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Peroxide-Mediated Oxidative Radical Cyclization to the Quinazolinone System: Efficient Syntheses of Deoxyvasicinone, Mackinazolinone and (±)-Leucomidine C

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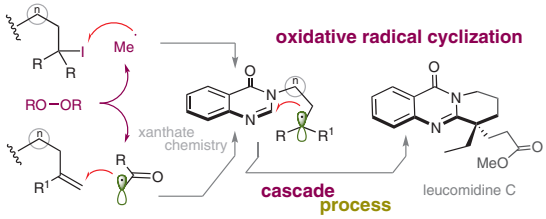

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Abstract An efficient protocol for obtaining fused quinazolinones through an oxidative free-radical cyclization under metal- and tin-free conditions is described. The oxidative cyclization of various *N*-3-ω-iodoalkyl derivatives to provide tricyclic systems using dicumyl peroxide as the sole reagent is studied. The method then is employed for the syntheses of 5-, 6-, and 7-membered fused quinazolinone analogues, including the natural products deoxyvasicinone and mackinazolinone. A xanthate-based oxidative radical cascade addition/cyclization process that allows the production of new menthol- and testosterone-quinazolinone conjugates, as well as the first total synthesis of leucomidine C, are also reported.

Key words quinazolinone, free radicals, peroxides, xanthates, leucomidine C

Quinazolinone (e.g., **1**), a benzo-fused pyrimidinone heterocyclic system, is a privileged structure that covers about two hundred naturally occurring alkaloids[1] and several synthetic commercially important drugs (Figure 1).[2] Members of this class of alkaloids display a wide range of pharmacological activities such as antipsychotic, analgesic, anti-inflammatory, anti-oxidant, antimicrobial, and antihypertensive. Examples of this family of natural products are the bronchodilator alkaloid vasicinone (**2**) and deoxyvasicinone (**3**), both isolated from the aerial parts of the evergreen subherbaceous bush *Adhatoda vasica*, which is used in traditional medicine for the treatment of colds, coughs, bronchitis, and asthma.[3] The homologue, piperidine-fused alkaloid mackinazolinone (**4**), was isolated from the leaves of *Mackinlaya subulate*, and showed antidepressive, antibacterial, and anti-inflammatory properties.[4] Furthermore, the alkaloid leucomidine C (**5**), isolated from the bark of *Leuconotis griffithii*, is another alkylated piperidine-fused quinazolinone that exhibits important cytotoxic activity.[5]

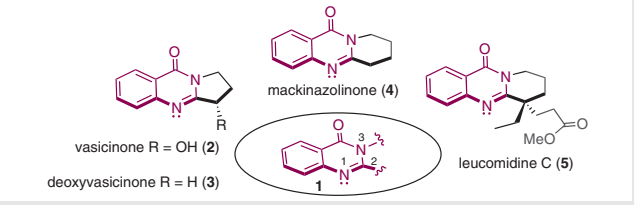

Figure 1 Structurally related quinazolinone natural products

Synthetically, the main approach for the preparation of quinazolinone derivatives is by the *de novo* construction of the heterocyclic system from anthranilic acid derivatives (i.e., 2-aminobenzamide, isatoic anhydride, etc.).[6] Several cascade processes for the construction of the quinazolinone skeleton have also been devised.[7] A conceptually different approach is the direct functionalization of the quinazolinone system itself. Therefore, the construction of the skeleton of fused derivatives (i.e., **1**–**4**) relies on N-3 alkylation and direct C–H functionalization at the C-2 position (or *vice versa*). To this end, different catalytic methods have been devised for the latter process, mainly using expensive precious metal salts.[6,8] The other general approach is via the oxidative radical inter-[9] or intramolecular C–H functionalization at C-2 (Scheme 1). Although these types of reactions have been increasingly used for C–H functionalization of a wide range of heterocyclic systems, this methodology has not been widely exploited for the assembly of quinazolinone-fused scaffolds. This method offers the advantage that alkyl, aryl, and acyl radicals can be cyclized to the quinazolinone system, as demonstrated in a pioneering study conducted by Bowman et al.[10] However, highly toxic and difficult to remove tin reagents were used in their work, and the presence of a mixture of side-products resulted in diminished yields (Scheme 1). More recently, a silver-mediated oxidative decarboxylative radical cyclization was described by Mhaske and Mahajan, starting from

