JOC The Journal of Organic Chemistry

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Selective α-Methylation of Ketones

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Cite This: J. Org. Chem. 2021, 86, 7333−7346 Read Online

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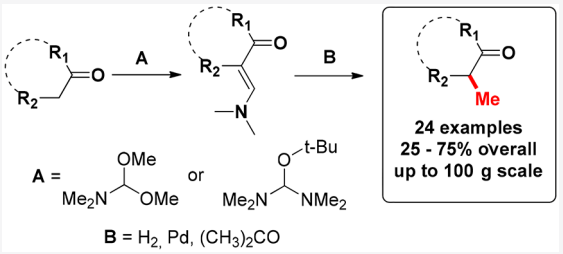
ABSTRACT: The convenient and scalable preparative approach for the two-step α-methylation of ketones is described. The optimized protocols for regioselective preparation of enaminones with further diastereoselective and functional groups tolerant hydrogenation to α-methylketones are developed. The scope and limitations of the proposed methodology are discussed. The advantages compared to known procedures are demonstrated. The unexpected role of acetone in the hydrogenation is suggested. The evaluation of the method for both early building block synthesis and late-stage CH-functionalization is shown. The elaborate procedures' preparability and scalability are demonstrated by the synthesis of several α-methyl ketones up to 100 g amount.



INTRODUCTION

The introduction of alkyl substituents into biologically active molecules in many cases leads to significant changes in their activity. Particularly, adding the simplest alkyl substituent—the methyl group—to pharmacologically active molecules often positively impacts their metabolic stability, solubility, selectivity, and binding affinity.[1] Numerous examples showcasing this phenomenon were given in the literature.[1,2] By far, both the most popular and the most impactful for derivatization of bioactive molecules, the methyl substituent is also referred to as "magic methyl".[1,2d]

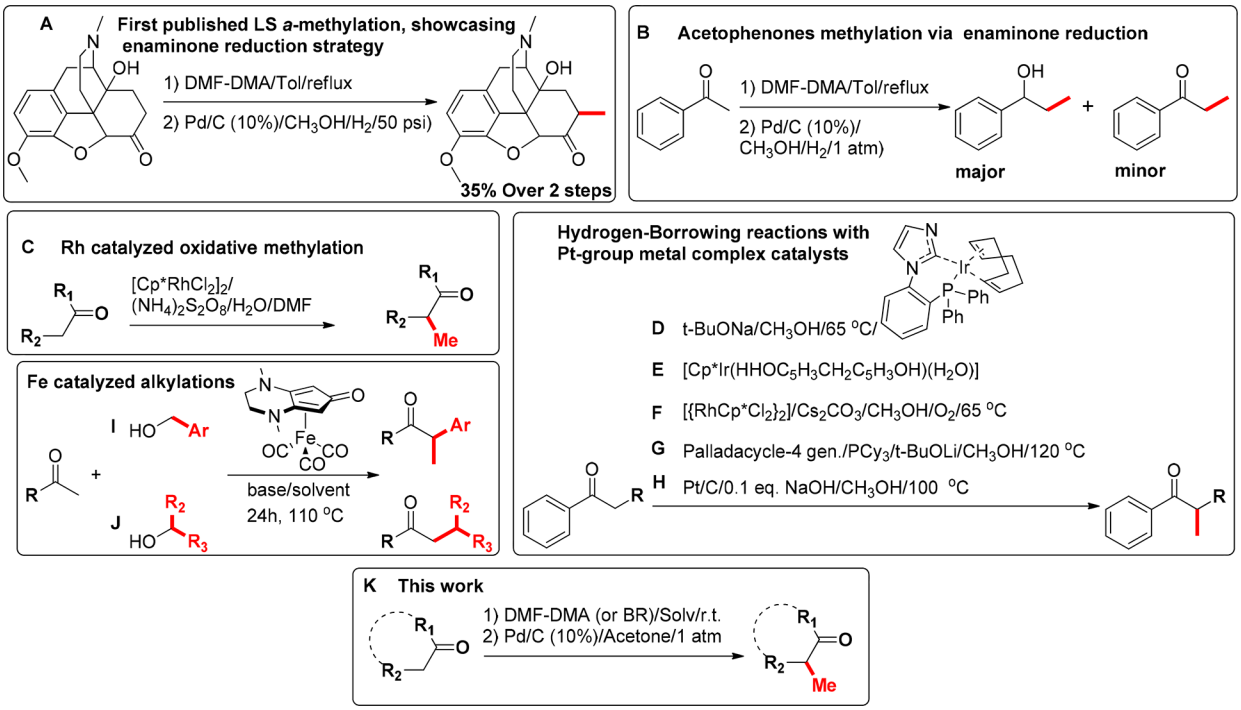
There are two fundamentally different approaches to the preparation of alkylated biomolecules. The first approach is "late-stage CH-functionalization"[3] which implies alkylation as a final step in the target compound synthesis. The other approach suggests to introduce an alkyl substituent into building blocks in the early stages. Both methodologies have their advantages and drawbacks. Even though the selectivity of late-stage CH-functionalization reactions is generally low, and the versatile protocols that cover the large chemical space of complex molecules have not yet been developed for such transformations, this remains a promising strategy, which has already seen some success in the past.[3b,4] Alkylation in the early stage of building blocks preparation requires the synthesis of new modified intermediates on the basis of analogy with the parent synthetic pathway. This implies de novo synthesis of the target molecules,[1] which might be viewed as a disadvantage in many cases. On the other hand, functionalization of the building blocks in early steps opens room for quick SAR investigations, which makes it very attractive for pharmaceutical companies.[1,5] In this study, α-methylene ketones were taken as the target substrates, and the efficient methyl group introduction approaches to the α-position were investigated. α-Methylene ketones as structural fragments occur in many drugs, drug candidates, and natural compounds; thus; the interest in the reactions enabling their selective alkylation grows increasingly over the past decades.

Typically, α-alkylation of ketones is performed by alkylation of corresponding enolates with alkyl halides or sequential chalcone reduction.[6] Both these approaches have significant limitations and suffer from low selectivity, poor scalability, and a number of possible side reactions. Later on, metal-catalyzed ketone methylation reactions,[7] as well as metal-free approaches,[7e,8] were developed. However, the drawbacks as the use of the toxic reagents or harsh reaction conditions still remain.[9] Kotick and co-workers[2e] have shown α-methylation of dihydrocodeine *via* hydrogenation of the corresponding enaminone intermediate (Scheme 1, **A**). One-pot Rh-catalyzed direct α-methylation procedures for α-methyleneketones, proposed by Li and co-workers,[9] and Chan and co-workers,[10] (Scheme 1, **C**) despite being fairly versatile, remain problematic for scale-up synthesis due to the costly catalysts. Regardless of the methylation *via* Bredereck-type reagents being merely somewhat beneath the surface, only one record describing the similar approach to α-monomethylation of acetophenones has been published to date (Scheme 1, **B**).[11] However, the noted method (**B**) leads mostly to alcohols instead of targeted methyl ketones. It happens due to the nonselective reduction step,[11] which is not surprising,

Received: January 19, 2021
Published: May 27, 2021

https://doi.org/10.1021/acs.joc.1c00148
J. Org. Chem. 2021, 86, 7333−7346

Scheme 1. Literature Examples of Ketones α-Alkylation (A–J) and Reaction Sequence Proposed in This Work (K)



considering that the reduction of aromatic carbonyls to corresponding benzylic alcohols in Pd/C-catalyzed hydrogenations is well-known in the literature.[12] The alkylation protocols that imply a hydrogen-borrowing strategy with alcohols as alkyl source, and a variety of heterogeneous (Scheme 1, **H**)[13] and homogeneous (Scheme 1, **D**–**G**, **I**, **J**)[14] metal catalysts, show promising results. Particularly, *N*-methylation of amines,[14a,d] α-methylation of 1-aryl-1-propanols,[13] β-methylation of 2-arylethanols,[13] 3-methylation of indoles,[13] and α-alkylation of methylketones have been described. Nevertheless, the listed approaches still have strong limitations, showing poor selectivity or leading to polymethylated products.[13,14] Recently developed iron-catalyzed hydrogen-borrowing reactions show reasonable yields and selectivity on α-alkylations of methylketones (Scheme 1, **I**, **J**). However, they are still not applicable for mono-α-methylations, and use "custom", commercially unavailable catalysts.[14e,f]

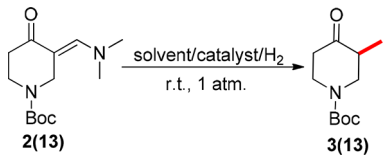
In our ongoing efforts to adapt existing and developing new effective approaches to the advanced building blocks for medicinal chemistry,[15] we propose the stepwise incorporation of dialkylaminoacetal, followed by selective hydrogenation (Scheme 1, **K**). Herein, we present the most general and scalable (up to 100 g) method for chemo- and regioselective α-methylation of ketones, tolerable toward many common functional groups, and consequently applicable to both late-stage and early BB functionalization. We have optimized the literature[16] conditions to achieve selective enaminones formation by reacting ketones with Bredereck's reagent ($(CH_3)_3COCH[N(CH_3)_2]_2$, further **BR**),[16a] and, in some cases, in a DMF-DMA system, which allowed us to prepare mono-substituted products.[16b] It is also noteworthy that enaminones, used as intermediates in this study, are valuable starting materials for many important reactions.[11,17]

RESULTS AND DISCUSSION

Considering that the catalytic hydrogenation-hydrogenolysis step looked the most challenging,[11] we decided to find optimal conditions for this transformation. We used a multidimensional optimization scheme, which included temperature, hydrogen pressure, substrate concentration, and catalyst content optimization, as well as catalyst choice and solvent choice. Herein, we present the best showcasing projections, particularly catalyst type and solvent type optimizations.

Enaminones readily react with dihydrogen in the presence of Pd/C catalyst at ambient conditions;[11] thus, in the first optimization cycle, we used available Pt-group metals on different beds. We chose *N*-Boc-4-piperidone as the model compound, since it is a showcasing substrate for the family of druglike and natural compounds, which are attractive targets for molecular "tuning" *via* C-alkylation (Scheme 2).[1,3b] The

Scheme 2. Optimization of the Hydrogenation Protocol for Enaminones 2 to Corresponding Methylketones 3, Using Enaminone 2(13) as the Model Compound



course of reactions was monitored by GC/MS using the column precalibrated to detect the substrate, and products, with dodecane as an internal standard. In the summary of these experiments, Pd/C (10%) had shown to provide both the best yield and selectivity (Table 1).

Knowing the optimal hydrogenation catalyst, we decided to study the influence of the solvent on the reaction course. For this, we took the solvents, which are most commonly used for heterogeneous catalytic hydrogenation, as *i*-PrOH, MeOH,

https://doi.org/10.1021/acs.joc.1c00148
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Table 1. Optimization of the Catalyst for Hydrogenation on the Model Enaminone 2(13)[a]

catalyst	time, h	conversion, %	yield, %	selectivity, %
Pd/C (10%)	24	85.9	85.1	99.0
$Pd/BaSO_4$ (5%)	24	0	0	0
Pd/Al_2O_3 (5%)	24	6.3	3.7	58.3
$Pd/CaCO_3$ (5%)	24	0	0	0
Pt/C (5%)	24	57.3	15.2	26.6
Pt/C (5%)	24	88.9	44.8	50.4
Ru/C (5%)	24	58.7	0	0
Rh/C (5%)	24	74.3	0	0

[a]Conditions: 1 atm H_2, room temperature, acetone, 2−4% molar of the catalyst used (based on the pure metal).

and THF, together with less popular AcOEt and acetone (Table 2).[18] The reaction progress was monitored by GC/MS

Table 2. Optimization of the Solvent for Hydrogenation on the Model Enaminone 2(13)[a]

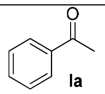
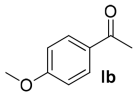
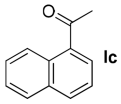
solvent	time, h	conversion, %	yield, %	selectivity, %
acetone	8	34.7	34.5	99.4
THF	8	41.6	36.0	86.6
AcOEt	8	65.3	37.5	57.4
i-PrOH	8	84.9	42.3	49.8
MeOH	8	100	35.5	35.5

[a]Conditions: 1 atm H_2, room temperature, Pd/C (10%), 4% molar of the Pd used (based on the pure metal).

analysis in the same manner as above for the catalyst selection iteration. THF and acetone showed the best selectivity (86.6% and 99.4%, respectively) and yields close to those of the "traditional" alcohols (Table 2). Summarizing the optimization study on the hydrogenation step, the system acetone/Pd/C(10%) has proven to be the most promising in terms of both yield and selectivity.

