4, 127.5, 131.1, 132.0, 137.2, 152.9, 156.8, 159.6, 176.6. IR (KBr): 3444.1, 3342.0, 1766.7, 1709.4, 1586.6, 1241.9, 1129.9, 839.2 cm^{-1}. MS (ESI): *m*/*z* = 385 [M – H], 409.2 [M + Na]. Anal. Calcd for $C_{20}H_{22}N_2O_6$: C, 62.16; H, 5.73; N, 7.25. Found: C, 62.13; H, 6.14; N, 7.36.
3b: White solid; mp 204–207 °C. ^{1}H NMR (200 MHz, DMSO-d_6): δ = 2.96 (d, *J* = 13.5 Hz, 1 H), 3.34 (d, *J* = 13.5 Hz, 1 H), 3.74 (s, 3 H, OCH_3), 6.96 (d, *J* = 8.8 Hz, 2 H), 7.16 (m, 4 H), 7.51 (d, *J* = 8.8 Hz, 2 H), 8.59 (s, 1 H). ^{13}C NMR (125 MHz, DMSO-d_6): δ = 43.0, 55.6, 70.5, 113.9, 114.6, 114.8, 127.1, 132.4, 132.5, 133.5, 158.6, 160.5, 160.6, 162.6, 170.9, 188.6. IR (KBr): 3373.9, 1757.5, 1713.4, 1608.3, 1511.7, 1403.6, 1257.7, 1225.7, 845.8 cm^{-1}. MS (ESI): *m*/*z* = 315 [M + H]. Anal. Calcd for $C_{17}H_{15}FN_2O_3$: C, 64.96; H, 4.81; N, 8.91. Found: C, 65.08; H, 5.09; N, 8.97.

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