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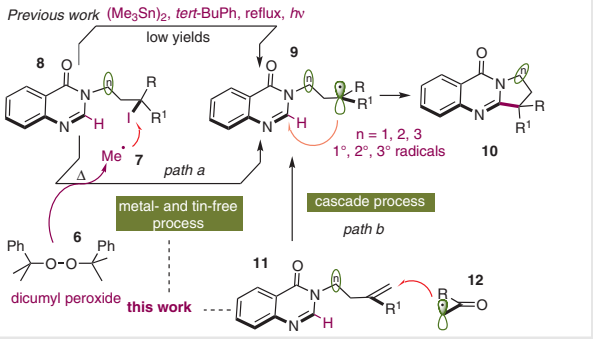
proline derivatives.[11] Unfortunately, the products were obtained in low yields. In other work, Procter et al. described a reductive homolytic cyclization to obtain the corresponding dihydroquinazolinone-fused products under SmI_2-catalyzed conditions.[12]

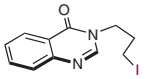
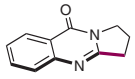
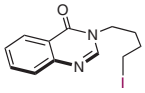
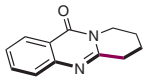
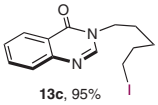
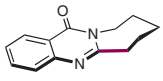
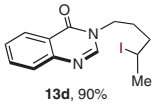
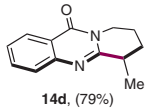
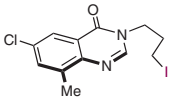
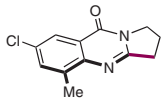
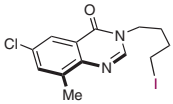
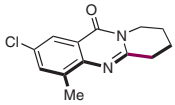
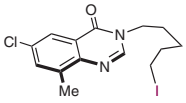
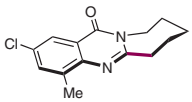
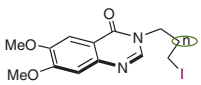


Scheme 1 Homolytic oxidative cyclization onto quinazolinones

In this context, expanding the synthetic utility of free radicals to explore novel strategies for assembling unique heterocycle-fused systems is ongoing. Herein, we report an efficient protocol for obtaining fused quinazolinones through a free-radical cyclization under metal- and tin-free conditions. This methodology relies on the use of dicumyl peroxide (DCP) as the only reagent, a procedure that we had previously developed for the cyclization of a series of alkyl iodides onto different heteroaromatic systems.[13] Under these conditions, we proposed that the methyl radical generated by the thermal decomposition of DCP would abstract the iodine atom and release the alkyl radical **9**, which is oxidatively cyclized to the heterocyclic system to afford the tricyclic system **10** (path a, Scheme 1). We also anticipated that implementing a cascade addition/cyclization process (also via **9**, path b) with the alkene **11** and radical **12** would lead to a new series of fused scaffolds, including a facile synthesis of leucomidine C, for which no total synthesis has yet been reported (Scheme 1). Under these conditions the use of a stoichiometric amount of the peroxide facilitates the oxidation process necessary to restore the conjugated system.[13]

Our endeavor started with the synthesis of *N*-alkyl iodides **13a–j** through the alkylation of commercial quinazolinones with the corresponding dihaloalkyl compounds, followed by a Finkelstein-type process to introduce the iodide substituent. Next, by utilizing reaction conditions described previously,[13] quinazolinones **13a**,**b** were allowed to react with 1.5 equivalents of DCP (added portionwise) in refluxing chlorobenzene. Gratifyingly, the desired tricyclic compounds deoxyvasicinone (**2**) and mackinazolinone (**4**) were isolated in 80% and 83% yields, respectively (Table 1, entries 1 and 2). It is worth noting that the same process, under previously examined tin-based conditions, afforded natural products **2** and **4**, but only in 20% and 30% yields, respectively, from the same starting materials and with all the inconvenience that the use of tin reagents implies.[10] Furthermore, under the DCP-mediated conditions, the quinazolinone derivatives **14c–g** were produced in fairly good yields from the corresponding iodide derivatives **13c–g** (entries 3–7), including those bearing an electron-attracting chlorine substituent on the aromatic system (entries 5–7). Hence, not only were 5- and 6-membered tricyclic analogues obtained efficiently, the 7-membered fused azepine **14g** was also prepared in 90% yield.

