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Novel 1,3-dipolar cycloadditions of fulvenes and hydrazonyl chlorides: a facile synthesis of the cyclopenta[*d*]pyridazines

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ABSTRACT

A simple and convenient route for one-pot synthesis of cyclopenta[*d*]pyridazine through 1,3-dipolar cycloaddition of fulvenes and hydrazonyl chlorides is described. The reaction of fulvenes with hydrazonyl chlorides in the presence of silver carbonate smoothly afforded a series of cyclopenta[*d*]pyridazines.

Fused pyridazines and their derivatives have been known to exhibit pharmacological properties, for example, anti-inflammatory activity,[1] antibacterial agents,[2] protein tyrosine phosphatase inhibitors,[3] and anticancer agents.[4] In addition, cyclopenta[*d*]pyridazine derivatives are also a structural subunit in the self-assembly of coordination of polymers or supramolecular complexes.[5] However, there have been only limited methods as facile and convenient syntheses of cyclopenta[*d*]pyridazines and their derivatives. Cyclopenta[*d*]pyridazines are prepared by the use of benzoylated cyclopentadienes or fulvenes with hydrazines under restricted conditions.[6] Among the cycloadditions of 6-dimethylaminofulvenes with 1,3-dipoles, such as nitrile oxides[7] and sydnones[8], 1,3-dipolar cycloadditions of fulvenes are of particular interest to construct fused heteroaromatics. Cyclopenta[*d*]pyridazines can be afforded by cycloaddition reaction of *tert*-butylfulvenes with tetrazines[9] or sydnones[8] with limited versatility of products. Recently, cyclopenta[*d*]pyridazines and fused pyridazines are gaining importance as substrates, such as coordination polymers, supramolecular complexes,[5,10] and ferrocene-based enantiomerically enriched chiral ligands for various metal catalysts.[11]

However, 1,3-dipolar cycloaddition of nitrile imines with fulvenes to construct versatile cyclopenta[*d*]pyridazines has not been reported. Almost all existing methods for the synthesis of cyclopenta[*d*]pyridazines have some synthetic shortcomings, such as rigid conditions and poor yields of target products, which limit their scope. All these methods include a classical modification and functionalization of fulvenes requiring restricted condition and difficult process to perform the reaction to afford the desired products.

Herein we report an efficient and convenient approach to a one-pot synthesis of cyclopenta[*d*]pyridazine under mild condition through the 1,3-dipolar cycloaddition of fulvene and nitrile imine, which is a plausible intermediate, and is afforded straightforwardly from hydrazonyl chloride.

The fulvenes **2** were obtained from the condensation reaction of dimethylformamide dimethylacetal and cyclopentadiene.[12] The suitable hydrazonyl chlorides **1** were directly derived from the corresponding hydrazones by treatment of *N*-chlorosuccinimide.[13] Treatment of hydrazonyl chlorides with fulvenes mediated by silver carbonate afforded cyclopenta[*d*]pyridazines through a plausible intermediate, nitrile imine, in the presence of KI as shown in Scheme 1.

For initial assessment, we examined the cycloaddition of **1** and **2** in the presence of a base. The result given in Table 1 reveals that silver carbonate was essential to afford the desired cyclopenta[*d*]pyridazine along with triethylamine as a base of choice at room temperature in moderate yield. A tetrahydrofuran solution of hydrazonyl chloride and fulvenes in the presence of triethylamine at room temperature failed to produce the desired cyclopenta[*d*]pyridazines (entry 1). The other bases, such as DBU and KOBu^t, were also ineffective to the reaction (entries 2 and 4). Under refluxing conditions, the product was obtained in poor yields with formation of unknown products (entries 5, 6, and 7). It was clear that silver carbonate and KI were essential to the 1,3-dipolar cycloadditions of hydrazonyl chlorides with aminofulvenes, and the reaction was smoothly completed in excellent yield (entries 8 and 9). The reaction did not produce the desired pyridazines

