JOC The Journal of Organic Chemistry

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Manganese-Promoted Ring-Opening Hydrazination of Cyclobutanols: Synthesis of Alkyl Hydrazines

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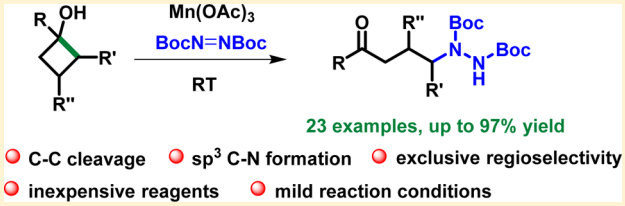
Supporting Information

ABSTRACT: We herein disclose an efficient manganese-promoted hydrazination of cyclobutanols through cyclic C−C bond cleavage. The ring opening occurs under mild reaction conditions, readily affording a variety of alkyl hydrazines in synthetically useful yields and exclusive regioselectivities. The chain reaction mechanism involving the addition of alkyl carbon radical to azodicarboxylate is proposed.

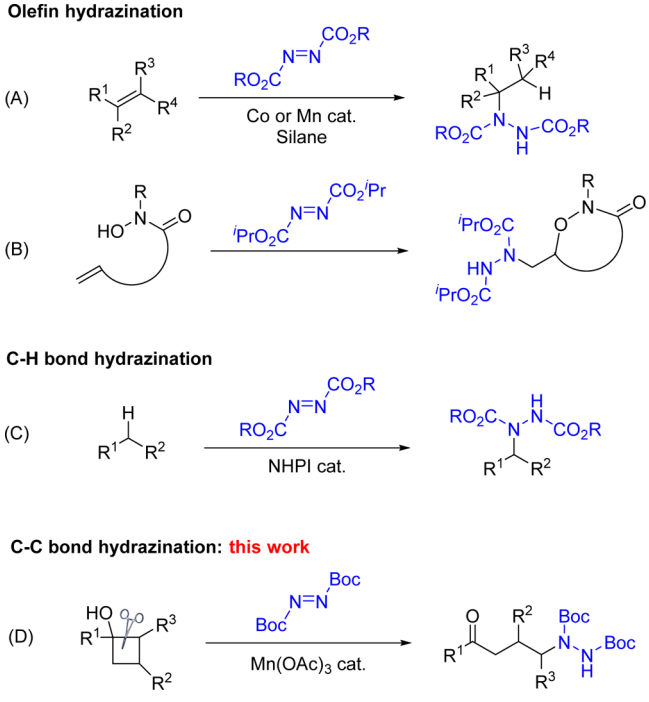


Alkylamine is a ubiquitous structural motif found in numerous natural products, pharmaceutical substances, and other biologically active compounds.[1] Therefore, the efficient synthesis of alkylamines is of high importance in both academia and industry. The conventional preparation of alkyl amines relies on the nucleophilic substitution of aliphatic alcohols or halides with amines or the direct reduction from alkyl nitriles. These transformations sometimes require harsh conditions in which many sensitive functional groups could not be tolerated. In this context, the development of new mild access to alkyl amines is still in demand.

Alkyl hydrazines can serve as privileged precursors for alkylamines and other useful synthetic building blocks.[2] They are generally produced through the displacement of alkyl halides by hydrazines, nucleophilic addition of carbanion to hydrazones, or Michael addition of hydrazines to unsaturated C−C bonds.[3] Recently, the addition of alkyl radical to azodicarboxylate has proven to be a robust strategy for the synthesis of alkyl hydrazines, and many remarkable efforts have been devoted to this field.[4] In 2004, Carreira et al. reported the cobalt- or manganese-catalyzed hydrohydrazination reaction of olefins and azodicarboxylate to synthesize alkyl hydrazines (Scheme 1A).[4a,b] In 2011, Alexanian et al. reported the metal-free oxyhydrazination of olefins with azodicarboxylate (Scheme 1B).[4c] In these studies, the carbon radicals were generated from a diversity of olefins. Recently, Inoue et al. reported the NHPI-catalyzed C−H bond hydrazination with azodicarboxylate, where the carbon radicals were directly generated by the activation of inert sp^3 C−H bonds (Scheme 1C).[4d]

The elaboration of inert C−C σ-bond into other useful chemical bonds always represents an intriguing yet challenging subject.[5] Owing to the assistance of ring strain, the cyclic C−C bond of cyclobutanols is prone to cleave under certain conditions.[6] By this feature, cyclobutanols have become prominent precursors for the synthesis of γ-substituted ketones,

Scheme 1. Types of Radical-Mediated Alkyl Hydrazination



which are sometimes difficult to obtain.[7] Two mechanistic pathways, transition-metal-catalyzed β-carbon elimination and radical-promoted cyclic C−C σ-bond scission, can be involved in the C−C cleavage step.[8,9] We have a longstanding interest in the radical-mediated ring-opening of cyclobutanols. Recently, we revealed the first silver-catalyzed ring-opening fluorination

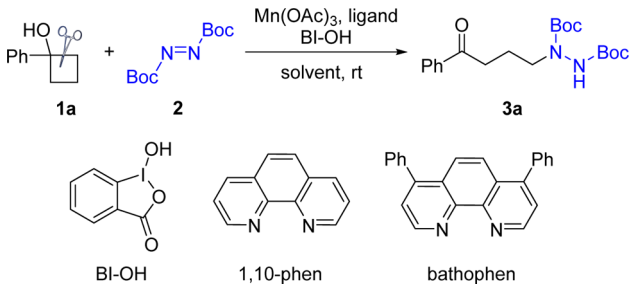
Received: June 15, 2016
Published: August 9, 2016

DOI: 10.1021/acs.joc.6b01433
J. Org. Chem. 2016, 81, 8043−8049

of cyclobutanols to afford the γ-fluorinated ketones.[10] Subsequently, a series of γ-chlorinated and brominated ketones were prepared under the silver catalysis.[11] To overcome the competitively intramolecular annulation occurred during the silver-catalyzed ring-opening of cyclobutanols,[12] a modified protocol by means of manganese catalysis was then achieved, facilitating the efficient synthesis of γ-azido-,[13] cyano-, alkynyl-,[14] and thio-substituted ketones.[15] Encouraged by these studies, we herein describe the manganese-promoted hydrazination of cyclobutanols by azodicarboxylate through cyclic C−C bond cleavage. The ring opening occurs under mild reaction conditions, furnishing a variety of alkyl hydrazines in synthetically useful yields and exclusive regioselectivities (Scheme 1D).