Table 1 Oxidative-Radical Cyclization on Quinazolinone Systems[a]

Entry	Substrate	Product (yield)
1	 **13a**, 92%	 deoxyvasicinone (**2**), 80%
2	 **13b**, 93%	 mackinazolinone (**4**), 83%
3	 **13c**, 95%	 **14c**, 79%
4	 **13d**, 90%	 **14d**, (79%)
5	 **13e**, 95%	 **14e**, 89%
6	 **13f**, 94%	 **14f**, 93%
7	 **13g**, 96%	 **14g**, 90%
8	 **13h** n = 1 **13i** n = 2 **13j** n = 3	no reaction

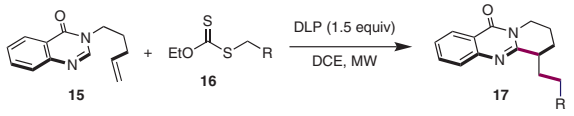
[a] Reaction conditions: **13** (1 equiv), DCP (1.5 equiv added portionwise), PhCl (0.02 M), reflux.

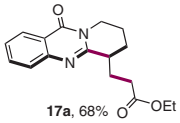
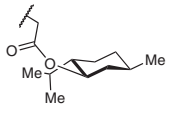
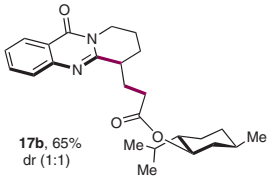
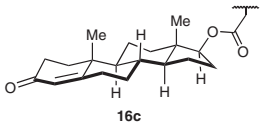
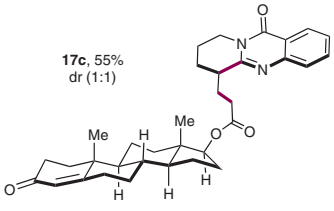
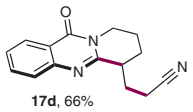
The cyclization of a secondary radical such as in the case of **13d** (Table 1, entry 4) was also implemented efficiently. Interestingly, when iodides **13h–j**, bearing methoxy substituents at the C-6 and C-7 positions, were subjected to the same conditions, the formation of the desired cyclized products was not observed (entry 8). Most of the starting materials were recovered unchanged in these three experiments. These reactions are inhibited for reasons that we do not currently understand.

At this point, we recognized that implementing a radical cascade addition/cyclization process might be useful to further study these oxidative cyclizations (Table 2). This process not only would allow the generation of secondary and eventually tertiary radicals, but would also expand the structural diversity of the products with the simultaneous construction of two C–C bonds. Xanthate-based radical chemistry, used in related cascade processes,[14] was of particular importance for this purpose, since under the standard conditions of these reactions, dilauryl peroxide (DLP) also acts as an initiator and oxidant,[15] similar to conditions using DCP.

Accordingly, olefin **15**, prepared from the N-alkylation of the quinazolinone and 5-bromo-1-pentene, was reacted with the xanthate **16a** to test the feasibility of the proposed protocol. In the first experiment, DLP (1.5 equiv) was added to a refluxing solution (DCE, 0.017 M) of substrates **15** and **16a** (1.2 equiv). Under these conditions, quinazolinone **17a** was isolated in 48% yield. Further experimentation led us to discover that increasing the amount of **16a** to 1.5 equivalents and performing the reaction under microwave irradiation [DLP (1.5 equiv), 0.3 equiv/15 min], resulted in an increased yield of 68% (Table 2, entry 1) in a shorter reaction time (75 min). With optimized conditions in hand, we next explored the scope of the cascade reaction using xanthates derived from menthol (**16b**) and testosterone (**16c**).[16] To our delight, the tandem reactions of these xanthates with olefin **15** proceeded efficiently and allowed access to novel quinazolinone conjugates **17b** and **17c** in good yields and as 1:1 diastereomeric mixtures (determined by ^{1}H NMR) (entries 2 and 3). In the same way, the use of the acetonitrile-derived xanthate **16d** offered good performance and afforded the tricyclic product **17d** in good yield.