We have compared the yields of the acetophenone enaminones obtained *via* our optimized protocol for hydrogenation (Scheme 3, Table 3, conditions **B**), with the yields obtained using the original procedure published by Borah and co-workers[11] (Scheme 3, Table 3, conditions **A**). As it is shown in Table 3, in the case of acetophenones **I(a−c)**, the switch to acetone as the media for the hydrogenation step allowed us to inverse the regioselectivity to predominantly the formation of desired methylketones **III(a−c)**, instead of the formation of benzylic alcohols **IV(a−c)**. The overall conversion is also significantly increased. Despite shifting the selectivity toward desired methylated ketones, the content of the benzylic alcohols in the reaction mixtures remained significant, which could be attributed by conjugation between π-electrons of the aromatic rings and carbonyl group, and consequently prolonged exposure times with the catalyst for these molecules. The latter gives space for optimization of the catalyst

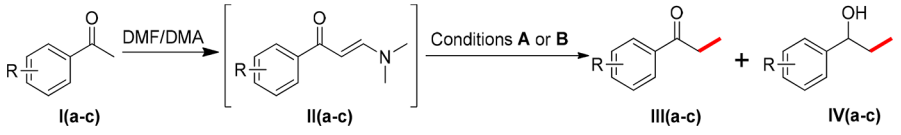
Table 3. Comparison of Hydrogenation Step for Characteristic Acetophenone Enaminones II(a−c), Known from the Literature (A)[11] and the Procedure Optimized in This Work (B)

Entry	Substrate I	Reaction	Yield, %	
			III(a-c)	IV(a-c)
1	 Ia	A	Trace	79
		B	58	34
2	 Ib	A	18	55
		B	45	39
3	 Ic	A	77	nd
		B	93	trace

composition, which might be a beneficial strategy for further investigation toward selective methylation of aromatic ketones.

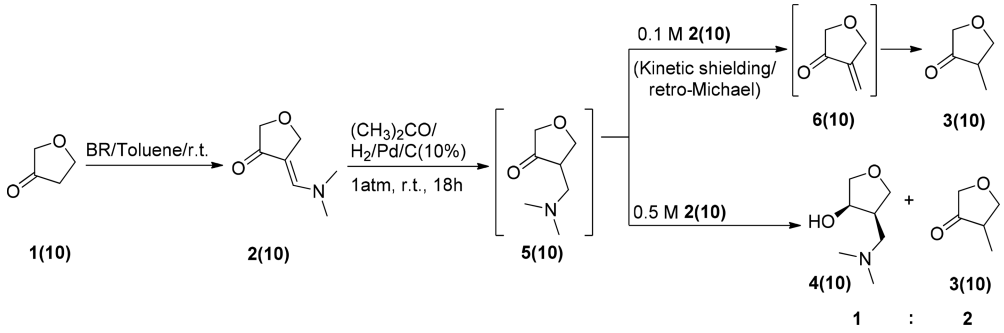
However, the nature behind the drastic increase of selectivity in cases when acetone was used as the reaction media remained unclear. It is known from the literature that alcohols are the main byproducts when reducing acetophenones in our conditions. We assumed the "kinetic shielding" of the competing ketone reduction by acetone. The difference in amounts of starting ketone and acetone is a lot (near 0.1 mol/L). Correspondingly, the keto group of the latter can compete with the keto group of the substrate during the reduction. To evaluate the relevance of this hypothesis, we have conducted its experimental proof. We used the standard GC/MS protocol for solvents quality checks, to quantify the possibility of the acetone reduction to isopropyl alcohol in our standard reaction conditions. We used 4-((dimethylamino)methylene)-dihydrofuran-3(2*H*)-one **2(10)** as a test object. This is an available compound with a low molecular weight, which does not bind with the filler of the GC column irreversibly. As a blank experiment, we next used the following: Acetone and catalyst were taken in the same ratio and treated with hydrogen gas under the same temperature and pressure parameters as a test reaction mixture. The 5% solution of isopropyl alcohol in acetone was used for instrument calibration. The series of experiments resulted in the average concentration of isopropanol of 1.6 g/L for 4-((dimethylamino)-methylene)-dihydrofuran-3(2*H*)-one **2(10)** reduction reaction mixtures and 8.9 g/L for blank experiments. It indicates the possibility of competing reduction reactions when the substrate was present in the mixture. On the other hand, for the number of saturated cyclic and heterocyclic enaminones, we found traces of dimethylamino(methyl)-alcohols when analyzing crude mixtures on GC/MS. We expected to observe a significantly

Scheme 3. General Scheme for Methylation of Acetophenones I *via* Subsequent Enaminones II Formation and Their Hydrogenation to Methylketones III



https://doi.org/10.1021/acs.joc.1c00148
J. Org. Chem. 2021, 86, 7333−7346

Scheme 4. Proposed Reaction Schemes for Enaminones Reduction at Different Substrate Concentrations (0.1 and 0.5 M of 2(10) in Acetone)



higher yield of such product on increased substrate concentration (Scheme 4).

With these data in hand, we provided the reduction experiment for the same test substrate. Its concentration in acetone 5-fold increased, thus removing the "kinetic shielding" assured by acetone. The reaction resulted in a mixture of methylketone **3(10)** and 4-((dimethylamino)methyl)-tetrahydrofuran-3-ol **4(10)** in close to a 2:1 ratio. The workout gave a 45% isolated yield of **3(10)** and 23% of aminoalcohol **4(10)**. The structure of 4-((dimethylamino)methyl)-tetrahydrofuran-3-ol **4(10)** was additionally confirmed by X-ray (Figure 1).[19]

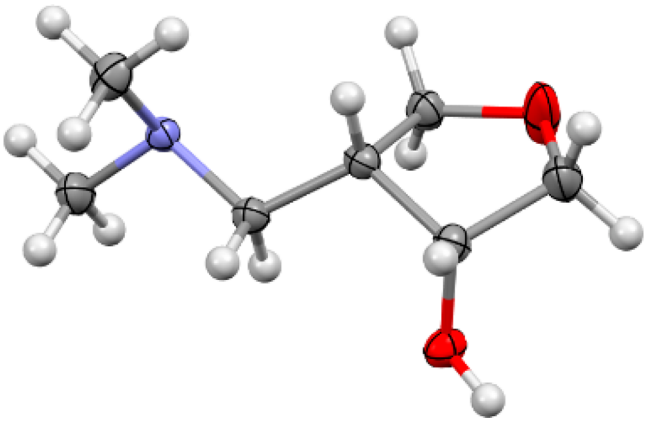


Figure 1. Structure of 4-((dimethylamino)methyl)tetrahydrofuran-3-ol **4(10)** according to X-ray data.

The exclusive formation of cis-product overall supports the hypothesis that the reduction of a carbonyl group happens due to prolonged exposure of the substrate with catalyst, provided in this case by increased substrate concentration. The formation of *N*,*N*-dimethylaminoalcohols at higher substrate concentrations, when the "kinetic shielding" role decreased, indicates the carbonyl reduction competing with the main reaction, which is Pd/C-induced retro-Michael-type elimination,[20] followed by reduction to the respective methyl ketone (Scheme 4).

The **BR**[16a] or DMF-DMA[11] systems were used, depending on the reactivity of the substrates. In general, using **BR** (procedure **B**, Table 4) instead of DMF-DMA leads to better yields. However, in cases of reactive fluid ketones, the difference was a little, so we used DMA-DMF as a more common and less expensive reagent (procedure **A**, Table 4). In the case of applying insoluble in **BR** or DMA-DMF ketones, we used toluene as a solvent (procedure **C**), which was warmed to 55 °C to increase the solubility if necessary (procedure **D**). These modifications allowed us to synthesize the varied set of low molecular weight enaminones (Figure 2, Table 4), including enaminone derivatives of natural compounds (entries 20−22, Table 4). It is notable that our optimized condition for the enaminones formation reactions, besides high regioselectivity, showed remarkable tolerance to the number of important functional groups, including fluorine (entry 9, Table 4), lactone (entry 21, Table 4), lactam (entry 19, Table 4), amides (entries 13−17, Table 4), and amines (entries 18, 20, Table 4). The methodology has shown poor results for nonprotected functional groups with active hydrogen, such as free amino, hydroxy, and carboxy functions, due to the possibility of their reaction with **BR** or DMF-DMA.

Importantly, the introduction of one enaminone fragment only occurs, even if there are two or more possibilities present. The high diastereoselectivity (de > 90%) at the reduction step is also observed in the cases of existent stereocenters in the starting ketones **1**. The *cis*-product formation is detected and proven by X-ray study[21] (Figure 3).

The transformation of ketones **1** to enaminones **2** proceeds with high conversion. In most cases, enaminones were taken for the reduction step without additional purification. The analytically pure compounds were isolated *via* crystallization, fraction distillation, column chromatography, or preparative HPLC purification (see Table 4 for the details).

The adjusted protocols for subsequent enaminones preparation, followed by reductive elimination of the dimethylamino function, using Pd/C(10%) as the catalyst in acetone media at ambient conditions, resulted in regio- and diastereoselective α-methylation of ketones with the conservation of a carbonyl function. The developed hydrogenation procedure allowed the use of crude starting materials from the enaminone preparation step for a wide scope of substrates in up to 100 g scale with overall two-step yields of the methylated ketones around 55−60% on average. The given synthetic approach has proven to be convenient and versatile for the wide variety of structural types and chemotypes of ketones, comprising alicyclic **1(1−9)** and heterocyclic **1(10−19)** compounds, acetophenones **I(a−c)**, aliphatic ketones **1(22,23)**, and natural compounds **1(21,22)**. Thus, it becomes an accessible instrument for both de novo synthesis and late-stage functionalization.