Our investigations of ring-opening hydrazination of cyclobutanols commenced with the extensive reaction parameters survey (Table 1). Initially, the reaction of phenyl-substituted

Table 1. Reaction Parameters Survey[a]



entry	ligand	solvent	BI-OH (equiv)	yield[b] (%)
1	1,10-phen	Toluene		<10
2	1,10-phen	THF		<10
3	1,10-phen	Dioxane		<10
4	1,10-phen	DCE		55
5	1,10-phen	MeOH		51
6	1,10-phen	DMF		<10
7	1,10-phen	CH_3CN		56
8	bathophen	CH_3CN		60
9	bpy	CH_3CN		<10
10	dtbpy	CH_3CN		<10
11[c]	bathophen	CH_3CN		67
12[c]	bathophen	CH_3CN	0.2	90
13[d]	bathophen	CH_3CN	0.2	66
14[e]	bathophen	CH_3CN	0.2	0

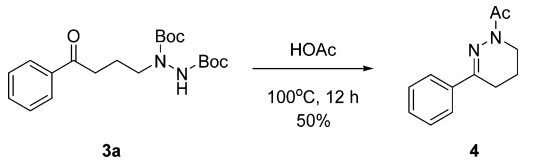
[a]Reaction conditions: **1a** (0.20 mmol), **2** (0.30 mmol, 1.5 equiv), $Mn(OAc)_3·H_2O$ (0.04 mmol, 0.2 equiv), and ligand (0.044 mmol, 0.22 equiv) in solvent (1.5 mL, 0.13 M) at rt. [b]Yields of isolated products. [c]0.3 M concentration. [d]0.1 equiv of $Mn(OAc)_3·H_2O$. [e]Without $Mn(OAc)_3·H_2O$.

cyclobutanol **1a** with azodicarboxylate **2** was carried out in the presence of manganese acetate as initiator and 1,10-phenantholine as ligand at room temperature. During the organic solvent screening (entries 1−7), acetonitrile demonstrated the best efficiency to give a modest yield (56%, entry 7). Then the effect of different *N*,*N*-bidentate ligands was examined (entries 8−10). It was found that the use of bathophenantholine could slightly improve the reaction yield to 60% (entry 10). The chemical yield was further elevated when the reaction was performed in concentrated solution (0.3 M, entry 11). Remarkably, the addition of 0.2 equiv of BI-OH significantly improved the outcome, affording the desired alkyl hydrazine product **3a** in 90% yield (entry 12). Reducing the amount of manganese acetate compromised the reaction outcome (entry 13). The reaction did not yield the desired product without manganese acetate (entry 14).

With the optimized reaction conditions in hand, we set out to evaluate the generality of this protocol. As shown in Scheme 2, the method exhibited a broad functionality tolerance that a diversity of alkyl hydrazines were readily furnished in synthetically useful yields. Neutral phenyl- and naphthyl-substituted cyclobutanols were suitable substrates; the former delivered a better yield (**1a** and **1b**). Cyclobutanols bearing electron-donating groups consistently resulted in good yields (**1c**−**f**). The steric hindrance did not have much influence on the reaction, as the *ortho*-occupied substrate still gave the expected product in high yield (**1h**). Surprisingly, the yields were compromised when the *meta*-occupied substrates were employed (**1g** and **1i**). The reactions with electron-deficient cyclobutanols led to an appreciably lower yield than electron-rich ones, affording the products in moderate yields (**1j**−**n**). Nevertheless, the example of **1l** was noteworthy, since the presence of aryl bromide offered the platform for later functionalization through cross-coupling reactions. Moreover, heteroaryl- (e.g., thienyl) and alkyl-substituted cyclobutanols were also competent to obtain the corresponding alkyl hydrazines in substantial yields (**1o**−**q**). Remarkably,susceptible functionalities, such as alkenyl and alkynyl, were left intact during the reaction, explicitly illustrating the excellent chemoselectivities (**1r** and **1s**). Though less reactive, the substrate with a multiply substituted cyclobutyl ring was also smoothly converted into the desired product in useful yield (**1t**).

Subsequently, we investigated the regioselectivities of the transformation. First, a sole isomeric cyclobutanol **1u** was subjected to the standard reaction conditions (Scheme 3a). The more substituted C−C bond was selectively cleaved, and the hydrazination occurred at the methine position to give the secondary alkyl hydrazine **3u** (dr ∼ 1:1) in high yield. Then, bicyclic substrates **1v** and **1w** were examined. The hydrazination exclusively took place on the ring to generate cyclopentyl hydrazine **3v** (dr ∼ 3.6:1) and cyclohexyl hydrazine **3w** (dr > 19:1) in good yields, respectively (Scheme 3b,c). Remarkably, product **3w** was obtained with good stereoselectivity as well, which was probably controlled by the steric hindrance adjacent to the C−N bond. The thermodynamically favored *trans*-configuration of **3w** was supported by the NOE analysis. These examples unambiguously suggested that this ring-opening hydrazination reaction underwent a highly regioselective pattern. It should be mentioned that under the same reaction conditions cyclopropanol was eligible to give the corresponding β-hydrazinated product but cyclopentanol failed.

To demonstrate the utility of this method, the product **3a** was converted into pyridazine derivative **4** in synthetically useful yield by simply treating it with hot acetic acid (eq 1).