Table 2 Synthesis of Quinazolinones via Radical Cascade Reactions[a]

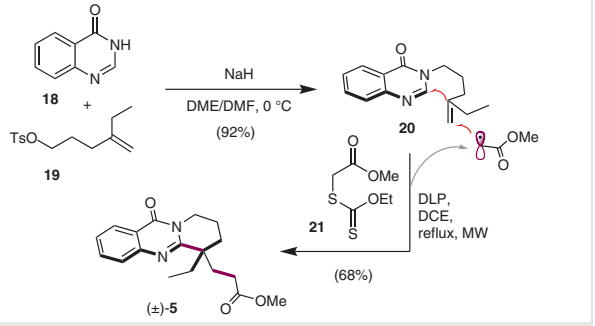


Entry	R (xanthate **16**)	Product (yield)
1	 **16a**	 **17a**, 68%
2	 **16b**	 **17b**, 65% dr (1:1)
3	 **16c**	 **17c**, 55% dr (1:1)
4	 **16d**	 **17d**, 66%

[a] Reaction conditions: **15** (1.0 equiv), **16** (1.5 equiv), DLP (1.5 equiv), DCE (0.017 M), microwave irradiation (100 W).

Thus, through this study, we have shown that the oxidative addition/cyclization cascade process represents a valuable and practical procedure for the preparation of a variety of quinazoline-fused scaffolds from relatively simple substrates.

We then turned our attention to the study of the oxidative cyclization of a tertiary radical. At the outset of these studies, we recognized that this process could be coupled with a short total synthesis of leucomidine C (**5**), by using the same oxidative addition/cyclization cascade process between olefin **20** and xanthate **21** (Scheme 2). Therefore, the required starting material **20** was prepared by the alkylation of quinazolinone **18** with known tosylate **19**.[17] Next, according to the reaction conditions for the cascade process outlined earlier, DLP (1.5 equiv) was slowly added to olefin **20** in the presence of the methyl acetate derived xanthate **21** (1.5 equiv) in refluxing 1,2-dichloroethane under microwave irradiation. We were pleased to observe that under these conditions (±)-leucomidine C (**5**) was obtained in 68% yield. This process highlights important issues such as the oxidative addition of a tertiary radical to the conjugated system that forged the all-carbon quaternary center,[18] as present in the natural product structure, along with the formation of two new C–C bonds. All spectroscopic data matched those previously reported for the natural product.[5]



Scheme 2 Total synthesis of leucomidine C (**5**)

In conclusion, an efficient protocol for obtaining fused quinazolinones through an oxidative free-radical cyclization under metal- and tin-free conditions is described. In the first part, we streamlined the oxidative cyclization of various *N*-3-ω-iodoalkyl derivatives to provide the tricyclic system using dicumyl peroxide as the sole reagent. Under these conditions, the oxidative cyclization process was much more efficient than previously reported with tin reagents. Thus, 5-, 6-, and 7-membered fused quinazolinone analogues, including the natural products deoxyvasicinone (**3**) and mackinazolinone (**4**), were efficiently obtained. We also implemented a xanthate-based oxidative radical cascade addition/cyclization process that allowed the production of new menthol- and testosterone-quinazolinone conjugates, and the first total synthesis of leucomidine C (**5**). Future studies will expand on this chemistry and explore its usefulness in the synthesis of more complex molecules in order to investigate their biological properties.

The starting materials and solvents were purchased from commercial suppliers and were used without prior purification. Solvents (THF, DMF and DME) were dried using standard procedures. All reactions were performed under an argon atmosphere. The reaction progress was monitored by analytical thin-layer chromatography using GF silica gel plates purchased from Merck. Visualization was achieved under short-wave UV light (254 nm). Column chromatography was performed on Aldrich silica gel (230–400 mesh particle size). Reactions under microwave irradiation were performed using a Microwave Synthesis System - CEM-Discover instrument. Melting points were determined on a Fisher apparatus and are not corrected. ^{1}H and ^{13}C NMR spectra were recorded on Jeol Eclipse-300 MHz and Bruker Avance 500 MHz spectrometers using $CDCl_3$ as the solvent. Chemical shifts are reported in parts per million (ppm) downfield from tetramethylsilane as the internal standard (δ = 0.0), or from the solvent as a reference ($CDCl_3$, δ = 7.26 for ^{1}H; δ = 77.16 for ^{13}C). NMR coupling constants are reported in hertz (Hz). Low- and high-resolution DART+ mass spectra were obtained on a Jeol JMS-T100LC spectrometer.