Nevertheless, despite the versatility for functional classes, some limitations of scope for the proposed ketones α-methylation strategy were also determined. Sulfur-containing ketones **1(24)** and **1(25)** reacted with **BR**, yielding 50% and 10% of enaminones **2(24)** and **2(25)**, respectively. However,

https://doi.org/10.1021/acs.joc.1c00148
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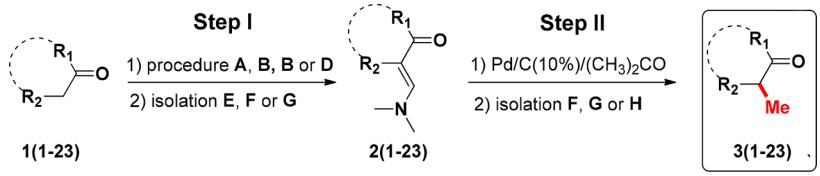
Table 4. Preparative Formation of α-Methylketones



			Step I		Step II
entry	starting ketone **1**	product **2**	procedures,[a] purification techniques,[b] yield of crude product[c,d]	product **3**	purification techniques,[b] yield of pure compound[c]
1	**1(1)**	**2(1)**	B, E, 85%	**3(1)**	H, 20%
2	**1(2)**	**2(2)**	A, F, 86%	**3(2)**	H, 74%
			B, F, 82%		
3	**1(3)**	**2(3)**	A, F, 78%	**3(3)**	H, 67%
			B, F, 72%		
4	**1(4)**	**2(4)**	B, F, 85%	**3(4)**	H, 72%
5	**1(5)**	**2(5)**	A, F, 84%	**3(5)**	H, 58%
6	**1(6)**	**2(6)**	A, G, 89%	**3(6)**	F, 48%
			B, G, 87%		
7	**1(7)**	**2(7)**	A, F, 87%	**3(7)**	F, 44%
			B, F, 58%		
8	**1(8)**	**2(8)**	B, F, 77%	**3(8)**	G, 32%
9	**1(9)**	**2(9)**	A, F, 92%	**3(9)**	G, 52%
			B, F, 82%		
10	**1(10)**	**2(10)**	A, E, 56%	**3(10)**	H, 73%
			C, E, 90%		
11	**1(11)**	**2(11)**	A, E, 72%	**3(11)**	H, 73%
			C, E, 94%		
12	**1(12)**	**2(12)**	C, E, 92%	**3(12)**	H, 78%
13	**1(13)**	**2(13)**	A, E, 88%	**3(13)**	F, 84%
			C, E, 95%		
14	**1(14)**	**2(14)**	A, E, 68%	**3(14)**	F, 81%
			C, E, 94%		
15	**1(15)**	**2(15)**	C, E, 76%	**3(15)**	F, 71%
16	**1(16)**	**2(16)**	A, E, 76%	**3(16)**	F, 62%
			C, E, 74%		
17	**1(17)**	**2(17)**	A, G, 88%	**3(17)**	F, 47%
			B, G, 75%		
18	**1(18)**	**2(18)**	A, G, 77%	**3(18)**	F, 49%
			C, G, 73%		
19	**1(19)**	**2(19)**	A, E, 84%	**3(19)**	F, 63%
			B, E, 69%		
20	**1(20)**	**2(20)**	A, G, 88%	**3(20)**	F, 52%
			C, G, 83%		
21	**1(21)**	**2(21)**	D, E, 95%	**3(21)**	E, 96%
22	**1(22)**	**2(22)**	A, F, 75%	**3(22)**	H, 69%
23	**1(23)**	**2(23)**	A, F, 68%	**3(23)**	H, 78%

[a]The preparative procedure (A–D) for compounds type **2** preparation is noted. The description of each procedure is in the Experimental Section. [b]The purification techniques (E–H) used for obtaining pure analytical samples of **2** and pure final compounds type **3** is noted. The description of each technique is in the Experimental Section. [c]All yields are preparative. [d]The compounds type **2** were used in the next step without additional purification as crude products with purity ~85–90%. The yield for crude products was provided.

we could not isolate any reduction products after treating **2(24)** and **2(25)** with hydrogen on Pd/C, presumably due to catalyst poisoning (Scheme 5).

On the other hand, despite proven efficiency as the tool for late-stage functionalization on the example of some notable natural compounds **1(20,21)**, the substrate differentiation remains a strong factor in the case of complex structures (Scheme 6). Camphor **1(26)** can form respective enaminone **2(26)**, but through the reduction step, it transformed to unexpected *N,N*-dimethylamino-derivative **5(26)** at any concentration of the substrate. It probably happens due to the extremely high sterical hindrance of the camphor core. So, the contact of the molecule with the catalyst is seriously hampered, which prevents the retro-Michael step. Increasing the steric restriction of the ketone can lead even to enaminone formation failure. We observed such a situation on the attempt utilizing the ketone **1(27)** in our reaction conditions. The next case is the loosing of regioselectivity in the reduction step. The ketone **1(28)** forms enaminone **2(28)** in good yield, and the reductive elimination of the *N,N*-DMA also went by the

https://doi.org/10.1021/acs.joc.1c00148
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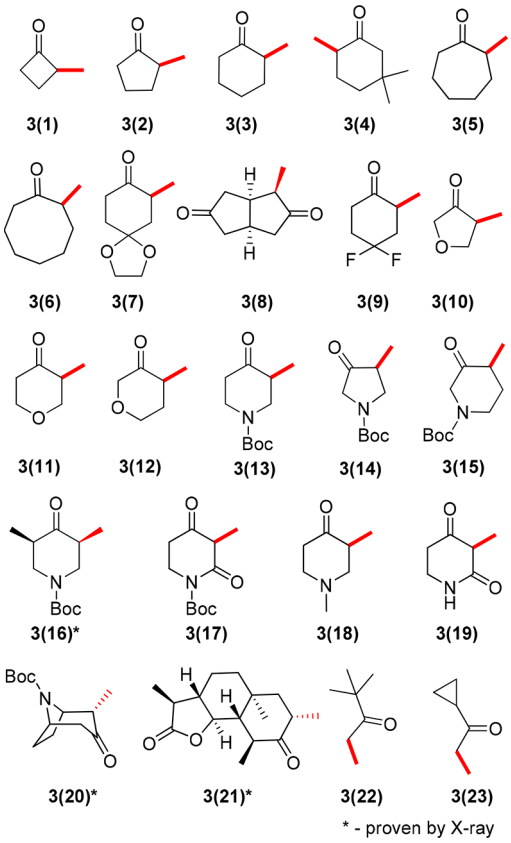
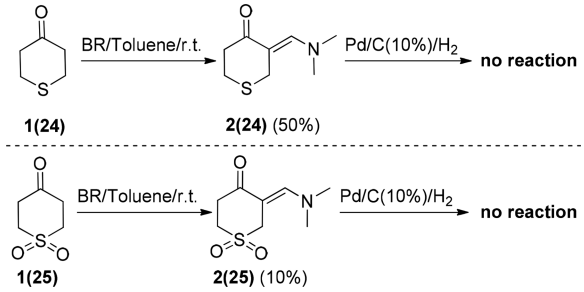


Figure 2. α-Methylketones **3(1−23)** synthesized in this study.

predicted way. However, another double bond occurred to be also susceptible to catalytic hydrogenation even in mild conditions, resulting in the inseparable mixture of **3(28)** and **7(28)** in a 2:1 ratio. The attempts to apply harsher conditions for the exclusive formation of **7(28)** at the hydrogenation step led only to the carbonyl reduction product added to the mixture above.

The limitations we faced, when probing our methylation reactions as a late-stage functionalization tool for complex molecules, however, show evident structure relation and leave substantial chemical space of natural and drug-like compounds to work with. Also, the formation of enaminones in the reduction failed cases leaves us the possibility of utilizing them in different reactions for the effective modification of natural-like compounds in the late stage.

Scheme 5. Sulphur Heterocyclic Ketones 1(24) and 1(25) in α-Methylation Reaction Sequence



CONCLUSION

We have developed the preparatively convenient, tolerable to many functional groups, inexpensive, and scalable approach for two-step methylation of α-methylketones. The approach is based on the efficient regioselective procedure for mono introduction of an *N*,*N*-dialkylaminomethylene fragment into the α-position of ketones in the first step, and the regio- and diastereoselective, high yielded, and functional group tolerable catalytic hydrogenation method based on Pd/C (10%) as catalyst and acetone as reaction media in the second. The role of acetone as the "kinetic shield" for avoiding keto group reduction is proven.

The versatility of the proposed methods was demonstrated on a wide scope of substrates, including some natural compounds. It makes the approach viable for both early- and late-stage ketones α-methylation. The overall simplicity of the experimental protocols and equipment used (see Supporting Information (SI) for the details) make the described synthetic sequence an easily accessible and powerful chemical toolkit. It is also noteworthy that preliminary experiments point toward the potency of the listed procedures to be successfully applied for the other alkylation reactions outside the methylation and wide exploration of enaminones obtained in different synthetic transformations.

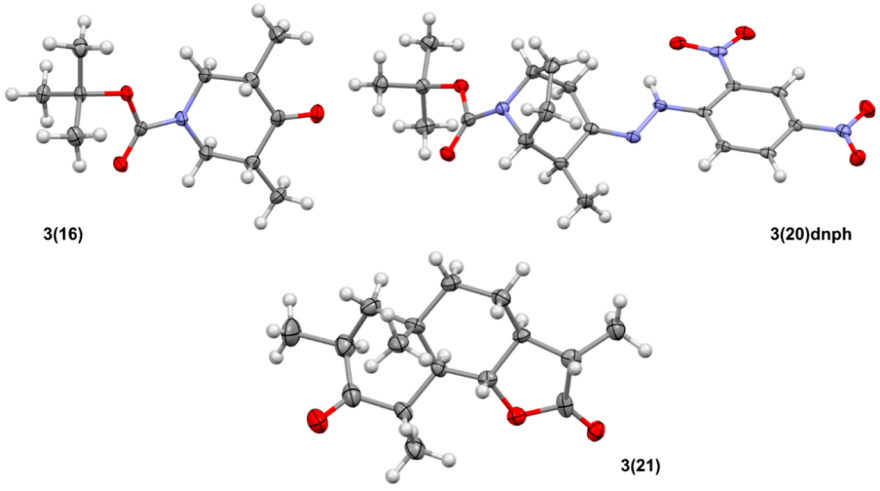


Figure 3. X-ray crystal structures for α-methylketones **3(16)**, **3(20)dnph** (as dinitrophenyl hydrazine derivative), and **3(21)**.

https://doi.org/10.1021/acs.joc.1c00148
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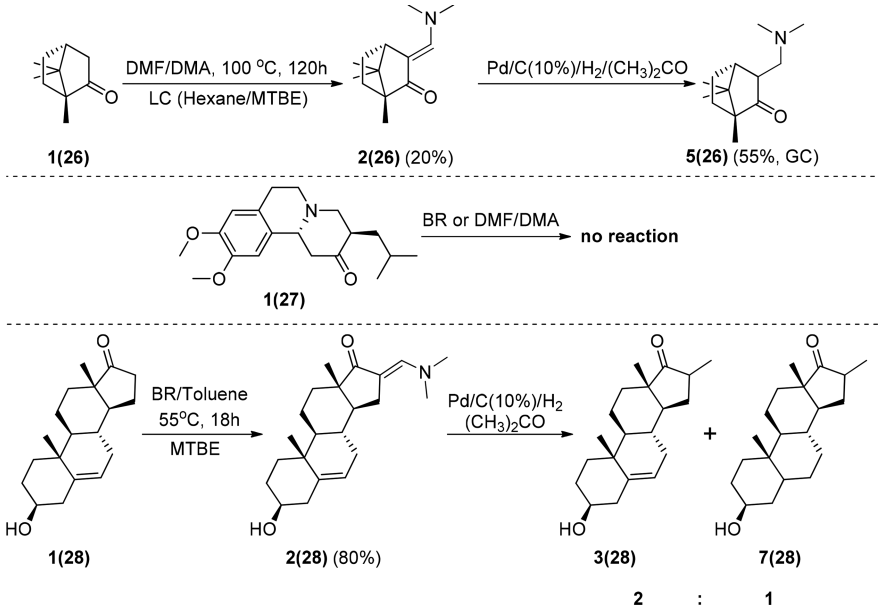
Scheme 6. Limitations on α-Methylation of Natural-like Ketones 1(26−28)



EXPERIMENTAL SECTION

General Information. The solvents were purified according to the standard procedures. All starting materials were obtained from Enamine Ltd. Melting points were measured on an automated melting point system. ^{1}H, ^{13}C, and ^{19}F NMR spectra were recorded on a Bruker 170 Avance 500 spectrometer (at 500 MHz for protons and 126 MHz for carbon-13) and a Varian Unity Plus 400 spectrometer (at 400 MHz for protons, 101 MHz for carbon-13, and 376 MHz for fluorine-19). Tetramethylsilane (^{1}H, ^{13}C) or C_6F_6 (^{19}F) was used as a standard. Elemental analyses were performed at the Laboratory of Organic Analysis, Institute of Organic Chemistry, National Academy of Sciences of Ukraine; their results were found to be in good agreement (±0.4%) with the calculated values. Preparative HPLC analyses were done on an Agilent 1200. Mass spectra were recorded on an Agilent 1100 LCMSD SL instrument (chemical ionization (APCI)). X-ray diffraction studies were performed on an automatic diffractometer (graphite monochromated Mo Kα radiation, CCD detector, ω-scanning, $2\theta_{max} = 60°$). CCDC-2027103 **4(10)**, CCDC-2027101 **3(16)**, CCDC-2027102 **3(20)dnph**, and CCDC-2027100 **3(21)** contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

General Procedures for Step I.