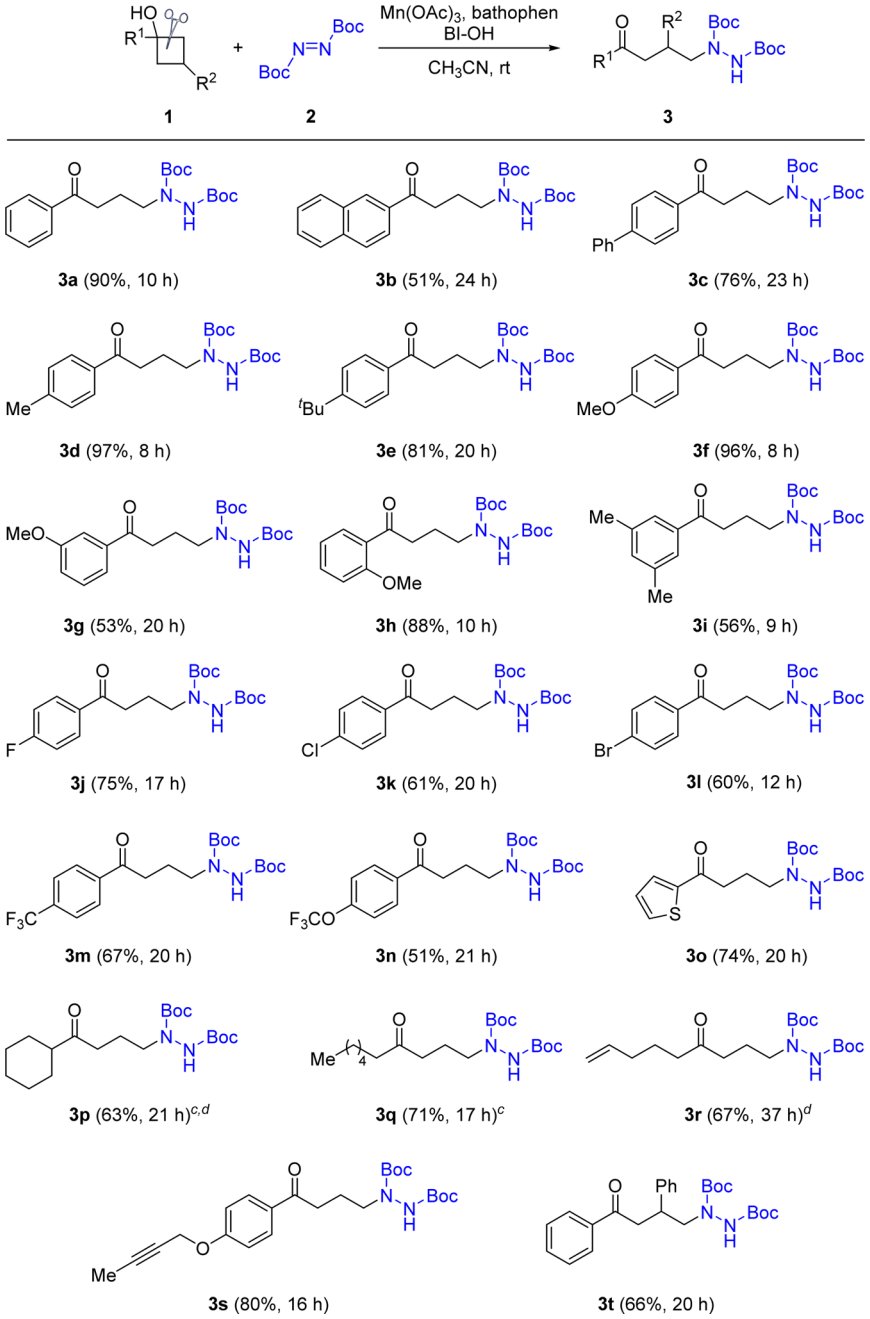


eq 1

On the basis of the experimental observations and the realization with our previously manganese-catalyzed ring-opening reactions,[13−15] the mechanistic pathways of this reaction were postulated (Figure 1). The transformation was

DOI: 10.1021/acs.joc.6b01433
J. Org. Chem. 2016, 81, 8043−8049

Scheme 2. Substrate Scope[a,b]



[a]Standard conditions: **1** (0.30 mmol), **2** (0.45 mmol, 1.5 equiv), $Mn(OAc)_3 \cdot H_2O$ (0.06 mmol, 0.2 equiv), bathophen (0.066 mmol, 0.22 equiv), and BI-OH (0.06 mmol, 0.2 equiv) in CH_3CN (1.0 mL, 0.3 M) at rt. [b]Yields of isolated products. [c]1,10-phen was used instead of bathophen. [d]BI-OH (0.3 mmol, 1.0 equiv) was used.

initiated by the single-electron oxidation of cyclobutanol **1** by Mn^V species, which was generated in situ from the interaction of Mn^{III} salt and hypervalent iodine reagent (path a)[16] or directly by Mn^{III} salt (pathb). The obtained cyclobutyloxy radical **I** could fragment into an alkyl carbon radical **II** after ring opening. The intermediate **II** was immediately added to azodicarboxylate **2**, forming the *N*-centered radical **III**. After abstraction of a hydrogen atom from cyclobutanol **1**, the intermediate **III** was eventually converted into the alkyl hydrazine product **3**, and the cyclobutyloxy radical **I** was regenerated.

In summary, we have described an efficient manganese-promoted hydrazination of cyclobutanols through cyclic C−C bond cleavage under mild reaction conditions. The transformation has good tolerance for functional groups, affording a variety of alkyl hydrazines in synthetically useful yields and unique regioselectivities. The chain-reaction mechanism involving the addition of alkyl carbon radical to azodicarboxylate has been proposed.

EXPERIMENTAL SECTION

General Information. All reactions were maintained under a nitrogen atmosphere. Commercially available reagents were used

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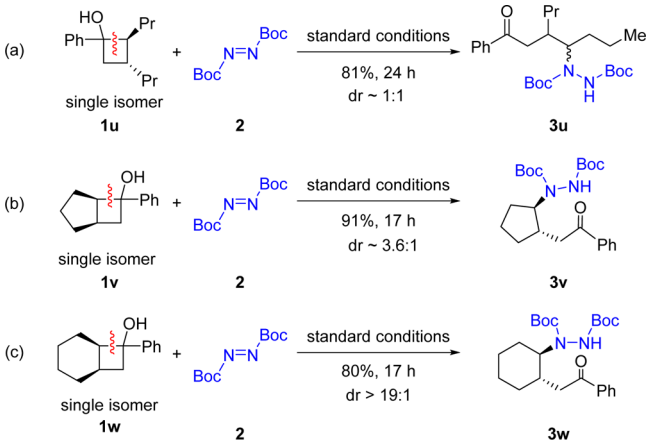
Scheme 3. Regiospecific Ring-Opening Hydrazination



without further purification. Chemical shifts in ^{1}H NMR spectra are reported in ppm from tetramethylsilane with the solvent resonance as internal standard ($CDCl_3$: δ 7.26). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quadruplet, br = broad, m = multiplet), coupling constants (Hz) and integration. ^{13}C NMR spectra were recorded with complete proton decoupling. Chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance as the internal standard ($CDCl_3$: δ 77.16). Infrared spectra were recorded on an FTIR spectrometer with the absorptions reported in wavenumbers (cm^{-1}). Products were purified by flash chromatogrgraphy on 300–400 mesh silica gels. All melting points were determined without correction.

General Procedure for the Ring-Opening Hydrazination of Cyclobutanols. Cyclobutanol **1** (0.3 mmol, 1.0 equiv), $Mn(OAc)_3 \cdot 2H_2O$ (0.06 mmol, 0.2 equiv), bathophen (0.066 mmol, 0.22 equiv), BI-OH (0.06 mmol, 0.2 equiv), and azodicarboxylate **2** (0.45 mmol, 1.5 equiv) were loaded in a flask which was subjected to evacuation/flushing with nitrogen three times. CH_3CN (1.0 mL) was added to the mixture via syringe, and the mixture was then stirred at room temperature until the starting material had been consumed as determined by TLC. The mixture was extracted with ethyl acetate (3 × 10 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, concentrated, and purified by flash column chromatography on silica gel (ethyl acetate/petroleum ether) to give the product **3**.

*Di-tert-butyl 1-(4-Oxo-4-phenylbutyl)hydrazine-1,2-dicarboxylate (**3a**).* Purification by column chromatography (petroleum ether/EtOAc = 10:1) afforded **3a** as a yellow solid (102.1 mg, 90% yield): mp 60–62 °C; IR (film, cm^{-1}) 3061, 2979, 1733, 1701, 1685, 1408 cm^{-1}; ^{1}H NMR (400 MHz, DMSO, 80 °C) δ 8.72 (br, 1H), 7.94 (d, J = 7.6 Hz, 2H), 7.61 (dd, J = 7.6, 7.6 Hz, 1H), 7.51 (dd, J = 7.6, 7.6 Hz, 2H), 3.40 (t, J = 6.8 Hz, 2H), 3.05 (t, J = 6.8 Hz, 2H), 1.89–1.80 (m, 2H), 1.42 (s, 9H), 1.38 (s, 9H); ^{13}C NMR (100 MHz, DMSO, 80 °C) δ 199.6, 155.0, 154.8, 137.1, 132.8, 128.5, 127.7, 79.6, 79.3, 48.9, 35.1, 28.1, 27.9, 21.9; HRMS [ESI-Q-TOF] calcd for $C_{20}H_{30}N_2O_5Na$ [M + Na^+] 401.2052, found 401.2051.