N-Alkyl Iodides 13a–g; General Procedure

To a suspension of NaH (95%, 72.5 mg, 3.02 mmol) in DMF (2 mL) and 1,2-dimethoxyethane (2 mL) was added a solution of the 4-hydroxyquinazolin-4(3*H*)-one (**18**) (300 mg, 2.01 mmol) in DME at 0 °C. After 15 min, the reaction mixture was treated with LiBr (357 mg, 4.1 mmol) and stirred for 15 min. The corresponding dihaloalkyl compound (1,3-dibromopropane, 1,4-dibromobutane, 1,4-dibromopentane or 1,4-dibromopentane) (0.2 mL, 2.05 mmol) was then added dropwise. The reaction mixture was stirred at room temperature for 5–6 h and then quenched with ice water. The resulting mixture was extracted with ethyl acetate and the combined organic layer was washed with water and brine, dried over Na_2SO_4, filtered and concentrated. The residue was used in the next step without further purification. The crude bromide was converted into the corresponding iodide by reaction with sodium iodide (4 equiv) in acetonitrile (30 mL/g bromide) at reflux for 24 h. After cooling, the solution was poured into water and extracted with dichloromethane. The organic layer was washed with saturated aqueous sodium sulfite solution and water, and then dried over Na_2SO_4. The solvent was removed in vacuo and the residue was purified by flash silica gel column chromatography (hexanes/ethyl acetate, 1:1) to provide pure product **13**.

3-(3-Iodopropyl)quinazolin-4(3*H*)-one (13a)

Yield: 395 mg (92%); white solid; mp 95 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.29 (d, *J* = 8.0 Hz, 1 H), 8.10 (s, 1 H), 7.74 (dt, *J* = 14.5, 8.1 Hz, 2 H), 7.51 (t, *J* = 7.3 Hz, 1 H), 4.11 (t, *J* = 6.7 Hz, 2 H), 3.18 (t, *J* = 6.5 Hz, 2 H), 2.32 (quin, *J* = 6.5 Hz, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 161.26, 148.17, 146.56, 134.49, 127.65, 127.54, 126.72, 122.12, 47.55, 32.00, 2.12.

HRMS-DART: *m*/*z* [M + H]$^+$ calcd for $C_{11}H_{12}IN_2O$: 314.99943; found: 314.99880.

3-(4-Iodobutyl)quinazolin-4(3*H*)-one (13b)

Yield: 417 mg (93%); white solid; mp 74 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.24 (td, *J* = 7.6, 1.7 Hz, 1 H), 7.99 (s, 1 H), 7.75–7.60 (m, 2 H), 7.45 (d, *J* = 6.3 Hz, 1 H), 3.97 (t, *J* = 6.1 Hz, 2 H), 3.15 (t, *J* = 5.2 Hz, 2 H), 1.95–1.77 (m, 4 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 161.06, 148.12, 146.38, 134.34, 127.54, 127.41, 126.72, 122.10, 45.79, 30.46, 30.32, 5.45.

HRMS-DART: *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{14}IN_2O$: 329.01508; found: 329.01707.

3-(5-Iodopentyl)quinazolin-4(3*H*)-one (13c)

Yield: 445 mg (95%); white solid; mp 88 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.24 (td, *J* = 7.7, 2.2 Hz, 1 H), 8.05–7.96 (m, 1 H), 7.66 (tt, *J* = 8.8, 4.7 Hz, 2 H), 7.51–7.39 (m, 1 H), 3.95 (q, *J* = 7.1 Hz, 2 H), 3.19–3.06 (m, 2 H), 1.79 (m, 4 H), 1.56–1.36 (m, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 161.05, 148.17, 146.52, 134.26, 127.51, 127.35, 126.70, 122.17, 46.85, 32.84, 28.35, 27.59, 6.40.

HRMS-DART: *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{16}IN_2O$: 343.03073; found: 343.02932.