A. A mixture of DMF-DMA (1.2 mol; 1.2 equiv) and ketone **1** (1 mol; 1 equiv) in DMF (2 L, the concentration of ketone **1** in DMF − 0.5 mol/L) was stirred at 100 °C on an oil bath for 18 h. The resultant mixture was concentrated in vacuo to give the crude title compound **2** with purity ∼85−90%. The crude product **2** was used in the next step without additional purification. The analytical samples were obtained according to the purification techniques listed below.

B. A mixture of **BR** (1.2 mol; 1.2 equiv) and ketone **1** (1 mol; 1 equiv) was stirred at 50 °C on an air bath for 18 h. The mixture was concentrated in vacuo to give the crude title compound **2** with purity ∼85−90%. The crude product **2** was used in the next step without additional purification. The analytical samples were obtained according to the purification techniques listed below.

C. A mixture of **BR** (1.1 mol; 1.1 equiv) and ketone **1** (1 mol; 1 equiv) in toluene (1 L, the concentration of ketone **1** in toluene − 1 mol/L) was stirred at RT for 18 h. The mixture was concentrated in vacuo to give the crude title compound **2** with purity ∼85−90%. The crude product **2** was used in the next step without additional purification. The analytical samples were obtained according to the purification techniques listed below.

D. A mixture of **BR** (1.1 mol; 1.1 equiv) and ketone **1** (1 mol; 1 equiv) in toluene (1 L, the concentration of ketone **1** in toluene − 1 mol/L) was stirred at 55 °C on an air bath for 18 h. The mixture was concentrated in vacuo to give the crude title compound **2** with purity ∼85−90%. The crude product **2** was used in the next step without additional purification. The analytical samples were obtained according to the purification techniques listed below.

General Procedures for Step II. Enaminone **2** (0.5 mol, 1 equiv) was dissolved in anhydrous acetone (1 L) under argon (the concentration of enaminone **2** in acetone − 0.5 mol/L). Then the 10% Pd on charcoal (0.02 mol; 0.04 equiv; 4 mol % of pure Pd) was added. The reaction mixture was purged with hydrogen and stirred under 1 atm hydrogen gas for 2 days. The catalyst was filtered from the reaction mixture and washed with acetone (2 × 100 mL). The combined organic layer was concentrated in vacuo to form the crude title compound. Then the crude compound was purified by one of the purification techniques listed below to obtain target methylated product **3**.

The Purification Techniques.

E. The crude product **3** was purified by the crystallization in an appropriate solvent pointed out below in the compound description section.

F. The crude product **2** or **3** was purified by the column chromatography on silica gel in an appropriate system of solvents pointed out below in the compound description section.

G. The crude product **2** or **3** was purified by the preparative HPLC on silica gel in an appropriate system of solvents pointed out below in the compound description section.

H. The crude product **3** was purified by the vacuum distillation. The temperature and the appropriate pressure are pointed out below in the compound description section.

Experimental Data and Analytical Data for Synthesized Compounds. Compounds type **2** and **3** were synthesized and isolated according to general procedures **A**−**D** and purified according to the purification techniques **E**−**H** listed above. The appropriate procedure and purification technique, yields, and compounds characterization data are indicated below. Yields of crude (for

https://doi.org/10.1021/acs.joc.1c00148
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compounds type **2**) and pure (for **2** and **3**) products are also noted in Table 4.

*(E)-2-((Dimethylamino)methylene)cyclobutanone (**2(1)**).* The compound was synthesized by the general procedure **A**. 106.4 g of the crude compound was obtained as a yellowish viscous oil in 85% yield. The analytical sample (63 mg) was acquired by the purification method **E** (crystallization solvent MTBE).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 6.87 (s, 1H), 2.93 (s, 6H), 2.74 (t, J = 5.6 Hz, 2H), 2.62 (t, J = 5.6 Hz, 2H). ^{13}C{^{1}H} NMR (126 MHz, Chloroform-*d*) δ 195.6, 138.7, 111.5, 44.1, 43.0, 20.1. EIMS, 70 eV, m/z (rel. int.): 126 $[M + H]^+$ (5); 125 $[M]^+$ (64); 110 (38); 97 (16); 96 (23); 82 (55); 81 (10); 69 (25); 68 (40); 53 (13); 43 (52); 42 (100); 41 (38); 39 (17). Anal. Calcd for $C_7H_{11}NO$: C, 67.17; H, 8.86; N, 11.19. Found: C, 67.18; H, 9.05; N, 11.27.

*(E)-2-((Dimethylamino)methylene)cyclopentanone (**2(2)**).* The compound was synthesized by both general procedures **A** (119.7 g, 86% yield) and **B** (114.1 g, 82% yield) as a yellowish viscous oil. The analytical sample (54 mg) was acquired by the purification method **F** (system of solvents MTBE/MeOH).

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.00 (s, 1H), 3.01 (s, 6H), 2.78 (t, J = 7.2 Hz, 2H), 2.00 (t, J = 7.9 Hz, 2H), 1.73 (p, J = 7.6 Hz, 2H). ^{13}C{^{1}H} NMR (126 MHz, Chloroform-*d*) δ 202.9, 146.0, 102.8, 42.0, 37.6, 27.2, 20.7. LCMS, positive mode, m/z: 140 $[M + H]^+$. Anal. Calcd for $C_8H_{13}NO$: C, 69.03; H, 9.41; N, 10.06. Found: C, 68.89; H, 9.39; N, 10.06.

*(E)-2-((Dimethylamino)methylene)cyclohexanone (**2(3)**).*[17b] The compound was synthesized by both general procedures **A** (119.5 g, 78% yield) and **B** (110.3 g, 72% yield) as a gray viscous oil. The analytical sample (67 mg) was acquired by the purification method **F** (system of solvents MTBE/MeOH).

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.29 (s, 1H), 3.03 (s, 6H), 2.64 (t, J = 6.2 Hz, 2H), 2.11 (t, J = 6.5 Hz, 2H), 1.70−1.52 (m, 4H). EIMS, 70 eV, m/z (rel. int.): 154 $[M]^+$ (9); 153 $[M]^+$ (87); 152 $[M - H]^+$ (12); 138 (100); 136 (38); 124 (16); 110 (36); 97 (18); 96 (28); 94 (13); 84 (14); 82 (69); 81 (19); 79 (10); 68 (16); 44 (23); 42 (43); 41 (18); 38 (12). Anal. Calcd for $C_9H_{15}NO$: C, 70.55; H, 9.87; N, 9.14. Found: C, 70.87; H, 10.00; N, 9.52.

*(E)-2-((Dimethylamino)methylene)-5,5-dimethylcyclohexanone (**2(4)**).* The compound was synthesized by the general procedure **B** (154.1 g, 85% yield) as a gray viscous oil. The analytical sample (64 mg) was acquired by the purification method **F** (system of solvents MTBE/MeOH).

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.28 (s, 1H), 3.05 (s, 6H), 2.67 (t, J = 6.8 Hz, 2H), 1.92 (s, 2H), 1.42 (t, J = 6.7 Hz, 2H), 0.89 (s, 6H). ^{13}C{^{1}H} NMR (126 MHz, Chloroform-*d*) δ 195.0, 150.0, 101.2, 52.4, 43.3, 36.3, 35.5, 30.7, 28.5, 22.3. LCMS, positive mode, m/z: 182 $[M + H]^+$. Anal. Calcd for $C_{11}H_{19}NO$: C, 72.88; H, 10.56; N, 7.73. Found: C, 73.03; H, 10.80; N, 7.57.

*(E)-2-((Dimethylamino)methylene)cycloheptanone (**2(5)**).*[22a] The compound was synthesized by the general procedure **A** (140.5 g, 84% yield) as a gray viscous oil. The analytical sample (57 mg) was acquired by the purification method **F** (system of solvents MTBE/MeOH).

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.18 (s, 1H), 2.98 (s, 6H), 2.54−2.49 (m, 2H), 2.44−2.37 (m, 2H), 1.70−1.60 (m, 2H), 1.53 (h, J = 6.0 Hz, 4H). EIMS, 70 eV, m/z (rel. int.): 168 $[M + H]^+$. Anal. Calcd for $C_{10}H_{17}NO$: C, 71.81; H, 10.25; N, 8.37. Found: C, 71.48; H, 10.37; N, 8.09.

*(E)-2-((Dimethylamino)methylene)cyclooctanone (**2(6)**).*[22a] The compound was synthesized by both general procedures **A** (161.3 g, 89% yield) and **B** (157.7 g, 87% yield) as a gray viscous oil. The analytical sample (67 mg) was acquired by the purification method **G** (system of solvents MeOH/H_2O).

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.27 (s, 1H), 3.02 (s, 6H), 2.58 (t, J = 6.1 Hz, 2H), 2.42 (t, J = 6.1 Hz, 2H), 1.61−1.49 (m, J = 5.3 Hz, 2H), 1.52−1.43 (m, 4H), 1.41−1.32 (m, 2H). EIMS, 70 eV, m/z (rel. int.): 182 $[M]^+$ (6); 181 $[M]^+$ (53); 138 (35); 124 (15); 110 (46); 98 (19); 97 (27); 96 (21); 85 (10); 84 (100); 82 (56); 71 (36); 68 (12); 58 (11); 55 (13); 44 (10); 42 (33); 41 (18). Anal. Calcd for $C_{11}H_{19}NO$: C, 72.88; H, 10.56; N, 7.73. Found: C, 72.86; H, 10.53; N, 7.74.

*(E)-7-((Dimethylamino)methylene)-1,4-dioxaspiro[4.5]-decan-8-one (**2(7)**).*[22b] The compound was synthesized by both general procedures **A** (183.8 g, 87% yield) and **B** (122.5 g, 58% yield) as a light brown oil. The analytical sample (64 mg) was acquired by the purification method **F** (system of solvents MTBE/MeOH).

^{1}H NMR (500 MHz, DMSO-d_6) δ 7.49 (s, 1H), 4.05−3.90 (m, 4H), 3.06 (s, 6H), 2.91 (s, 2H), 2.50 (t, J = 7.1 Hz, 2H), 1.94 (t, J = 7.0 Hz, 2H). LCMS, positive mode, m/z:228 $[M + H_2O - H]^+$. LCMS, negative mode, m/z: 183 $[M - N(CH_3)_2 + OH - H]^-$. Anal. Calcd for $C_{11}H_{17}NO_3$: C, 62.54; H, 8.11; N, 6.63. Found: C, 62.58; H, 7.81; N, 6.84.

*(3aR,6aR,Z)-1-((Dimethylamino)methylene)tetrahydro-pentalene-2,5(1H,3H)-dione (**2(8)**).*[22c] The compound was synthesized by the general procedure **B** (148.8 g, 77% yield) as a gray viscous oil. The analytical sample (59 mg) was acquired by the purification method **F** (system of solvents MTBE/MeOH).

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.29 (s, 1H), 3.78 (q, J = 8.2 Hz, 1H), 3.07 (s, 6H), 2.99−2.87 (m, 1H), 2.68−2.48 (m, 3H), 2.36−2.19 (m, 2H), 2.11 (dd, J = 17.6, 8.7 Hz, 1H). EIMS, 70 eV, m/z (rel. int.): 194 $[M + H]^+$ (8); 193 $[M]^+$ (63); 178 (11); 151 (12); 150 (100); 136 (17); 124 (16); 122 (19); 108 (14); 107 (16); 94 (13); 82 (29); 79 (13); 42 (21). Anal. Calcd for $C_{11}H_{15}NO_2$: C, 68.37; H, 7.82; N, 7.25. Found: C, 68.22; H, 7.93; N, 7.18.