*Di-tert-butyl 1-(4-(Naphthalen-2-yl)-4-oxobutyl)hydrazine-1,2-dicarboxylate (**3b**).* Purification by column chromatography (petroleum ether/EtOAc = 10:1) afforded **3b** as a yellow solid (65.3 mg, 51% yield): mp 88–90 °C: IR (film, cm^{-1}) 2978, 1732, 1699, 1663, 1409, 1247 cm^{-1}; ^{1}H NMR (400 MHz, DMSO, 80 °C) δ 8.72 (br, 1H), 8.59 (s, 1H), 8.09 (d, J = 7.6 Hz, 1H), 8.02–7.95 (m, 3H), 7.67–7.59 (m, 2H), 3.45 (t, J = 6.8 Hz, 2H), 3.19 (t, J = 7.2 Hz, 2H), 1.95–1.88 (m, 2H), 1.42 (s, 9H), 1.38 (s, 9H); ^{13}C NMR (100 MHz, DMSO, 80 °C) δ 199.6, 155.0, 154.9, 135.1, 134.4, 132.3, 129.4, 129.3, 128.3, 128.2, 127.6, 126.8, 123.6, 79.7, 79.3, 35.2, 28.1, 28.0, 27.9, 22.1; HRMS [ESI-Q-TOF] calcd for $C_{24}H_{32}N_2O_5Na$ [M + Na^+] 451.2209, found 451.2210.

*Di-tert-butyl 1-(4-([1,1′-Biphenyl]-4-yl)-4-oxobutyl)hydrazine-1,2-dicarboxylate (**3c**).* Purification by column chromatography (petroleum ether/EtOAc = 12:1) afforded **3c** as a white solid (102.9 mg, 76% yield): mp 129–131 °C; IR (film, cm^{-1}) 2982, 1728, 1703, 1685, 1400, 1208 cm^{-1}; ^{1}H NMR (400 MHz, DMSO, 80 °C) δ 8.72 (br, 1H), 8.02 (d, J = 8.4 Hz, 2H), 7.79 (d, J = 8.4 Hz, 2H), 7.72 (d, J = 7.6 Hz, 2H), 7.49 (dd, J = 7.2, 7.2 Hz, 2H), 7.41 (dd, J = 7.2, 7.2 Hz, 1H), 3.42 (t, J = 6.8 Hz, 2H), 3.07 (t, J = 7.2 Hz, 2H), 1.90–1.84 (m, 2H), 1.42 (s, 9H), 1.38 (s, 9H); ^{13}C NMR (100 MHz, DMSO, 80 °C) δ 199.2, 155.0, 154.9, 144.5, 139.1, 135.8, 129.0, 128.4, 128.2, 126.9, 126.8, 79.7, 79.3, 35.2, 28.1, 28.0, 22.0; HRMS [ESI-Q-TOF] calcd for $C_{26}H_{34}N_2O_5Na$ [M + Na^+] 477.2365, found 477.2356.

*Di-tert-butyl 1-(4-Oxo-4-(p-tolyl)butyl)hydrazine-1,2-dicarboxylate (**3d**).* Purification by column chromatography (petroleum ether/EtOAc = 10:1) afforded **3d** as a yellow solid (114.2 mg, 97% yield): mp 75–77 °C; IR (film, cm^{-1}) 2978, 1736, 1707, 1680, 1408, 1304 cm^{-1}; ^{1}H NMR (400 MHz, DMSO, 80 °C) δ 8.73 (br, 1H), 7.84 (d, J = 7.6 Hz, 2H), 7.31 (d, J = 7.6 Hz, 2H), 3.39 (t, J = 6.4 Hz, 2H), 3.00 (t, J = 7.2 Hz, 2H), 2.38 (s, 3H), 1.85–1.81 (m, 2H), 1.41 (s, 9H), 1.38 (s, 9H); ^{13}C NMR (100 MHz, DMSO, 80 °C) δ 199.5, 155.4, 155.3, 143.6, 135.1, 129.5, 128.3, 80.1, 79.7, 49.4, 35.5, 28.5, 28.4, 22.5, 21.4; HRMS [ESI-Q-TOF] calcd for $C_{21}H_{32}N_2O_5Na$ [M + Na^+] 415.2209, found 415.2209.

*Di-tert-butyl 1-(4-(4-(tert-Butyl)phenyl)-4-oxobutyl)hydrazine-1,2-dicarboxylate (**3e**).* Purification by column chromatography (petroleum ether/EtOAc = 15:1) afforded **3e** as a yellow oil (105.1 mg, 81% yield): IR (film, cm^{-1}) 2969, 1799, 1735, 1707, 1405, 1247 cm^{-1}. ^{1}H NMR (400 MHz, DMSO, 80 °C) δ 8.70 (br, 1H), 7.88 (d, J = 8.4 Hz, 2H), 7.52 (d, J = 8.4 Hz, 2H), 3.40 (t, J = 6.8 Hz, 2H), 3.01 (t, J = 7.2 Hz, 2H), 1.88–1.81 (m, 2H), 1.41 (s, 9H), 1.38 (s, 9H), 1.32 (s, 9H); ^{13}C NMR (100 MHz, DMSO, 80 °C) δ 199.1, 156.0, 155.0, 154.8, 134.5, 127.7, 125.3, 79.6, 79.3, 48.9, 35.1, 34.7, 30.8, 28.0, 27.9, 22.0; HRMS [ESI-Q-TOF] calcd for $C_{24}H_{38}N_2O_5Na$ [M + Na^+] 457.2678, found 457.2681.

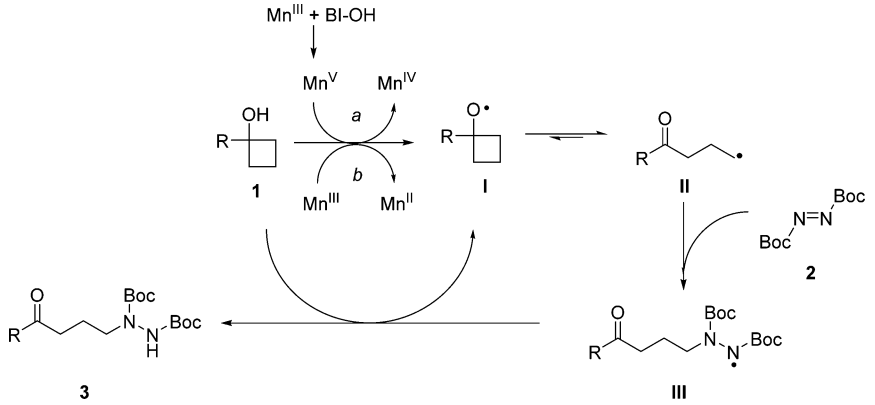


Figure 1. Proposed mechanism.