3-(4-Iodopentyl)quinazolin-4(3*H*)-one (13d)

Yield: 315 mg (90%); white solid; mp 91 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.30 (ddd, *J* = 8.0, 1.5, 0.6 Hz, 1 H), 8.03 (s, 1 H), 7.80–7.66 (m, 2 H), 7.50 (ddd, *J* = 8.2, 6.8, 1.5 Hz, 1 H), 4.24–4.09 (m, 1 H), 4.09–3.94 (m, 2 H), 2.03–1.84 (m, 6 H), 1.77–1.64 (m, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 161.14, 148.16, 146.40, 134.37, 127.57, 127.45, 126.79, 122.15, 45.94, 39.54, 29.94, 28.99, 28.47.

HRMS-DART: *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{16}IN_2O$: 343.03073; found: 343.03058.

6-Chloro-3-(3-iodopropyl)-8-methylquinazolin-4(3*H*)-one (13e)

Yield: 354 mg (95%); white solid; mp 80 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.13–8.07 (m, 2 H), 7.55 (dq, *J* = 2.5, 0.9 Hz, 1 H), 4.10 (t, *J* = 6.6 Hz, 2 H), 3.17 (t, *J* = 6.5 Hz, 2 H), 2.57 (s, 3 H), 2.31 (quin, *J* = 6.6 Hz, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 160.52, 145.51, 145.36, 138.41, 135.11, 132.71, 123.60, 123.06, 47.55, 31.87, 17.41, 2.20.

HRMS-DART: *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{13}ClIN_2O$: 362.97611; found: 362.97599.

6-Chloro-3-(4-iodobutyl)-8-methylquinazolin-4(3*H*)-one (13f)

Yield: 363 mg (94%); white solid, mp 91 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.12–8.05 (m, 1 H), 8.00 (s, 1 H), 7.59–7.49 (m, 1 H), 4.00 (t, *J* = 6.7 Hz, 2 H), 3.19 (t, *J* = 6.3 Hz, 2 H), 2.55 (s, 3 H), 1.89 (tt, *J* = 6.6, 2.5 Hz, 4 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 160.43, 145.38, 145.29, 138.33, 135.04, 132.67, 123.71, 123.10, 45.87, 30.39, 30.26, 17.39, 5.33.

HRMS-DART: *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{15}ClIN_2O$: 376.99176; found: 376.99139.

6-Chloro-3-(5-iodopentyl)-8-methylquinazolin-4(3*H*)-one (13g)

Yield: 346 mg (96%); white solid, mp 93 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.14–8.06 (m, 1 H), 8.01 (s, 1 H), 7.53 (t, *J* = 3.3 Hz, 1 H), 3.98 (dd, *J* = 8.8, 5.7 Hz, 2 H), 3.17 (t, *J* = 6.8 Hz, 2 H), 2.56 (s, 3 H), 1.94–1.74 (m, 4 H), 1.59–1.42 (m, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 160.44, 145.45, 138.29, 134.99, 132.60, 123.70, 123.18, 100.00, 46.95, 32.84, 28.29, 27.59, 17.40, 6.30.

HRMS-DART: *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{17}ClIN_2O$: 391.00741; found: 391.00835.

Oxidative-Radical Cyclization on Quinazolinone Systems; General Procedure

In a round-bottomed flask, the alkyl iodide derivative **13a–g** (100 mg, 0.31 mmol) was dissolved in degassed chlorobenzene (2.2 mL) and heated to reflux. Dicumyl peroxide (DCP) (129 mg, 0.47 mmol) was added in portions (0.3 equiv/1 h) under an N_2 atmosphere for 5 h. After consumption of the starting material, the reaction mixture was then allowed to cool to room temperature and the solvent was evaporated in vacuo. The residue was purified by flash column chromatography (n-hexane/EtOAc, 7:3) to afford the products **2**, **4** and **14c–g**.

Deoxyvasicinone (2)

Yield: 47 mg (80%); yellow solid; mp 110 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.35–8.25 (m, 1 H), 7.77–7.68 (m, 1 H), 7.64 (ddd, *J* = 8.2, 1.3, 0.6 Hz, 1 H), 7.44 (ddd, *J* = 8.1, 7.0, 1.3 Hz, 1 H), 4.29–4.15 (m, 2 H), 3.18 (t, *J* = 8.0 Hz, 2 H), 2.36–2.21 (m, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 161.07, 159.54, 149.19, 134.25, 126.85, 126.44, 126.31, 120.53, 46.58, 32.59, 19.58.