*(E)-2-((Dimethylamino)methylene)-4,4-difluorocyclo-hexanone (**2(9)**).*[22b] The compound was synthesized by both general procedures **A** (174.1 g, 92% yield) and **B** (155.2 g, 82% yield) as a light brown viscous oil. The analytical sample (62 mg) was acquired by the purification method **F** (system of solvents MTBE/MeOH).

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.54 (s, 1H), 3.18 (t, J = 14.7 Hz, 2H), 3.10 (s, 6H), 2.52 (t, J = 7.2 Hz, 2H), 2.23 (tt, J = 13.8, 7.2 Hz, 2H). Anal. Calcd for $C_9H_{13}F_2NO$: C, 57.13; H, 6.93; N, 7.40. Found: C, 57.34; H, 7.02; N, 7.23.

*(E)-4-((Dimethylamino)methylene)dihydrofuran-3(2H)-one (**2(10)**).* The compound was synthesized by both general procedures **A** (79.1 g, 56% yield) and **C** (127.1 g, 90% yield) as a yellowish viscous oil. The analytical sample (85 mg) was acquired by the purification method **E** (crystallization solvent MTBE).

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.14 (s, 1H), 4.99 (s, 2H), 3.85 (s, 2H), 3.00 (s, 6H). ^{13}C{^{1}H} NMR (126 MHz, Chloroform-*d*) δ 197.2, 146.2, 98.4, 71.5, 69.8, 45.9. LCMS, positive mode, m/z: 142 $[M + H]^+$. Anal. Calcd for $C_7H_{11}NO_2$: C, 59.56; H, 7.85; N, 9.92. Found: C, 59.44; H, 7.76; N, 9.84.

*(E)-3-((Dimethylamino)methylene)dihydro-2H-pyran-4(3H)-one (**2(11)**).* The compound was synthesized by both general procedures **A** (111.8 g, 72% yield) and **C** (145.9 g, 94% yield) as a yellowish viscous oil. The analytical sample (85 mg) was acquired by the purification method **E** (crystallization solvent MTBE).

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.41 (s, 1H), 3.86 (s, 2H), 3.68 (t, J = 5.7 Hz, 2H), 3.08 (s, 6H), 2.76 (t, J = 5.5 Hz, 3H). ^{13}C{^{1}H} NMR (126 MHz, Chloroform-*d*) δ 191.9, 150.4, 99.4, 73.1, 65.5, 43.2, 25.9. LCMS, positive mode, m/z: 156 $[M + H]^+$. Anal. Calcd for $C_8H_{13}NO_2$: C, 61.91; H, 8.44; N, 9.03. Found: C, 62.10; H, 8.60; N, 9.07.

*(E)-4-((Dimethylamino)methylene)dihydro-2H-pyran-3(4H)-one (**2(12)**).* The compound was synthesized by the general procedure **C** (143.8 g, 92% yield) as a yellowish viscous oil. The analytical sample (81 mg) was acquired by the purification method **E** (crystallization solvent MTBE).

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.41 (s, 1H), 3.86 (s, 2H), 3.68 (t, J = 5.7 Hz, 2H), 3.08 (s, 6H), 2.76 (t, J = 5.5 Hz, 2H). ^{13}C{^{1}H} NMR (126 MHz, Chloroform-*d*) δ 191.9, 150.4, 99.4, 73.1, 65.8, 43.2, 25.9. LCMS, positive mode, m/z: 156 $[M + H]^+$. Anal. Calcd for $C_8H_{13}NO_2$: C, 61.91; H, 8.44; N, 9.03. Found: C, 62.13; H, 8.31; N, 9.09.

*(E)-tert-Butyl 3-((Dimethylamino)methylene)-4-oxopiperidine-1-carboxylate (**2(13)**).* The compound was synthesized by both general procedures **A** (223.8 g, 88% yield) and **C** (241.6 g, 95% yield) as a

https://doi.org/10.1021/acs.joc.1c00148
J. Org. Chem. 2021, 86, 7333−7346

gray viscous oil. The analytical sample (79 mg) was acquired by the purification method **E** (crystallization solvent MTBE).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.46 (s, 1H), 4.52 (s, 2H), 3.57 (t, J = 6.4 Hz, 2H), 3.08 (s, 6H), 2.41 (t, J = 6.4 Hz, 2H), 1.44 (s, 9H). ^{13}C{^{1}H} NMR (126 MHz, Chloroform-*d*) δ 194.5, 154.8, 149.3, 101.1, 79.8, 43.5, 41.7, 41.3, 37.6, 28.4. EIMS, 70 eV, m/z (rel. int.): 253 [M − H]$^-$ (5); 109 (65); 80 (20); 67 (22); 56 (43); 55 (22); 54 (19); 53 (15); 50 (12); 45 (19); 44 (100); 42 (17); 41 (89); 40 (34); 39 (57); 38 (10). Anal. Calcd for $C_{13}H_{22}N_2O_3$: C, 61.39; H, 8.72; N, 11.01. Found: C, 61.38; H, 8.83; N, 10.91.

(E)-tert-Butyl 3-((Dimethylamino)methylene)-4-oxopyrrolidine-1-carboxylate ***(2(14))***. The compound was synthesized by both general procedures **A** (163.4 g, 68% yield) and **C** (225.9 g, 94% yield) as a gray viscous oil. The analytical sample (87 mg) was acquired by the purification method **E** (crystallization solvent MTBE).

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.28 (s, 1H), 4.65 (d, J = 14.5 Hz, 1H), 4.33 (s, 1H), 3.63 (dd, J = 12.6, 5.9 Hz, 1H), 3.05 (s, 6H), 2.37 (q, J = 7.6, 7.0 Hz, 1H), 1.41 (s, 9H). ^{13}C{^{1}H} NMR (126 MHz, Chloroform-*d*) δ 195.5, 154.2, 148.7, 100.0, 79.3, 47.8, 43.5, 36.1, 28.6. LCMS, negative mode, m/z: 240 [M]$^-$. Anal. Calcd for $C_{12}H_{20}N_2O_3$: C, 59.98; H, 8.39; N, 11.66. Found: C, 59.76; H, 8.34; N, 11.27.

(E)-tert-Butyl 4-((Dimethylamino)methylene)-3-oxopiperidine-1-carboxylate ***(2(15))***.[22d] The compound was synthesized by the general procedure **C** (193.3 g, 76% yield) as a gray viscous oil. The analytical sample (54 mg) was acquired by the purification method **E** (crystallization solvent MTBE).

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.42 (s, 1H), 3.76 (s, 2H), 3.40 (t, J = 5.9 Hz, 2H), 3.08 (s, 6H), 2.71 (t, J = 6.0 Hz, 2H), 1.40 (s, 9H). LCMS, positive mode, m/z: 255 [M + H]$^+$. Anal. Calcd for $C_{13}H_{22}N_2O_3$: C, 61.39; H, 8.72; N, 11.01. Found: C, 61.78; H, 9.00; N, 11.01.

(R,E)-tert-Butyl 3-((Dimethylamino)methylene)-5-methyl-4-oxopiperidine-1-carboxylate ***(2(16))***.[22e] The compound was synthesized by both general procedures **A** (203.9 g, 76% yield) and **C** (198.5 g, 74% yield) as a gray viscous oil. The analytical sample (61 mg) was acquired by the purification method **E** (crystallization solvent MTBE).

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.29 (s, 1H), 4.69−4.60 (m, 1H), 4.33 (s, 1H), 3.67−3.58 (m, 1H), 3.05 (s, 7H), 2.42−2.33 (m, 1H), 1.41 (s, 9H), 1.00−0.93 (m, 3H). LCMS, positive mode, m/z: 269 [M + H]$^+$. Anal. Calcd for $C_{14}H_{24}N_2O_3$: C, 62.66; H, 9.01; N, 10.44. Found: C, 63.02; H, 8.91; N, 10.26.

(Z)-tert-Butyl 3-((Dimethylamino)methylene)-2,4-dioxopiperidine-1-carboxylate ***(2(17))***.[22f] The compound was synthesized by both general procedures **A** (236.1 g, 88% yield) and **B** (201.2 g, 75% yield) as a gray viscous oil. The analytical sample (73 mg) was acquired by the purification method **G** (system of solvents MeCN/H_2O).

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.04 (s, 1H), 3.71 (t, J = 6.1 Hz, 2H), 3.39 (s, 3H), 3.03 (s, 3H), 2.37 (t, J = 6.1 Hz, 2H), 1.44 (s, 9H). LCMS, positive mode, m/z: 269 [M + H]$^+$. Anal. Calcd for $C_{13}H_{20}N_2O_4$: C, 58.19; H, 7.51; N, 10.44. Found: C, 58.24; H, 7.77; N, 10.74.

(E)-3-((Dimethylamino)methylene)-1-methylpiperidin-4-one ***(2(18))***.[22g] The compound was synthesized by both general procedures **A** (129.5 g, 77% yield) and **C** (122.8 g, 73% yield) as a gray viscous oil. The analytical sample (58 mg) was acquired by the purification method **G** (system of solvents MeOH/H_2O).

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.23 (s, 1H), 3.02 (s, 6H), 2.52−2.46 (m, 2H), 2.27 (s, 3H), 2.19 (t, J = 6.2 Hz, 2H). LCMS, positive mode, m/z: 169 [M + H]$^+$. Anal. Calcd for $C_9H_{16}N_2O$: C, 64.25; H, 9.59; N, 16.65. Found: C, 64.48; H, 9.83; N, 16.67.

(Z)-3-((Dimethylamino)methylene)piperidine-2,4-dione ***(2(19))***.[22h] The compound was synthesized by both general procedures **A** (141.3 g, 84% yield) and **B** (116.1 g, 69% yield) as a gray viscous oil. The analytical sample (60 mg) was acquired by the purification method **E** (crystallization solvent MTBE).

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.83 (s, 1H), 7.15 (s, 1H), 3.29 (s, 3H), 3.16 (td, J = 6.4, 3.3 Hz, 2H), 3.05 (s, 3H), 2.29 (t, J = 6.4 Hz, 2H). LCMS, positive mode, m/z: 169 [M + H]$^+$. Anal. Calcd for $C_8H_{12}N_2O_2$: C, 57.13; H, 7.19; N, 16.66. Found: C, 56.86; H, 7.25; N, 16.44.

(E)-tert-Butyl 2-((Dimethylamino)methylene)-3-oxo-8-azabicyclo[3.2.1]octane-8-carboxylate ***(2(20))***.[23d] The compound was synthesized by both general procedures **A** (24.7 g, 88% yield) and **C** (23.2 g, 83% yield) as a gray viscous oil. The analytical sample (67 mg) was acquired by the purification method **G** (system of solvents MeCN/H_2O).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.47−7.28 (m, 1H), 5.53−5.13 (m, 1H), 4.52−4.19 (m, 1H), 3.08 (s, 6H), 2.21 (s, 1H), 2.18−2.06 (m, 2H), 1.88−1.78 (m, 1H), 1.69 (s, 2H), 1.42 (s, 9H). LCMS, positive mode, m/z: 281 [M + H]$^+$. Anal. Calcd for $C_{15}H_{24}N_2O_3$: C, 64.26; H, 8.63; N, 9.99. Found: C, 64.22; H, 9.02; N. 9,81.

(3S,3aS,5aS,9S,9aS,9bS,E)-7-((Dimethylamino)methylene)-3,5a,9-trimethyloctahydronaphtho[1,2-b]-furan-2,8(3H,9bH)-dione ***(2(21))***. The compound was synthesized by the general procedure **D** (0.29 g, 95% yield) as a gray viscous oil. The analytical sample (21 mg) was acquired by the purification method **E** (crystallization solvent MTBE).