DOI: 10.1021/acs.joc.6b01433
J. Org. Chem. 2016, 81, 8043–8049

*Di-tert-butyl 1-(4-(4-Methoxyphenyl)-4-oxobutyl)hydrazine-1,2-dicarboxylate (**3f**).* Purification by column chromatography (petroleum ether/EtOAc = 10:1) afforded **3f** as a yellow solid (117.7 mg, 96% yield): mp 58−60 °C; IR (film, cm^{-1}) 2978, 1735, 1706, 1678, 1393, 1211 cm^{-1}. ^1H NMR (400 MHz, DMSO, 80 °C) δ 8.68 (br, 1H), 7.92 (d, J = 8.8 Hz, 2H), 7.02 (d, J = 8.8 Hz, 2H), 3.85 (s, 3H), 3.39 (t, J = 6.8 Hz, 2H), 2.97 (t, J = 7.2 Hz, 2H), 1.86−1.79 (m, 2H), 1.41 (s, 9H), 1.38 (s, 9H); ^{13}C NMR (100 MHz, DMSO, 80 °C) δ 198.0, 163.1, 155.0, 154.9, 130.1, 130.0, 113.9, 79.6 79.3, 55.5, 49.0, 34.8, 28.1, 27.9, 22.1; HRMS [ESI-Q-TOF] calcd for $C_{21}H_{32}N_2O_6Na$ [M + Na^+] 431.2158, found 431.2152.

*Di-tert-butyl 1-(4-(3-Methoxyphenyl)-4-oxobutyl)hydrazine-1,2-dicarboxylate (**3g**).* Purification by column chromatography (petroleum ether/EtOAc = 10:1) afforded **3g** as a yellow oil (64.8 mg, 53% yield): IR (film, cm^{-1}) 3075, 1705, 1687, 1598, 1393, 1254 cm^{-1}; ^1H NMR (400 MHz, DMSO, 80 °C) δ 8.71 (br, 1H) 7.53 (d, J = 7.6 Hz, 1H), 7.46−7.40 (m, 2H), 7.19 (dd, J = 8.0, 1.6 Hz, 1H), 3.83 (s, 3H), 3.40 (t, J = 6.8 Hz, 2H), 3.03 (t, J = 7.2 Hz, 2H), 1.88−1.80 (m, 2H), 1.41 (s, 9H), 1.38 (s, 9H); ^{13}C NMR (100 MHz, DMSO, 80 °C) δ 199.4, 159.6, 155.0, 154.8, 138.5, 129.7, 120.2, 118.9, 112.8, 79.6, 79.3, 55.4, 48.9, 35.3, 28.1, 27.9, 21.9; HRMS [ESI-Q-TOF] calcd for $C_{21}H_{32}N_2O_6Na$ [M + Na^+] 431.2158, found 431.2154.

*Di-tert-butyl 1-(4-(2-Methoxyphenyl)-4-oxobutyl)hydrazine-1,2-dicarboxylate (**3h**).* Purification by column chromatography (petroleum ether/EtOAc = 10:1) afforded **3h** as a white solid (108.0 mg, 88% yield): mp 63−65 °C; IR (film, cm^{-1}) 3070, 2978, 1718, 1698, 1663, 1411 cm^{-1}. ^1H NMR (400 MHz, DMSO, 80 °C) δ 8.65 (br, 1H), 7.52−7.46 (m, 2H), 7.14 (d, J = 8.0 Hz, 1H), 7.01 (dd, J = 7.6, 7.6 Hz, 1H), 3.87 (s, 3H), 3.36 (t, J = 6.8 Hz, 2H), 2.93 (t, J = 7.2 Hz, 2H), 1.83−1.75 (m, 2H), 1.40 (s, 9H), 1.39 (s, 9H); ^{13}C NMR (100 MHz, DMSO, 80 °C) δ 201.6, 158.0, 155.0, 154.8, 133.0, 129.1, 128.8, 120.4, 112.6, 79.6, 79.2, 55.8, 40.3, 28.0, 27.9, 22.1; HRMS [ESI-Q-TOF] calcd for $C_{21}H_{32}N_2O_6Na$ [M + Na^+] 431.2158, found 431.2160.

*Di-tert-butyl 1-(4-(3,5-Dimethylphenyl)-4-oxobutyl)hydrazine-1,2-dicarboxylate (**3i**).* Purification by column chromatography (petroleum ether/EtOAc = 10:1) afforded **3i** as a yellow oil (68.0 mg, 56% yield): IR (film, cm^{-1}) 2977, 1735, 1708, 1686, 1393, 1248 cm^{-1}. ^1H NMR (400 MHz, DMSO, 80 °C) δ 8.69 (br, 1H), 7.54 (s, 2H), 7.25 (s, 1H), 3.39 (t, J = 6.8 Hz, 2H), 3.00 (t, J = 7.2 Hz, 2H), 2.34 (s, 6H), 1.87−1.79 (m, 2H), 1.42 (s, 9H), 1.39 (s, 9H); ^{13}C NMR (100 MHz, DMSO, 80 °C) δ 199.8, 155.0, 154.8, 137.7, 137.3, 134.1, 125.5, 79.6, 79.3, 49.0, 35.3, 28.1, 27.9, 22.0, 20.7; HRMS [ESI-Q-TOF] calcd for $C_{22}H_{34}N_2O_5Na$ [M + Na^+] 429.2365, found 429.2358.

*Di-tert-butyl 1-(4-(4-Fluorophenyl)-4-oxobutyl)hydrazine-1,2-dicarboxylate (**3j**).* Purification by column chromatography (petroleum ether/EtOAc = 12:1) afforded **3j** as a yellow oil (89.0 mg, 75% yield): IR (film, cm^{-1}) 3074, 1705, 1687, 1597, 1406, 1231 cm^{-1}; ^1H NMR (400 MHz, DMSO, 80 °C) δ 8.70 (br, 1H), 8.01 (dd, J = 8.8, 5.6 Hz, 2H), 7.30 (dd, J = 8.8, 8.8 Hz, 2H), 3.39 (t, J = 6.8 Hz, 2H), 3.03 (d, J = 7.2 Hz, 2H), 1.89−1.79 (m, 2H), 1.41 (s, 9H), 1.37 (s, 9H); ^{13}C NMR (100 MHz, DMSO, 80 °C) δ 198.2, 164.9 (d, J_{C-F} = 249.9 Hz), 155.0, 154.8, 133.8 (d, J_{C-F} = 2.8 Hz), 130.7 (d, J_{C-F} = 8.8 Hz), 115.6 (d, J_{C-F} = 21.6 Hz), 79.6, 79.3, 48.9, 35.1, 28.1, 27.9, 21.9; ^{19}F NMR (376 MHz, DMSO, 80 °C) δ −106.7; HRMS [ESI-Q-TOF] calcd for $C_{20}H_{29}FN_2O_5Na$ [M + Na^+] 419.1958, found 419.1951.