HRMS-DART: *m*/*z* [M + H]$^+$ calcd for $C_{11}H_{11}N_2O$: 187.08714; found: 187.08788.

Mackinazolinone (4)

Yield: 50 mg (83%); yellow solid; mp 100 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.24 (dd, *J* = 7.9, 1.6 Hz, 1 H), 7.70 (ddt, *J* = 9.7, 7.0, 1.4 Hz, 1 H), 7.61–7.55 (m, 1 H), 7.45–7.37 (m, 1 H), 4.06 (t, *J* = 6.1 Hz, 2 H), 2.99 (t, *J* = 6.5 Hz, 2 H), 2.10–1.83 (m, 4 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 162.28, 154.97, 147.50, 134.27, 126.73, 126.48, 126.17, 120.52, 42.42, 32.03, 22.20, 19.42.

HRMS-DART: *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{13}N_2O$: 201.10279; found: 201.10270.

7,8,9,10-Tetrahydroazepino[2,1-*b*]quinazolin-12(6*H*)-one (14c)

Yield: 49 mg (79%); yellow solid; mp 95 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.29–8.23 (m, 1 H), 7.71 (ddd, *J* = 8.4, 7.1, 1.5 Hz, 1 H), 7.65–7.58 (m, 1 H), 7.43 (ddd, *J* = 8.1, 7.1, 1.3 Hz, 1 H), 4.45–4.35 (m, 2 H), 3.13–3.03 (m, 2 H), 1.86 (dd, *J* = 12.2, 7.7 Hz, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 162.04, 159.83, 147.50, 134.25, 127.12, 126.85, 126.48, 120.33, 42.97, 37.81, 29.66, 28.18, 25.51.

HRMS-DART: *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{15}N_2O$: 215.11844; found: 215.11841.

6-Methyl-6,7,8,9-tetrahydro-11*H*-pyrido[2,1-*b*]quinazolin-11-one (14d)

Yield: 49 mg (79%); yellow solid; mp 89 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.24 (d, *J* = 8.0 Hz, 1 H), 7.74–7.59 (m, 2 H), 7.45–7.36 (m, 1 H), 4.27 (dt, *J* = 14.1, 5.9 Hz, 1 H), 3.90 (ddd, *J* = 13.4, 7.4, 5.8 Hz, 1 H), 3.03 (dt, *J* = 8.7, 6.7 Hz, 1 H), 2.16–1.92 (m, 3 H), 1.68–1.57 (m, 1 H), 1.48 (d, *J* = 7.0 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 162.36, 158.58, 147.53, 134.12, 126.81, 126.67, 126.16, 120.26, 42.25, 35.56, 27.69, 20.24, 19.61.

HRMS-DART: *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{15}N_2O$: 215.11844; found: 215.11941.

7-Chloro-5-methyl-2,3-dihydropyrrolo[2,1-*b*]quinazolin-9(1*H*)-one (14e)

Yield: 57 mg (89%); yellow solid; mp 81 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.04 (d, *J* = 2.5 Hz, 1 H), 7.48 (d, *J* = 2.5 Hz, 1 H), 4.17 (t, *J* = 7.3 Hz, 2 H), 3.16 (t, *J* = 8.0 Hz, 2 H), 2.54 (s, 3 H), 2.27 (quin, *J* = 7.8 Hz, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 160.39, 158.60, 146.57, 137.61, 134.81, 131.28, 123.35, 121.54, 46.58, 32.70, 19.66, 17.69.

HRMS-DART: *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{12}ClN_2O$: 235.06382; found: 235.06408.

2-Chloro-4-methyl-6,7,8,9-tetrahydro-11*H*-pyrido-[2,1-*b*]quinazolin-11-one (14f)

Yield: 61 mg (93%); yellow solid; mp 84 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.08 (d, *J* = 2.5 Hz, 1 H), 7.51 (dd, *J* = 2.5, 0.8 Hz, 1 H), 4.08 (t, *J* = 6.3 Hz, 2 H), 3.01 (t, *J* = 6.7 Hz, 2 H), 2.57 (s, 3 H), 2.08–1.91 (m, 4 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 161.61, 153.82, 144.74, 137.35, 134.65, 130.97, 123.43, 121.32, 42.41, 32.12, 22.10, 19.35, 17.15.