^{1}H NMR (500 MHz, DMSO-d_6) δ 7.33 (s, 1H), 4.07 (q, J = 5.4 Hz, 1H), 3.86 (t, J = 10.5 Hz, 1H), 3.01 (s, 6H), 2.47−2.35 (m, 2H), 1.97 (dq, J = 10.7, 7.1 Hz, 1H), 1.79−1.68 (m, 1H), 1.64−1.42 (m, 4H), 1.38−1.25 (m, 1H), 1.14 (d, J = 6.9 Hz, 3H), 1.05 (d, J = 7.0 Hz, 3H), 0.82 (s, 3H). ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6) δ 197.7, 179.6, 151.3, 100.1, 84.3, 51.8, 51.6, 50.7, 43.4, 42.6, 42.0, 40.3, 35.3, 23.3, 19.5, 18.7, 12.7. LCMS, positive mode, m/z: 306 [M + H]$^+$. Anal. Calcd for $C_{18}H_{27}NO_3$: C, 70.79; H, 8.91; N, 4.59. Found: C, 70.99; H, 9.25; N, 4.79.

(E)-1-(Dimethylamino)-4,4-dimethylpent-1-en-3-one ***(2(22))***.[23b] The compound was synthesized by the general procedure **A** (116.4 g, 75% yield) as a gray viscous oil. The analytical sample (55 mg) was acquired by the purification method **F** (system of solvents EtOAc/Hex).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.71−7.52 (m, 1H), 5.34−5.13 (m, 1H), 2.93 (br, 6H), 1.14 (s, 9H). EIMS, 70 eV, m/z (rel. int.): 155 [M]$^+$ (7); 98 (100). Anal. Calcd for $C_9H_{17}NO$: C, 69.63; H, 11.04; N, 9.02. Found: C, 69.97; H, 10.94; N, 9.35.

(E)-1-Cyclopropyl-3-(dimethylamino)prop-2-en-1-one ***(2(23))***.[23b] The compound was synthesized by the general procedure **A** (94.6 g, 68% yield) as a yellowish viscous oil. The analytical sample (57 mg) was acquired by the purification method **F** (system of solvents EtOAc/Hex).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.35 (d, J = 7.8 Hz, 1H), 5.80 (d, J = 7.8 Hz, 1H), 1.75 (m, 1H), 0.98 (m, 2H), 0.67 (m, 2H). EIMS, 70 eV, m/z (rel. int.): 139 [M]$^+$ (47); 98 (100). Anal. Calcd for $C_8H_{13}NO$: C, 69.03; H, 9.41; N, 10.06. Found: C, 69.35; H, 9.33; N, 10.35.

(E)-3-((Dimethylamino)methylene)dihydro-2H-thiopyran-4(3H)-one ***(2(24))***. The compound was synthesized by the general procedure **C** (85.6 g, 50% yield) as a yellowish viscous oil. The analytical sample (48 mg) was acquired by the purification method **E** (crystallization solvent MTBE).

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.29 (s, 1H), 3.75 (s, 2H), 3.05 (s, 6H), 2.80 (t, J = 6.4 Hz, 2H), 2.51−2.44 (m, 2H). ^{13}C{^{1}H} NMR (151 MHz, Chloroform-*d*) δ 196.0, 149.2, 103.2, 43.7, 39.2, 34.8, 25.9. LCMS, negative mode, m/z: 143 [M − N(CH$_3$)$_2$ + OH − H]. Anal. Calcd for $C_8H_{13}NOS$: C, 56.11; H, 7.65; N, 8.18; S, 18.72. Found: C, 55.93; H, 7.31; N, 7.85; S, 19.04.

(E)-3-((Dimethylamino)methylene)dihydro-2H-thiopyran-4(3H)-one 1,1-dioxide ***(2(25))***. The compound was synthesized by the general procedure **C** (2.3 g, 10% yield) as a yellowish viscous oil. The analytical sample (46 mg) was acquired by the purification method **F** (system of solvents MTBE/MeOH).

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.63 (s, 1H), 4.22 (s, 2H), 3.34 (t, J = 6.7 Hz, 2H), 3.16 (s, 6H), 2.89 (t, J = 6.7 Hz, 2H). ^{13}C{^{1}H} NMR (151 MHz, Chloroform-*d*) δ 192.7, 151.8, 93.3, 51.1, 50.4, 44.0, 35.9. LCMS, positive mode, m/z: 204 [M + H]$^+$. Anal. Calcd for $C_8H_{13}NO_3S$: C, 47.27; H, 6.45; N, 6.89; S, 15.77. Found: C, 47.45; H, 6.43; N, 6.71; S, 15.89.

https://doi.org/10.1021/acs.joc.1c00148
J. Org. Chem. 2021, 86, 7333−7346

*(1R,4S,E)-3-((Dimethylamino)methylene)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-one (**2(26)**).* The compound was synthesized by the general procedure **A** (4.2 g, 20% yield) as a gray viscous oil. The analytical sample (34 mg) was acquired by the purification method **G** (system of solvents Hexane/MTBE).

^{1}H NMR (500 MHz, Chloroform-*d*) δ 6.95 (s, 1H), 2.97−2.83 (m, 7H), 2.02−1.86 (m, 1H), 1.60−1.48 (m, 1H), 1.43−1.33 (m, 1H), 1.34−1.24 (m, 1H), 0.98−0.68 (m, 9H). ^{13}C{^{1}H} NMR (126 MHz, Chloroform-*d*) δ 207.2, 141.1, 111.0, 56.3, 48.2, 48.0, 42.2, 30.3, 28.4, 20.7, 19.0, 9.6. EIMS, 70 eV, *m*/*z* (rel. int.): 208 [M + H]$^+$ (12); 207 [M]$^+$ (83); 192 (14); 179 (48); 165 (24); 164 (100); 150 (10); 136 (32); 124 (10); 119 (12); 94 (10); 82 (16); 42 (13); 41 (11). Anal. Calcd for $C_{13}H_{21}NO$: C, 75.32; H, 10.21; N, 6.76. Found: C, 75.54; H, 9.96; N, 6.78.

*(3S,8R,9S,10R,13S,14S,E)-16-((Dimethylamino)methylene)-3-hydroxy-10,13-dimethyl-3,4,7,8,9,10,11,12,13,14, 15,16-dodecahydro-1H-cyclopenta[a]phenanthren-17(2H)-one (**2(28)**).* The compound was synthesized by the general procedure **D** (0.27 g, 80% yield) as a gray viscous oil. The analytical sample (21 mg) was acquired by the purification method **G** (system of solvents Hexane/MTBE).

^{1}H NMR (400 MHz, DMSO-d_6) δ 6.99 (s, 1H), 5.30 (d, *J* = 4.6 Hz, 1H), 4.59 (d, *J* = 4.6 Hz, 1H), 3.31 (s, 6H), 2.73 (dd, *J* = 13.2, 6.3 Hz, 1H), 2.31−1.93 (m, 4H), 1.76 (d, *J* = 13.3 Hz, 1H), 1.72−1.52 (m, 5H), 1.48−1.28 (m, 3H), 1.22−1.03 (m, 2H), 0.97 (s, 5H), 0.74 (s, 3H). ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6) δ 206.8, 145.7, 142.0, 120.6, 102.0, 70.5, 51.3, 50.6, 45.9, 42.8, 42.0, 37.4, 36.8, 32.3, 32.0, 31.0, 27.4, 20.6, 19.7, 14.9. LCMS, positive mode, *m*/*z*: 344 [M + H]$^+$. Anal. Calcd for $C_{22}H_{33}NO_2$: C, 76.92; H, 9.68; N, 4.08. Found: C, 76.59; H, 9.89; N, 4.34.

*2-Methylcyclobutanone (**3(1)**).* The crude compound was purified by method **H** (bp = 40 °C, 50 mmHg). 8.4 g of the target product obtained as a colorless liquid in 20% yield.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 3.29 (m, 1H), 3.03 (m, 1H), 2.89 (m, 1H), 2.20 (qd, *J* = 10.6, 5.0 Hz, 1H), 1.53 (m, 1H), 1.13 (d, *J* = 7.4 Hz, 3H). ^{13}C{^{1}H} NMR (126 MHz, Chloroform-*d*) δ 212.5, 54.9, 44.7, 18.6, 14.0. EIMS, 70 eV, *m*/*z* (rel. int.): 84 [M]$^+$ (44); 56 (100); 55 (21); 43 (15); 42 (76); 41 (56); 39 (32). Anal. Calcd for C_5H_8O: C, 71.39; H, 9.59. Found: C, 71.48; H, 9.60.

*2-Methylcyclopentanone (**3(2)**).* The crude compound was purified by method **H** (bp = 38−40 °C, 10 mmHg). 36.3 g of the target product obtained as a colorless liquid in 74% yield.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 2.32−2.14 (m, 2H), 2.14−2.00 (m, 2H), 1.99−1.91 (m, 1H), 1.80−1.68 (m, 1H), 1.49−1.39 (m, 1H), 1.04 (d, *J* = 7.0 Hz, 3H). ^{13}C{^{1}H} NMR (126 MHz, Chloroform-*d*) δ 221.9, 43.9, 37.6, 31.8, 20.6, 14.1. EIMS, 70 eV, *m*/*z* (rel. int.): 98 [M]$^+$ (80); 83 (21); 70 (28); 69 (46); 56 (24); 55 (80); 43 (12); 42 (100); 41 (44); 39 (34). Anal. Calcd for $C_6H_{10}O$: C, 73.43; H, 10.27. Found: C, 73.62; H, 10.24.

*2-Methylcyclohexanone (**3(3)**).* The crude compound was purified by method **H** (bp = 51−54 °C, 10 mmHg). 37.6 g of the target product obtained as a colorless liquid in 67% yield.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 2.40−2.30 (m, 2H), 2.24 (m, 1H), 2.03 (m, 2H), 1.80 (m, 1H), 1.70−1.53 (m, 2H), 1.32 (qd, *J* = 12.3, 4.0 Hz, 1H), 0.97 (d, *J* = 6.6 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ 213.5, 45.3, 41.8, 36.1, 27.9, 25.1, 14.7. EIMS, 70 eV, *m*/*z* (rel. int.): 112 [M]$^+$ (50); 84 (31); 83 (14); 69 (43); 68 (61); 67 (13); 56 (63); 55 (72); 53 (14); 44 (15); 42 (56); 41 (100); 40 (15); 39 (78). Anal. Calcd for $C_7H_{12}O$: C, 74.95; H, 10.78. Found: C, 75.23; H, 10.52.

*2,5,5-Trimethylcyclohexanone (**3(4)**).* The crude compound was purified by method **H** (bp = 69−72 °C, 10 mmHg). 50.5 g of the target product obtained as a colorless liquid in 72% yield.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 2.27 (tt, *J* = 12.3, 6.0 Hz, 1H), 2.21−2.04 (m, 2H), 2.01−1.88 (m, 1H), 1.72−1.38 (m, 3H), 1.04−0.95 (m, 6H), 0.82 (s, 3H). ^{13}C{^{1}H} NMR (126 MHz, Chloroform-*d*) δ 213.3, 54.7, 44.2, 38.2, 36.9, 31.7, 31.7, 25.4, 14.4. EIMS, 70 eV, *m*/*z* (rel. int.): 141 [M + H]$^+$ (4); 140 [M]$^+$ (46); 125 (20); 98 (11); 97 (18); 96 (49); 84 (10); 83 (100); 69 (19); 57 (12); 56 (47); 55 (46); 41 (26); 39 (12). Anal. Calcd for $C_9H_{16}O$: C, 77.09; H, 11.50. Found: C, 76.79; H, 11.15.

*2-Methylcycloheptanone (**3(5)**).*[23c] The crude compound was purified by method **F** (system of solvents Hexane/MTBE). 36.6 g of the target product obtained as a colorless viscous oil in 58% yield.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 2.65−2.52 (m, 1H), 2.51−2.40 (m, 2H), 1.92−1.71 (m, 4H), 1.68−1.52 (m, 1H), 1.50−1.26 (m, 3H), 1.05 (d, *J* = 6.9 Hz, 3H). EIMS, 70 eV, *m*/*z* (rel. int.): 127 [M + H]$^+$ (6); 126 (62); 111 (11); 98 (100); 97 (30); 93 (17); 84 (34); 83 (42); 82 (39); 70 (35); 69 (50); 68 (22); 67 (30); 56 (40); 55 (99); 43 (13); 42 (50); 41 (65); 39 (37). Anal. Calcd for $C_8H_{14}O$: C, 76.14; H, 11.18. Found: C, 76.30; H, 11.11.