*Di-tert-butyl 1-(4-(4-Chlorophenyl)-4-oxobutyl)hydrazine-1,2-dicarboxylate (**3k**).* Purification by column chromatography (petroleum ether/EtOAc = 10:1) afforded **3k** as a yellow solid (75.7 mg, 61% yield): mp 98−100 °C; IR (film, cm^{-1}) 2977, 1732, 1685, 1588, 1393, 1204 cm^{-1}; ^1H NMR (400 MHz, DMSO, 80 °C) δ 8.72 (br, 1H), 7.94 (d, J = 8.4 Hz, 2H), 7.56 (d, J = 8.4 Hz, 2H), 3.39 (t, J = 6.8 Hz, 2H), 3.04 (T, J = 7.2 Hz, 2H), 1.87−1.79 (m, 2H), 1.41 (s, 9H), 1.38 (s, 9H); ^{13}C NMR (100 MHz, DMSO, 80 °C) δ 198.6, 155.0, 154.8, 137.9, 135.7, 129.6, 128.7, 79.7, 79.3, 35.1, 28.1, 27.9, 21.8; HRMS [ESI-Q-TOF] calcd for $C_{20}H_{29}ClN_2O_5Na$ [M + Na^+] 435.1663, found 435.1663.

*Di-tert-butyl 1-(4-(4-Bromophenyl)-4-oxobutyl)hydrazine-1,2-dicarboxylate (**3l**).* Purification by column chromatography (petroleum ether/EtOAc = 12:1) afforded **3l** as a white solid (81.8 mg, 60% yield): mp 58−60 °C; IR (film, cm^{-1}) 3070, 2977, 1735, 1676, 1585, 1410 cm^{-1}. ^1H NMR (400 MHz, DMSO, 80 °C) δ 8.72 (br, 1H), 7.86 (d, J = 8.4 Hz, 2H), 7.71 (d, J = 8.4 Hz, 2H), 3.39 (t, J = 6.8 Hz, 2H), 3.03 (t, J = 7.2 Hz, 2H), 1.87−1.79 (m, 2H), 1.41 (s, 9H), 1.38 (s, 9H); ^{13}C NMR (100 MHz, DMSO, 80 °C) δ 198.8, 155.0, 154.8, 136.0, 131.6, 129.7, 126.9, 79.6, 79.3, 48.8, 35.1, 28.1, 27.9, 21.8; HRMS [ESI-Q-TOF] calcd for $C_{20}H_{29}BrN_2O_5Na$ [M + Na^+] 479.1158, found 479.1152.

*Di-tert-butyl 1-(4-Oxo-4-(4-(trifluoromethyl)phenyl)butyl)-hydrazine-1,2-dicarboxylate (**3m**).* Purification by column chromatography (petroleum ether/EtOAc = 12:1) afforded **3m** as a yellow oil (89.1 mg, 67% yield): IR (film, cm^{-1}) 2980, 1694, 1582, 1394, 1244, 1129 cm^{-1}; ^1H NMR (400 MHz, DMSO, 80 °C) δ 8.68 (br, 1H), 8.18−8.10 (m, 2H), 7.88−7.80 (m, 2H), 3.50−3.38 (m, 2H), 3.14−3.05 (m, 2H), 2.08−1.82 (m, 2H), 1.41−1.37 (m, 18H); ^{13}C NMR (100 MHz, DMSO, 80 °C) δ 199.5, 155.5, 155.3, 140.7, 133.0 (q, J_{C-F} = 31.9 Hz), 129.0, 126.0 (q, J_{C-F} = 3.7 Hz), 124.3 (q, J_{C-F} = 271.0 Hz), 80.1, 79.8, 49.2, 35.9, 28.5, 28.3, 22.2; ^{19}F NMR (376 MHz, DMSO, 80 °C) δ −61.8; HRMS [ESI-Q-TOF] calcd for $C_{21}H_{29}F_3N_2O_5Na$ [M + Na^+] 469.1926, found 469.1921.

*Di-tert-butyl 1-(4-Oxo-4-(4-(trifluoromethoxy)phenyl)butyl)-hydrazine-1,2-dicarboxylate (**3n**).* Purification by column chromatography (petroleum ether/EtOAc = 10:1) afforded **3n** as a yellow oil (71.0 mg, 51% yield): IR (film, cm^{-1}) 2979, 1690, 1602, 1393, 1252, 1208 cm^{-1}; ^1H NMR (400 MHz, DMSO, 80 °C) δ 8.69 (br, 1H), 8.06 (d, J = 8.8 Hz, 2H), 7.46 (d, J = 8.0 Hz, 2H), 3.40 (t, J = 6.8 Hz, 2H), 3.06 (t, J = 6.8 Hz, 2H), 1.89−1.81 (m, 2H), 1.41 (s, 9H), 1.37 (s, 9H); ^{13}C NMR (100 MHz, DMSO, 80 °C) δ 198.9, 155.5, 155.3, 152.0, 136.3, 130.7, 121.0, 120.5 (q, J_{C-F} = 256.1 Hz), 80.1, 79.8, 49.2, 35.6, 28.5, 28.4, 22.3; ^{19}F NMR (376 MHz, DMSO, 80 °C) δ −56.6; HRMS [ESI-Q-TOF] calcd for $C_{21}H_{29}F_3N_2O_6Na$ [M + Na^+] 485.1875, found 485.1886.

*Di-tert-butyl 1-(4-Oxo-4-(thiophene-2-yl)butyl)hydrazine-1,2-dicarboxylate (**3o**).* Purification by column chromatography (petroleum ether/EtOAc = 10:1) afforded **3o** as a yellow oil (85.6 mg, 74% yield): IR (film, cm^{-1}) 3092, 1704, 1665, 1585, 1415, 1241 cm^{-1}; ^1H NMR (400 MHz, DMSO, 80 °C) δ 8.68 (br, 1H), 7.92 (dd, J = 4.8, 0.8 Hz, 1H), 7.87 (dd, J = 3.6, 0.8 Hz, 1H), 7.21 (dd, J = 4.8, 3.6 Hz, 1H), 3.39 (t, J = 6.8 Hz, 2H), 2.98 (t, J = 7.2 Hz, 2H), 1.89−1.80 (m, 2H), 1.42 (s, 9H), 1.38 (s, 9H); ^{13}C NMR (100 MHz, DMSO, 80 °C) δ 192.5, 155.0, 154.8, 143.9, 134.0, 132.5, 128.4, 79.7, 79.3, 48.9, 35.8, 28.1, 27.9, 22.2; HRMS [ESI-Q-TOF] calcd for $C_{18}H_{28}N_2O_5SNa$ [M + Na^+] 407.1617, found 407.1615.