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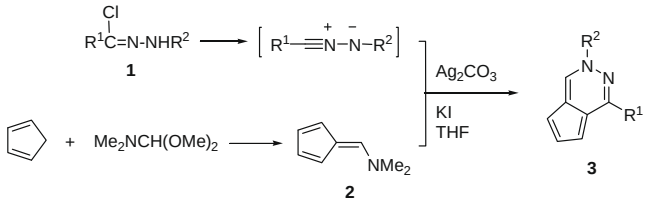
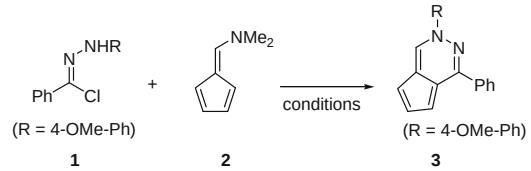
without silver carbonate, and hydrazonyl chloride was recovered moderately after the reaction (entry 10). The other bases, such as Na_2CO_3 and K_2CO_3 instead of Ag_2CO_3, were not much effective to the reaction.[14] The other solvents used in this reaction were not effective to the reaction. Moreover, hydrazonyl chloride remained after the reaction when benzene and dichloromethane were used as solvents presumably because of poor solubility of silver carbonate in these types of non-polar aprotic solvents (entries 11 and 12).

The reactions that were executed under refluxing condition in the presence of silver carbonate did not give rise to better results than that of room temperature condition presumably because of inducing dimerized product formation of hydrazonyl chloride (entry 13). To evaluate the scope and limitation for this procedure to the synthesis of cyclopenta[*d*]pyridazines, we performed a number of cycloaddition reaction with various aromatic hydrazonyl chlorides and fulvenes as given in Table 2. All of the reactions were run at room temperature and hydrazonyl chlorides **1a–p** (1.0 equiv), Ag_2CO_3 (1.1 equiv), fulvene (2.5 equiv), and catalytic



Scheme 1. Reaction of hydrazonyl chloride and fulvene.

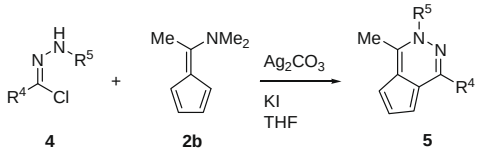
Table 1
Reaction of hydrazonyl chloride and fulvene



Entry	Reaction condition	Yield[c] (%)
1	NEt_3, THF, rt, 72 h	0[a]
2	DBU, THF, rt, 13 h	0
3	DBU, CH_2Cl_2, rt, 13 h	0
4	$KOBu^t$, THF, rt, 13 h	0[b]
5	NEt_3, THF, reflux, 3 h	35
6	NEt_3, benzene, reflux, 3 h	37
7	NEt_3, toluene, reflux, 3 h	32
8	Ag_2CO_3, THF, rt, 13 h	15
9	Ag_2CO_3, KI, THF, rt, 13 h	85
10	NEt_3, KI, THF, rt, 13 h	0[a]
11	Ag_2CO_3, KI, CH_2Cl_2, rt, 13 h	56
12	Ag_2CO_3, KI, benzene, rt, 13 h	58
13	Ag_2CO_3, KI, benzene, reflux, 3 h	45

[a] Hydrazonyl chloride was recovered after reaction.
[b] No substrate was recovered after the reaction.
[c] Isolated yield of **3**.