*2-Methylcyclooctanone (**3(6)**).* The crude compound was purified by method **F** (system of solvents Hexane/MTBE). 33.7 g of the target product obtained as a colorless viscous oil in 48% yield.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 2.64−2.53 (m, 1H), 2.45−2.29 (m, 2H), 1.98−1.81 (m, 2H), 1.82−1.71 (m, 1H), 1.72−1.34 (m, 6H), 1.28−1.12 (m, 1H), 1.03 (dd, *J* = 6.8, 2.2 Hz, 3H). ^{13}C{^{1}H} NMR (126 MHz, Chloroform-*d*) δ 220.0, 45.1, 40.3, 33.0, 26.9, 26.5, 25.6, 24.5, 16.7. EIMS, 70 eV, *m*/*z* (rel. int.): 141 [M + H]$^+$ (3); 140 [M]$^+$ (30); 112 (23); 111 (14); 98 (100); 97 (26); 96 (13); 93 (12); 84 (27); 83 (38); 81 (17); 70 (28); 69 (40); 68 (13); 67 (15); 56 (45); 55 (80); 54 (11); 43 (20); 42 (39); 41 (64); 39 (30). Anal. Calcd for $C_9H_{16}O$: C, 77.09; H, 11.50. Found: C, 77.11; H, 11.35.

*7-Methyl-1,4-dioxaspiro[4.5]decan-8-one (**3(7)**).* The crude compound was purified by method **F** (system of solvents Hexane/MTBE). 37.4 g of the target product obtained as a colorless viscous oil in 44% yield.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 4.17−3.73 (m, 4H), 2.77−2.52 (m, 2H), 2.33 (ddd, *J* = 14.3, 5.1, 2.9 Hz, 1H), 2.08−1.87 (m, 3H), 1.69 (t, *J* = 13.1 Hz, 1H), 0.99 (d, *J* = 6.6 Hz, 3H). ^{13}C{^{1}H} NMR (126 MHz, Chloroform-*d*) δ 211.9, 107.4, 64.7, 64.6, 42.7, 41.3, 38.0, 34.6, 14.3. EIMS, 70 eV, *m*/*z* (rel. int.): 170 [M]$^+$ (5); 114 (46); 100 (25); 99 (100); 55 (12). Anal. Calcd for $C_9H_{14}O_3$: C, 63.51; H, 8.29. Found: C, 63.49; H, 8.69.

*1-Methyltetrahydropentalene-2,5(1H,3H)-dione (**3(8)**).* The crude compound was purified by method **G** (system of solvents MeCN/H_2O). 24.4 g of the target product obtained as a colorless viscous oil in 32% yield.

^{1}H NMR (400 MHz, DMSO-d_6) δ 3.04−2.52 (m, 2H), 2.44 (dtd, *J* = 9.8, 8.4, 4.8 Hz, 3H), 2.32−1.79 (m, 4H), 0.98 (d, *J* = 7.0 Hz, 2H), 0.94 (d, *J* = 7.1 Hz, 1H). ^{13}C{^{1}H} NMR (126 MHz, Chloroform-*d*) δ 219.9, 219.7, 219.2, 218.3, 48.0, 47.6, 44.7, 44.3, 43.4, 43.4, 43.0, 42.3, 41.9, 38.7, 34.0, 33.9, 13.3. LCMS, positive mode, *m*/*z*: 153 [M + H]$^+$. Anal. Calcd for $C_9H_{12}O_2$: C, 71.03; H, 7.95. Found: C, 71.14; H, 8.04.

*4,4-Difluoro-2-methylcyclohexanone (**3(9)**).* The crude compound was purified by method **F** (system of solvents Hexane). 38.5 g of the target product obtained as a colorless viscous oil in 52% yield.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 2.65 (m, 2H), 2.42 (m, 3H), 2.30−2.03 (m, 1H), 1.88 (dtd, *J* = 31.4, 13.4, 3.9 Hz, 1H), 1.05 (d, *J* = 6.6 Hz, 3H). ^{13}C{^{1}H} NMR (126 MHz, Chloroform-*d*) δ 209.0, 121.5 (dd, *J* = 244.0, 239.3 Hz), 41.0 (dd, *J* = 25.9, 24.0 Hz), 40.1 (d, *J* = 9.5 Hz), 36.4 (d, *J* = 9.5 Hz), 33.4 (t, *J* = 26.1 Hz), 14.0. ^{19}F NMR (376 MHz, Chloroform-*d*) δ −95.9 (d, *J* = 243.0 Hz), −102.6 (d, *J* = 242.9 Hz). EIMS, 70 eV, *m*/*z* (rel. int.): 149 [M + H]$^+$ (8); 148 [M]$^+$ (100); 92 (37); 86 (58); 85 (40); 79 (15); 77 (63); 73 (48); 69 (68); 59 (18); 56 (17); 55 (71); 54 (13); 51 (22); 42 (29); 41 (32); 39 (27). Anal. Calcd for $C_7H_{10}F_2O$: C, 56.75; H, 6.80. Found: C, 57.03; H, 6.68.

*4-Methyldihydrofuran-3(2H)-one (**3(10)**).* The crude compound was purified by method **H** (bp = 46−48 °C, 10 mmHg). 36.5 g of the target product obtained as a colorless liquid in 73% yield.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 4.49 (t, *J* = 8.8 Hz, 1H), 4.07 (d, *J* = 17.1 Hz, 1H), 3.83 (d, *J* = 17.1 Hz, 1H), 3.71 (t, *J* = 9.3 Hz, 1H), 2.54 (h, *J* = 7.8 Hz, 1H), 1.16 (d, *J* = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (126 MHz, Chloroform-*d*) δ 217.1, 73.7, 70.7, 42.0, 11.3. EIMS, 70 eV, *m*/*z* (rel. int.): 100 [M]$^+$ (19); 42 (100); 41 (48); 40 (13); 39 (31). Anal. Calcd for $C_5H_8O_2$: C, 59.98; H, 8.05. Found: C, 60.32; H, 7.87.

https://doi.org/10.1021/acs.joc.1c00148
J. Org. Chem. 2021, 86, 7333−7346

*3-Methyldihydro-2H-pyran-4(3H)-one (**3(11)**).* The crude compound was purified by method **H** (bp = 58−61 °C, 10 mmHg). 41.7 g of the target product obtained as a colorless liquid in 73% yield.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 4.20 (m, 1H), 4.12 (ddd, *J* = 11.2, 6.4, 1.7 Hz, 1H), 3.67 (td, *J* = 11.5, 3.1 Hz, 1H), 3.28 (t, *J* = 10.8 Hz, 1H), 2.70−2.53 (m, 2H), 2.35 (dt, *J* = 14.2, 2.8 Hz, 1H), 0.95 (d, *J* = 6.7 Hz, 3H). ^{13}C{^{1}H} NMR (126 MHz, Chloroform-*d*) δ 208.5, 74.1, 68.7, 46.1, 42.4, 9.8. EIMS, 70 eV, *m*/*z* (rel. int.): 114 [M]$^+$ (46); 73 (100); 57 (11); 56 (40); 55 (15); 43 (15); 42 (56); 41 (22); 39 (14). Anal. Calcd for $C_6H_{10}O_2$: C, 63.14; H, 8.83. Found: C, 62.76; H, 9.04.

*4-Methyldihydro-2H-pyran-3(4H)-one (**3(12)**).* The crude compound was purified by method **H** (bp = 67−68 °C, 10 mmHg). 44.5 g of the target product obtained as a colorless liquid in 78% yield.

^{1}H NMR (400 MHz, Acetonitrile-d_3) δ 3.97−3.82 (m, 3H), 3.77 (td, *J* = 11.2, 3.3 Hz, 1H), 2.60 (m, 1H), 2.14 (m, 1H), 1.77−1.62 (m, 1H), 1.04 (d, *J* = 6.7 Hz, 3H). ^{13}C{^{1}H} NMR (126 MHz, Acetonitrile-d_3) δ 209.4, 74.1, 65.9, 41.7, 34.0, 13.5. EIMS, 70 eV, *m*/*z* (rel. int.): 114 [M]$^+$ (65); 69 (17); 56 (100); 55 (20); 42 (14); 41 (63); 39 (21). Anal. Calcd for $C_6H_{10}O_2$: C, 63.14; H, 8.83. Found: C, 63.50; H, 8.72.

*tert-Butyl 3-Methyl-4-oxopiperidine-1-carboxylate (**3(13)**).* The crude compound was purified by method **F** (system of solvents Hexane). 89.6 g of the target product obtained as a white crystalline solid in 84% yield (mp = 54−55 °C).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 4.21−4.09 (m, 2H), 3.21 (ddd, *J* = 14.1, 10.3, 4.5 Hz, 1H), 2.80 (s, 1H), 2.57−2.31 (m, 3H), 1.45 (s, 9H), 1.00 (d, *J* = 6.6 Hz, 3H). ^{13}C{^{1}H} NMR (126 MHz, Chloroform-*d*) δ 209.7, 154.5, 80.4, 49.8, 44.8, 43.8, 40.7, 28.4, 11.7. EIMS, 70 eV, *m*/*z* (rel. int.): 213 [M]$^+$ (2); 158 (17); 140 (14); 113 (14); 70 (11); 57 (100); 56 (25); 44 (11); 42 (14); 41 (34); 39 (13). Anal. Calcd for $C_{11}H_{19}NO_3$: C, 61.95; H, 8.98; N, 6.57. Found: C, 61.60; H, 8.93; N, 6.82.

*tert-Butyl 3-Methyl-4-oxopyrrolidine-1-carboxylate (**3(14)**).* The crude compound was purified by method **F** (system of solvents Hexane). 80.7 g of the target product obtained as a colorless viscous oil in 81% yield.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 4.09 (s, 1H), 3.85 (s, 1H), 3.63 (d, *J* = 19.4 Hz, 1H), 3.13 (dd, *J* = 11.1, 9.1 Hz, 1H), 2.59 (d, *J* = 10.5 Hz, 1H), 1.45 (s, 9H), 1.14 (d, *J* = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (126 MHz, Chloroform-*d*) δ 209.1, 154.3, 80.3, 52.6, 49.7, 42.4, 28.4, 12.6. EIMS, 70 eV, *m*/*z* (rel. int.): 199 [M]$^+$ (3); 144 (12); 143 (12); 126 (14); 71 (13); 57 (100); 56 (28); 43 (12); 42 (35); 41 (60); 39 (24). Anal. Calcd for $C_{10}H_{17}NO_3$: C, 60.28; H, 8.60; N, 7.03. Found: C, 60.36; H, 8.47; N, 7.41.

*tert-Butyl 4-Methyl-3-oxopiperidine-1-carboxylate (**3(15)**).* The crude compound was purified by method **F** (system of solvents Hexane). 75.7 g of the target product obtained as a colorless viscous oil in 71% yield.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 4.05 (m, 1H), 3.86 (m, 2H), 3.35 (s, 1H), 2.42 (dp, *J* = 13.0, 6.6 Hz, 1H), 2.13−2.01 (m, 1H), 1.59 (qd, *J* = 12.1, 5.4 Hz, 1H), 1.42 (s, 9H), 1.09 (d, *J* = 6.7, 3H). ^{13}C{^{1}H} NMR (126 MHz, Chloroform-*d*) δ 207.9, 154.5, 80.4, 54.1, 42.5, 41.7, 30.8, 28.3, 14.1. EIMS, 70 eV, *m*/*z* (rel. int.): 213 [M]$^+$ (13); 157 [M − *t*-Bu]$^+$ (31); 140 (26); 129 (18); 128 (10); 114 [M − Boc + H]$^+$ (10); 85 (14); 84 (27); 57 (100); 56 (32); 55 (14); 43 (61); 42 (53); 41 (82); 39 (43). Anal. Calcd for $C_{11}H_{19}NO_3$: C, 61.95; H, 8.98; N, 6.57. Found: C, 62.18; H, 9.27; N, 6.97.