*Di-tert-butyl 1-(4-Cyclohexyl-4-oxobutyl)hydrazine-1,2-dicarboxylate (**3p**).* Purification by column chromatography (petroleum ether/EtOAc = 15:1) afforded **3p** as a yellow oil (72.2 mg, 63% yield): IR (film, cm^{-1}) 2978, 1800, 1737, 1705, 1393, 1211 cm^{-1}; ^1H NMR (400 MHz, DMSO, 80 °C) δ 8.64 (br, 1H), 3.28 (t, J = 6.8 Hz, 2H), 2.48 (t, J = 7.2 Hz, 2H), 2.38−2.30 (m, 1H), 1.81−1.75 (m, 2H), 1.72−1.58 (m, 5H), 1.42 (s, 9H), 1.40 (s, 9H), 1.30−1.15 (m, 5H); ^{13}C NMR (100 MHz, DMSO, 80 °C) δ 212.4, 154.9, 154.8, 82.3, 79.6, 79.3, 49.7, 48.8, 36.8, 28.1, 28.0, 27.9, 27.6, 25.5, 25.1, 21.4; HRMS [ESI-Q-TOF] calcd for $C_{20}H_{36}N_2O_5Na$ [M + Na^+] 407.2522, found 407.2536.

*Di-tert-butyl 1-(4-Oxodecyl)hydrazine-1,2-dicarboxylate (**3q**).* Purification by column chromatography (petroleum ether/EtOAc = 12:1) afforded **3q** as a yellow oil (82.0 mg, 71% yield): IR (film, cm^{-1}) 2957, 1707, 1456, 1366, 1151, 1050 cm^{-1}; ^1H NMR (400 MHz, DMSO, 80 °C) δ 8.63 (br, 1H), 3.28 (t, J = 6.8 Hz, 2H), 2.43 (t, J = 7.2 Hz, 2H), 2.36 (t, J = 7.2 Hz, 2H), 1.71−1.63 (m, 2H), 1.50−1.45 (m, 2H), 1.42 (s, 9H), 1.40 (s, 9H), 1.29−1.25 (m, 6H), 0.87 (t, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, DMSO, 80 °C) δ 209.8, 154.9, 154.8, 79.6, 79.3, 48.8, 41.9, 38.9, 30.9, 28.2, 28.0, 27.9, 23.2, 21.8, 21.5, 13.6; HRMS [ESI-Q-TOF] calcd for $C_{20}H_{38}N_2O_5Na$ [M + Na^+] 409.2678, found 409.2681.

*Di-tert-butyl 1-(4-Oxonon-8-en-1-yl)hydrazine-1,2-dicarboxylate (**3r**).* Purification by column chromatography (petroleum ether/EtOAc = 10:1) afforded **3r** as a yellow oil (74.6 mg, 67% yield): IR (film, cm^{-1}) 3077, 2979, 1706, 1641, 1479, 1367 cm^{-1}; ^1H NMR (400 MHz, DMSO, 80 °C) δ 8.69 (br, 1H), 5.85−5.73 (m, 1H), 5.04−4.92 (m, 2H), 3.28 (t, J = 6.8 Hz, 2H), 2.43 (t, J = 7.2 Hz, 2H), 2.39 (t, J = 7.2 Hz, 2H), 2.01 (dd, J = 14.4, 7.2 Hz, 2H), 1.71−1.64 (m, 2H), 1.62−

DOI: 10.1021/acs.joc.6b01433
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1.54 (m, 2H), 1.41 (s, 9H), 1.40 (s, 9H); ^{13}C NMR (100 MHz, DMSO, 80 °C) δ 210.1, 155.4, 138.6, 115.3, 80.1, 79.7, 49.2, 41.7, 39.4, 33.0, 28.5, 28.4, 23.0, 21.9; HRMS [ESI-Q-TOF] calcd for $C_{19}H_{34}N_2O_5Na$ [M + Na$^+$] 393.2365, found 393.2346.

*Di-tert-butyl 1-(4-(4-(But-2-yn-1-yloxy)phenyl)-4-oxobutyl)-hydrazine-1,2-dicarboxylate (**3s**).* Purification by column chromatography (petroleum ether/EtOAc = 10:1) afforded **3s** as a yellow oil (107.0 mg, 80% yield): IR (film, cm^{-1}) 3335, 2979, 2376, 1737, 1577, 1368 cm^{-1}; ^{1}H NMR (400 MHz, DMSO, 80 °C) δ 8.74 (br, 1H), 7.92 (d, J = 8.8 Hz, 2H), 7.06 (d, J = 8.8 Hz, 2H), 4.81 (q, J = 2.0 Hz, 2H), 3.40 (t, J = 6.8 Hz, 2H), 2.99 (t, J = 7.2 Hz, 2H), 1.88−1.80 (m, 5H), 1.42 (s, 9H), 1.38 (s, 9H); ^{13}C NMR (100 MHz, DMSO, 80 °C) δ 198.5, 161.7, 155.5, 155.3, 130.9, 130.4, 115.2, 84.5, 80.1, 79.8, 74.7, 56.9, 49.5, 35.3, 28.5, 28.4, 22.6, 3.4; HRMS [ESI-Q-TOF] calcd for $C_{24}H_{34}N_2O_6Na$ [M + Na$^+$] 469.2315, found 469.2299.

*Di-tert-butyl 1-(4-Oxo-2,4-diphenylbutyl)hydrazine-1,2-dicarboxylate (**3t**).* Purification by column chromatography (petroleum ether/EtOAc = 10:1) afforded **3t** as a yellow oil (90.3 mg, 66% yield): IR (film, cm^{-1}) 3062, 2979, 1735, 1707, 1598, 1393 cm^{-1}; ^{1}H NMR (400 MHz, DMSO, 80 °C) δ 8.77 (br, 1H), 7.91 (d, J = 7.2 Hz, 2H), 7.58 (dd, J = 7.2, 7.2 Hz, 1H), 7.47 (dd, J = 7.6, 7.6 Hz, 2H), 7.30 (d, J = 7.2 Hz, 2H), 7.24 (dd, J = 7.2, 7.2 Hz, 2H), 7.15 (dd, J = 7.2, 7.2 Hz, 1H), 3.65−3.45 (m, 5H), 1.42 (s, 9H), 1.34 (s, 9H); ^{13}C NMR (100 MHz, DMSO, 80 °C) δ 199.0, 155.4, 155.3, 142.9, 137.7, 133.3, 129.0, 128.5, 128.3, 128.2, 126.6, 80.3, 79.9, 41.9, 40.0, 28.5, 28.3, 28.1; HRMS [ESI-Q-TOF] calcd for $C_{26}H_{34}N_2O_5Na$ [M + Na$^+$] 477.2365, found 477.2353.