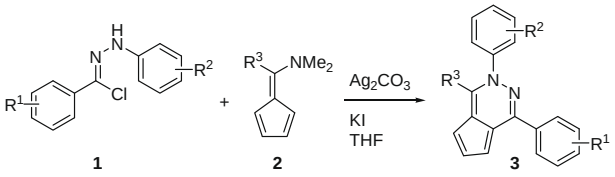
Table 3
The 1,3-dipolar cycloaddition of aliphatic hydrazonyl chlorides with aminofulvenes



Entry	Hydrazonyl chloride	Pyridazine	Yield[a] (%)
1	**4a** (R^4 = isobutyl, R^5 = 4-OMe-Ph)	**5a** (R^4 = isobutyl, R^5 = 4-OMe-Ph)	65
2	**4b** (R^4 = methyl, R^5 = 4-OMe-Ph)	**5b** (R^4 = methyl, R^5 = 4-OMe-Ph)	62
3	**4c** (R^4 = cyclohexyl, R^5 = 4-OMe-Ph)	**5c** (R^4 = cyclohexyl, R^5 = 4-OMe-Ph)	76
4	**4d** (R^4 = isopropyl, R^5 = 4-OMe-Ph)	**5d** (R^4 = isopropyl, R^5 = 4-OMe-Ph)	85
5	**4e** (R^4 = 3-OMe-Ph, R^5 = *t*-butyl)	**5e** (R^4 = 3-OMe-Ph, R^5 = *t*-butyl)	78

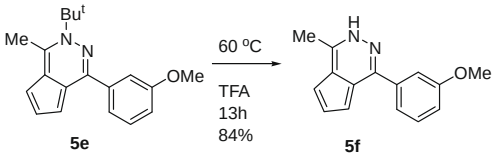
[a] Isolated yield of **5**.

Table 2
The 1,3-dipolar cycloaddition of aromatic hydrazonyl chlorides with aminofulvenes



Entry	Hydrazonyl chloride	Fulvene	Pyridazine	Yield[a] (%)
1	**1a** (R^1 = R^2 = H)	**2a** (R^3 = H	**3a** (R^1 = R^2 = R^3 = H)	81
2	**1b** (R^1 = R^2 = H)	**2b** (R^3 = Me)	**3b** (R^1 = R^2 = H, R^3 = Me)	82
3	**1c** (R^1 = H, R^2 = 4-OMe)	**2a**	**3c** (R^1 = H, R^2 = 4-OMe, R^3 = H)	85
4	**1d** (R^1 = H, R^2 = 4-OMe)	**2b**	**3d** (R^1 = H, R^2 = 4-OMe, R^3 = Me)	86
5	**1e** (R^1 = H, R^2 = 3-Br)	**2a**	**3e** (R^1 = H, R^2 = 3-Br, R^3 = H)	72
6	**1f** (R^1 = H, R^2 = 3-Br)	**2b**	**3f** (R^1 = H, R^2 = 3-Br, R^3 = Me)	76
7	**1g** (R^1 = H, R^2 = 3,4-di Cl)	**2a**	**3g** (R^1 = H, R^2 = 3,4-di Cl, R^3 = H)	67
8	**1h** (R^1 = H, R^2 = 3,4-di Cl)	**2b**	**3h** (R^1 = H, R^2 = 3,4-di Cl, R^3 = Me)	68
9	**1i** (R^1 = H, R^2 = 4-F)	**2a**	**3i** (R^1 = H, R^2 = 4-F, R^3 = H)	76
10	**1j** (R^1 = H, R^2 = 4-F)	**2b**	**3j** (R^1 = H, R^2 = 4-F, R^3 = Me)	75
11	**1k** (R^1 = H, R^2 = 2-Cl)	**2a**	**3k** (R^1 = H, R^2 = 2-Cl, R^3 = H)	69
12	**1l** (R^1 = H, R^2 = 2-Cl)	**2b**	**3l** (R^1 = H, R^2 = 2-Cl, R^3 = Me)	72
13	**1m** (R^1 = H, R^2 = 2,3-di Cl)	**2b**	**3m** (R^1 = H, R^2 = 2,3-di Cl, R^3 = Me)	69
14	**1n** (R^1 = H, R^2 = 2,5-di Cl)	**2b**	**3n** (R1 = H, R^2 = 2,5-di Cl, R^3 = Me)	72
15	**1o** (R^1 = H, R^2 = 4-Me)	**2b**	**3o** (R^1 = H, R^2 = 4-Me, R^3 = Me)	82
16	**1p** (R^1 = H, R^2 = 3-OMe)	**2b**	**3p** (R^1 = H, R^2 = 3-OMe, R^3 = Me)	81

[a] Isolated yield of **3**.