*tert-Butyl 3,5-Dimethyl-4-oxopiperidine-1-carboxylate (**3(16)**).* The crude compound was purified by method **F** (system of solvents Hexane). 70.5 g of the target product obtained as a white crystalline solid in 62% yield (mp = 75−77 °C).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 4.31 (s, 1H), 2.75−2.42 (m, 2H), 1.46 (s, 9H), 0.98 (d, *J* = 6.2 Hz, 6H). ^{13}C{^{1}H} NMR (126 MHz, Chloroform-*d*) δ 210.9, 154.4, 80.4, 51.2, 44.5, 28.4, 11.1. EIMS, 70 eV, *m*/*z* (rel. int.): 227 [M]$^+$ (3); 172 (23); 170 (13); 154 (12); 127 (31); 112 (11); 71 (16); 70 (18); 57 (100); 56 (28); 44 (17); 43 (14); 42 (27); 41 (45); 40 (15). Anal. Calcd for $C_{12}H_{21}NO_3$: C, 63.41; H, 9.31; N, 6.16. Found: C, 63.45; H, 9.23; N, 6.09.

*tert-Butyl 3-Methyl-2,4-dioxopiperidine-1-carboxylate (**3(17)**).* The crude compound was purified by method **G** (system of solvents MeCN/H_2O). 53.4 g of the target product obtained as a white powder in 47% yield (mp = 86−87 °C).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 4.55 (ddd, *J* = 14.4, 5.8, 2.3 Hz, 1H), 3.71 (ddd, *J* = 14.3, 12.1, 3.8 Hz, 1H), 3.56 (q, *J* = 6.6 Hz, 1H), 2.73−2.46 (m, 2H), 1.53 (s, 9H), 1.29 (d, *J* = 6.6 Hz, 3H). ^{13}C{^{1}H} NMR (126 MHz, Chloroform-*d*) δ 166.9, 166.3, 153.3, 102.3, 81.3, 42.2, 28.6, 28.3, 9.0. LCMS, negative mode, *m*/*z*: 227 [M]$^-$; 226 [M − H]$^-$. Anal. Calcd for $C_{11}H_{17}NO_4$: C, 58.14; H, 7.54; N, 6.16. Found: C, 58.52; H, 7.29; N, 6.12.

*1,3-Dimethylpiperidin-4-one (**3(18)**).* The crude compound was purified by method **F** (system of solvents Hexane/MTBE). 31.2 g of the target product obtained as a yellow oil in 49% yield.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 3.06−2.95 (m, 2H), 2.69−2.52 (m, 2H), 2.39−2.23 (m, 5H), 2.02 (t, *J* = 11.2 Hz, 1H), 0.95 (d, *J* = 6.7 Hz, 3H). ^{13}C{^{1}H} NMR (126 MHz, Chloroform-*d*) δ 210.5, 63.3, 56.2, 45.3, 44.2, 40.8, 11.9. EIMS, 70 eV, *m*/*z* (rel. int.): 128 [M + H]$^+$ (5); 127 [M]$^+$ (62); 84 (32); 71 (26); 70 (34); 57 (19); 56 (12); 55 (15); 44 (15); 43 (97); 42 (100); 41 (25); 39 (17). Anal. Calcd for $C_7H_{13}NO$: C, 66.11; H, 10.30; N, 11.01. Found: C, 66.31; H, 10.21; N, 11.23.

*3-Methylpiperidine-2,4-dione (**3(19)**).* The crude compound was purified by method **F** (system of solvents MeCN/MeOH). 40.0 g of the target product obtained as a white powder in 63% yield (mp = 125−126 °C).

^{1}H NMR (400 MHz, DMSO-d_6) δ 9.56 (s, 1H), 8.09 (s, 1H), 6.78 (s, 1H), 3.62 (q, *J* = 6.8 Hz, 1H), 3.54 (dddd, *J* = 12.9, 10.5, 4.5, 2.0 Hz, 1H), 3.26 (dtd, *J* = 13.5, 6.0, 2.6 Hz, 1H), 3.13 (td, *J* = 7.2, 2.5 Hz, 2H), 2.58−2.53 (m, 1H), 2.44−2.29 (m, 3H), 1.56 (s, 2H), 1.04 (d, *J* = 6.8 Hz, 3H). ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6) δ 207.1, 170.4, 170.2, 161.6, 101.1, 52.4, 37.9, 37.7, 35.5, 28.5, 8.7, 8.2. (keto-enol tautomerism was observed) EIMS, 70 eV, *m*/*z* (rel. int.): 128 [M + H]$^+$ (7); 127 [M]$^+$ (100); 99 (45); 98 (15); 85 (24); 83 (14); 72 (15); 71 (10); 57 (31); 56 (84); 55 (31); 53 (11); 43 (14); 42 (16); 41 (10). Anal. Calcd for $C_6H_9NO_2$: C, 56.68; H, 7.14; N, 11.02. Found: C, 56.65; H, 7.20; N, 11.25.

*(2R)-tert-Butyl 2-Methyl-3-oxo-8-azabicyclo[3.2.1]octane-8-carboxylate (**3(20)**).* The crude compound was purified by method **F** (system of solvents Hexane/MTBE). 6.22 g of the target product obtained as a yellow oil in 52% yield.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 4.66−4.07 (m, 2H), 2.82−2.33 (m, 2H), 2.33−2.12 (m, 1H), 2.11−1.88 (m, 2H), 1.68−1.51 (m, 2H), 1.46 (d, *J* = 4.7 Hz, 9H), 1.15 (d, *J* = 7.3 Hz, 2H), 0.99 (d, *J* = 6.8 Hz, 1H). ^{13}C{^{1}H} NMR (126 MHz, Chloroform-*d*) δ 212.6, 208.4, 153.3, 79.9, 57.8, 53.1, 52.2, 46.4, 29.5, 28.4 (d, *J* = 4.0 Hz), 16.8. EIMS, 70 eV, *m*/*z* (rel. int.): 239 [M]$^+$ (5); 166 (14); 124 (14); 82 (19); 69 (13); 68 (81); 67 (30); 57 (100); 56 (15); 55 (21); 41 (49); 39 (15). Anal. Calcd for $C_{13}H_{21}NO_3$: C, 65.25; H, 8.85; N, 5.85. Found: C, 65.41; H, 9.18; N, 5.50.

*(3S,3aS,5aS,7S,9S,9aS,9bS)-3,5a,7,9-Tetramethyloctahydronaphtho[1,2-b]furan-2,8(3H,9bH)-dione (**3(21)**).* The crude compound was purified by method **E** (solvent Hexane). 0.13 g of the target product obtained as a white powder in 96% yield (mp = 34−37 °C).

^{1}H NMR (500 MHz, Chloroform-*d*) δ 3.79 (td, *J* = 10.6, 2.8 Hz, 1H), 2.78−2.64 (m, 1H), 2.40−2.29 (m, 1H), 2.31−2.20 (m, 1H), 2.22−2.14 (m, 1H), 1.92 (td, *J* = 10.3, 2.8 Hz, 1H), 1.87−1.78 (m, 1H), 1.73−1.67 (m, 1H), 1.67−1.32 (m, 4H), 1.33−1.15 (m, 7H), 1.03 (dd, *J* = 6.6, 2.7 Hz, 3H), 0.85 (d, *J* = 2.7 Hz, 2H). ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6) δ 217.7, 179.5, 83.9, 51.6, 49.4, 48.1, 45.9, 41.1, 40.1, 36.7, 35.7, 23.1, 21.2, 18.4, 16.0, 12.7. LCMS, positive mode, *m*/*z*: 265 [M + H]$^+$. Anal. Calcd for $C_{16}H_{24}O_3$: C, 72.69; H, 9.15. Found: C, 72.59; H, 8.76.

*2,2-Dimethylpentan-3-one (**3(22)**).* The crude compound was purified by method **H** (34−37 °C, 20 mmHg). 39.4 g of the target product obtained as a colorless liquid in 69% yield.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 2.47 (q, *J* = 7.2 Hz, 2H), 1.10 (s, 9H), 0.99 (t, *J* = 7.2 Hz, 3H). ^{13}C{^{1}H} NMR (126 MHz, Chloroform-*d*) δ 216.6, 44.0, 29.6, 26.5, 8.1. EIMS, 70 eV, *m*/*z* (rel.

https://doi.org/10.1021/acs.joc.1c00148
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int.): 114 $[M]^+$ (20); 57 (100); 41 (22). Anal. Calcd for $C_7H_{14}O$: C, 73.63; H, 12.36. Found: C, 73.45; H, 12.41.

*1-Cyclopropylpropan-1-one (**3(23)**).*[23d] The crude compound was purified by method **H** (bp = 38−42 °C, 20 mmHg). 38.3 g of the target product obtained as a colorless liquid in 78% yield. ^1H NMR (400 MHz, Chloroform-*d*) δ 2.54 (q, J = 7.2 Hz, 2H), 1.88 (m, 1H), 1.06 (t, J = 7.2 Hz, 3H), 0.98 (m, 2H), 0.89 (m, 2H). EIMS, 70 eV, m/z (rel. int.): 98 $[M]^+$ (24); 69 (100); 41 (40). Anal. Calcd for $C_6H_{10}O$: C, 73.43; H, 10.27. Found: C, 73.28; H, 10.33.

The compound **4(10)** was obtained according to general procedure for Step B. One mole (141.17 g) of starting enaminone **2(10)** and 0.5 L of acetone were used. The mixture of **3(10)** and **4(10)** was obtained in a ratio of 2:1 (0.5 and 0.25 mol of **3(10)** and **4(10)**, respectively) and was separated by distillation (**4** is distilled at 77−78 °C, 5 mmHg). 31.9 g of the target product **4(10)** obtained as a colorless liquid in 22% total yield.

(3R,4R*)-4-((Dimethylamino)methyl)tetrahydrofuran-3-ol (**4(10)**).* ^1H NMR (400 MHz, Chloroform-*d*) δ 5.61 (br, 1H), 4.52 (td, J = 6.0, 3.8 Hz, 1H), 4.03−3.93 (m, 1H), 3.87 (td, J = 8.0, 7.3, 1.6 Hz, 1H), 3.75 (dd, J = 9.5, 3.8 Hz, 1H), 3.52 (dd, J = 8.6, 6.1 Hz, 1H), 2.82 (t, J = 11.7 Hz, 1H), 2.51−2.39 (m, 1H), 2.38−2.32 (m, 1H), 2.31 (s, 6H). $^{13}C\{^1H\}$ NMR (126 MHz, Chloroform-*d*) δ 74.7, 72.6, 70.6, 57.9, 44.8, 39.2. LCMS, positive mode, m/z: 146 $[M + H]^+$. Anal. Calcd for $C_7H_{15}NO_2$: C, 57.90; H, 10.41; N, 9.65. Found: C, 58.20; H, 10.49; N, 9.66.

The compound **5(26)** was obtained using the similar method (Step B in Table 4), but the H_2 pressure in the autoclave was 10 atm. The analytical sample was obtained by chromatography. The characteristics of the compound were identical with those previously reported.[23e]

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.1c00148.

Copies of NMR and GCMS spectra, X-ray crystallography data descriptions (PDF)

Accession Codes

CCDC 2027100−2027103 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The work was supported by Enamine Ltd. Chromatographic separation and purification was performed at the Preparative Chromatography Department of Enamine Ltd. under the supervision of Mrs. Olga Maksymenko. The authors thank the Ministry of Education & Science of Ukraine for the grant support (project 0120U102179), Prof. Andrey A. Tolmachev for his encouragement and support, and Dr. Halyna Buvailo for her help with manuscript preparation.

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