*Di-tert-butyl 1-(5-(2-Oxo-2-phenylethyl)octan-4-yl)hydrazine-1,2-dicarboxylate (**3u**).* Purification by column chromatography (petroleum ether/EtOAc = 10:1) afforded **3u** as a yellow oil (112.7 mg, 81% yield, dr ∼ 1:1): IR (film, cm^{-1}) 3062, 1740, 1704, 1598, 1392, 1241 cm^{-1}; ^{1}H NMR (400 MHz, DMSO, 80 °C) δ 8.24 (br, 2H, two isomers), 7.93 (dd, J = 7.6, 7.6 Hz, 4H, two isomers), 7.62−7.56 (m, 2H, two isomers), 7.49 (dd, J = 7.6, 7.6 Hz, 4H, two isomers), 4.20−4.05 (m, 2H, two isomers), 3.45−2.95 (m, 3H, two isomers), 2.80 (dd, J = 17.6, 5.2 Hz, 1H, one isomer), 2.30−2.15 (m, 2H, two isomers), 1.65−1.15 (m, 52H, two isomers), 0.90−0.80 (m, 12H, two isomers); ^{13}C NMR (100 MHz, DMSO, 80 °C) δ 200.3 and 199.9 (two isomers), 156.2 and 155.5 (two isomers), 138.1 and 138.0 (two isomers), 133.1 and 133.0 (two isomers), 128.9 and 128.8 (two isomers), 128.1 and 128.1 (two isomers), 79.9 and 79.7 (two isomers), 58.6 and 58.6 (two isomers), 39.9 and 39.6 (two isomers), 37.1 and 33.8 (two isomers), 32.3 and 31.2 (two isomers), 31.6 and 31.6 (two isomers), 28.5 and 28.5 (two isomers), 28.3 and 28.2 (two isomers), 20.6 and 20.6 (two isomers), 19.8 and 19.7 (two isomers), 14.6 and 14.4 (two isomers), 14.1 and 14.1 (two isomers); HRMS [ESI-Q-TOF] calcd for $C_{26}H_{42}N_2O_5Na$ [M + Na$^+$] 485.2991, found 485.2970.

*Di-tert-butyl 1-(2-(2-Oxo-2-phenylethyl)cyclopentyl)hydrazine-1,2-dicarboxylate (**3v**).* Purification by column chromatography (petroleum ether/EtOAc = 10:1) afforded **3v** as a yellow oil (114.4 mg, 91% yield, dr ∼ 3.6:1): IR (film, cm^{-1}) 3062, 2975, 1738, 1703, 1686, 1392 cm^{-1}; ^{1}H NMR (400 MHz, DMSO, 80 °C) δ 8.50 (br, 2H, two isomers), 7.97−7.92 (m, 4H, two isomers), 7.60 (dd, J = 7.2, 7.2 Hz, 2H, two isomers), 7.49 (dd, J = 7.6, 7.6 Hz, 4H, two isomers), 4.53−4.10 (m, 2H, two isomers), 3.60−3.15 (m, 2H, two isomers), 3.00−2.70 (m, 2H, two isomers), 2.45−2.22 (m, 2H, two isomers), 1.90−1.15 (m, 48H, two isomers); ^{13}C NMR (100 MHz, DMSO, 80 °C) (major isomer) δ 200.2, 156.2, 155.2, 137.7, 133.2, 129.0, 128.2, 80.1, 79.7, 42.4, 37.9, 29.6, 28.4, 28.4, 27.5, 21.7; HRMS [ESI-Q-TOF] calcd for $C_{23}H_{34}N_2O_5Na$ [M + Na$^+$] 441.2365, found 441.2369.

*Di-tert-butyl 1-(2-(2-Oxo-2-phenylethyl)cyclohexyl)hydrazine-1,2-dicarboxylate (**3w**).* Purification by column chromatography (petroleum ether/EtOAc = 10:1) afforded **3w** as a yellow solid (104.1 mg, 80% yield, dr > 19:1): mp 86−87 °C; IR (film, cm^{-1}) 3071, 2975, 1745, 1693, 1679, 1399 cm^{-1}; ^{1}H NMR (400 MHz, DMSO, 80 °C) δ 8.28 (br, 1H), 7.90 (dd, J = 7.6, 1.2 Hz, 2H), 7.59 (dd, J = 7.2, 7.2 Hz, 1H), 7.49 (dd, J = 7.6, 7.6 Hz, 2H), 3.80−3.69 (m, 1H), 2.75−2.60 (m, 1H), 2.10−2.00 (m, 1H), 1.83−1.70 (m, 3H), 1.62−1.54 (m, 1H), 1.50−1.20 (m, 3H), 1.41 (s, 9H), 1.36 (s, 9H), 1.13−1.03 (m, 2H); ^{13}C NMR (100 MHz, DMSO) δ 200.2, 156.1, 155.1, 138.1, 133.1, 128.9, 128.1, 80.1, 79.7, 42.5, 36.1, 32.1, 30.1, 28.5, 28.4, 25.7, 25.6; HRMS [ESI-Q-TOF] calcd for $C_{24}H_{36}N_2O_5$ [M + Na$^+$] 455.2522, found 455.2511.

*1-(3-Phenyl-5,6-dihydropyridazin-1(4H)-yl)ethan-1-one (**4**).* Compound **3a** (70 mg, 0.18 mmol) was dissolved in AcOH (5 mL) and heated to 100 °C for 12 h. Upon completion, the mixture was extracted with ethyl acetate (3 × 10 mL). The combined organic extracts were washed with satd $NaHCO_3$ and then brine, dried over Na_2SO_4, filtered, concentrated, and purified by column chromatography (petroleum ether/EtOAc = 5:1) to afford **4** as a brown solid (18.6 mg, 50% yield): mp 62−64 °C; IR (film, cm^{-1}) 2926, 2853, 1657, 1407, 1268, 1164 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79−7.75 (m, 2H), 7.43−7.37 (m, 3H), 3.84 (dd, J = 6.0, 6.0 Hz, 2H), 2.65 (dd, J = 6.4, 6.4 Hz, 2H), 2.44 (s, 3H), 2.05−1.96 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.0, 146.2, 137.0, 128.7, 128.0, 124.8, 38.0, 22.2, 20.9, 17.1; HRMS [ESI-Q-TOF] calcd for $C_{12}H_{15}N_2O$ [M + H$^+$] 203.1184, found 203.1193.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b01433.

Product characterization (^{1}H, ^{13}C, and ^{19}F NMR spectra) (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

C.Z. is grateful for financial support from Soochow University, the National Natural Science Foundation of China (Grant No. 21402134), the Natural Science Foundation of Jiangsu (Grant No. BK20140306), and the Priority Academic Program Development of Jiangsu Higher Education Institutions (PAPD).

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DOI: 10.1021/acs.joc.6b01433
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DOI: 10.1021/acs.joc.6b01433
J. Org. Chem. 2016, 81, 8043−8049