Scheme 2. Synthesis of 4-(3-methoxyphenyl)-1-methyl-2*H*-cyclopenta[*d*]-pyridazine.

amount of KI in THF were used as reactants to give rise to the desired cycloadducts **3a**–**p**.[15] As shown in Table 2, in most of the cases, the cycloadducts **3a**–**p** were isolated in moderate to excellent yield. Various substituents on aromatics, such as OMe, F, Br, and Cl, were well tolerated to give cycloaddition products in excellent yields. In general, 6-methyl-6-dimethylaminofulvene **3b** gave rise to a better yield than that of 6-dimthylaminofulvene **3a**.

As shown in Table 3, aliphatic hydrazonyl chlorides were also examined to afford the corresponding aliphatic cyclopenta[*d*]-pyridazines. All the reactions were performed with the same reaction condition as mentioned above.

Treatment of hydrazonyl chlorides **4a**–**d** with aminofulvene **2b** smoothly gave rise to the desired cyclopenta[*d*]pyridazine **5a**–**e** in moderate yields. It is noteworthy to report that hydrazonyl chloride **4e** which has a *t*-butyl functionality that can be easily removed from the cyclopenta[*d*]pyridazine to construct the unsubstituted pyridazine produced the corresponding pyridazine **5e** in moderate yield.

Subsequently, deprotection of *t*-butyl functionality on **5e** afforded the corresponding deprotected pyridazine **5f** under heated condition by the use of trifluoroacetic acid in 84% yield (Scheme 2).

The successful utilization of cycloaddition of aliphatic or aromatic hydrazonyl chloride with aminofulvene to construct various cyclopenta[*d*]pyridazine provides an important methodology for the extension of cyclopenta[*d*]pyridazine skeletons. Ongoing studies are being directed toward the further elaboration of cyclopenta[*d*]pyridazine derivatives, extending the scope of the parent compound to improve the corresponding biological activities and their uses.

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14. The other bases, such as K_2CO_3 and Na_2CO_3, were tested and afforded the product in lower yields with remaining starting material, K_2CO_3 (25% in yield) and Na_2CO_3 (15% in yield), than that of Ag_2CO_3, respectively.
15. *Typical procedure*: To a stirred solution of 1-(chlorophenylmethylene)-2-(4-methoxyphenyl)hydrazine **1d** (100 mg, 0.383 mmol), 6-methyl-6-*N*,*N*-dimethylaminofulvene **2b** (124 mg, 0.958 mmol) in THF (3 mL) solution was added Ag_2CO_3 (116 mg, 0.421 mmol) and KI (5 mg, 30 μmol). The reaction mixture was stirred at room temperature for 13 h. After completion of the reaction, the reaction mixture was poured into water and extracted with ethyl acetate. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography to afford **3d** as a yellow solid (103 mg, 86%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.95 (d, J = 8.8 Hz, 2H), 7.55–7.46 (m, 4H), 7.43–7.42 (m, 2H), 7.04–6.97 (m, 4H), 3.86 (s, 3H), 2.66 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.4, 149.4, 144.0, 143.2, 131.0, 130.2, 129.9, 129.3, 129.0, 126.9, 123.4, 118.8, 113.9, 108.3, 108.1, 55.3, 17.2; MS *m/e* (relative intensity) 314 (100, M^+), 299 (10.0); LC/MS *m/z* calcd for $C_{21}H_{18}N_2O$ (MH^+) 314.14, found 315.2.