HRMS-DART: *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{14}ClN_2O$: 249.07947; found: 249.07925.

2-Chloro-4-methyl-7,8,9,10-tetrahydroazepino[2,1-*b*]quinazolin-12(6*H*)-one (14g)

Yield: 60 mg (90%); yellow solid; mp 89 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.01–7.97 (m, 1 H), 7.45–7.35 (m, 1 H), 4.33–4.25 (m, 2 H), 3.02–2.98 (m, 2 H), 2.48 (s, 3 H), 1.83–1.70 (m, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 161.42, 158.55, 144.71, 137.74, 134.64, 131.31, 123.82, 121.19, 43.08, 37.87, 29.62, 28.10, 25.53, 17.08.

HRMS-DART: *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{16}ClN_2O$: 263.09512; found: 263.09506.

***N*-Alkylation of 3*H*-Quinzolin-4-ones; General Procedure**

To a suspension of NaH (95%, 72.5 mg, 3.02 mmol) in DMF (2 mL) and 1,2-dimethoxyethane (2 mL) was added a solution of 4-hydroxyquinazolin-4(3*H*)-one (**18**) (300 mg, 2.01 mmol) in DME at 0 °C. After 15 min, the reaction mixture was treated with LiBr (357 mg, 4.1 mmol) and stirred for 15 min, then 5-bromo-1-pentene (95%, 0.42 ml, 2.25 mmol) or tosylate **19** (0.26 mL, 2.26 mmol) was added dropwise. The reaction mixture was stirred at room temperature for 5–6 h and then quenched with ice water. The resulting mixture was extracted with ethyl acetate, and the organic layer was separated, washed with water and brine, dried over Na_2SO_4, filtered and concentrated. The product was purified by flash silica gel column chromatography (hexanes/EtOAc, 1:1) to provide pure *N*-alkylated products.

3-(Pent-4-en-1-yl)quinazolin-4(3*H*)-one (15)

Yield: 405 mg (92%); white solid; mp 70–71 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.34–8.27 (m, 1 H), 8.00 (s, 1 H), 7.78–7.66 (m, 2 H), 7.54–7.45 (m, 1 H), 5.80 (ddtd, *J* = 16.9, 10.3, 6.6, 0.9 Hz, 1 H), 5.14–4.99 (m, 2 H), 3.99 (t, *J* = 7.3 Hz, 2 H), 2.14 (q, *J* = 7.0 Hz, 2 H), 1.90 (quin, *J* = 7.3 Hz, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 161.17, 148.21, 146.68, 136.95, 134.25, 127.52, 127.34, 126.76, 122.26, 116.10, 46.56, 30.65, 28.23.

HRMS-DART: *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{15}N_2O$: 215.11844; found: 215.11884.

3-(4-Methylenehexyl)quinazolin-4(3*H*)-one (20)

Yield: 372 mg (90%); yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.31 (ddd, *J* = 8.0, 1.4, 0.6 Hz, 1 H), 8.02 (s, 1 H), 7.81–7.66 (m, 2 H), 7.51 (ddd, *J* = 8.1, 6.8, 1.6 Hz, 1 H), 4.94–4.61 (m, 2 H), 4.15–3.94 (m, 2 H), 2.17–1.93 (m, 6 H), 1.03 (t, *J* = 7.4 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 161.19, 149.58, 148.22, 146.76, 134.27, 127.52, 127.36, 126.78, 122.28, 108.92, 46.91, 33.11, 28.69, 27.09, 12.40.

HRMS-DART: *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{19}N_2O$: 243.14974; found: 243.14898.

Radical Cascades; General Procedure

A solution of quinazolinone **15** or **20** (50 mg, 0.23 mmol), xanthate **16** or **21** (73 mg, 0.35 mmol), dilauroyl peroxide (DLP) (30 mg, 0.07 mmol) in degassed 1,2-dichloroethane (1.1 mL) was heated in a sealed vial at 85 °C under microwave irradiation (100 W) for 15 min under and argon atmosphere, and then DLP (0.3 equiv) was added every 15 min five times. The reaction mixture was cooled to room temperature and diluted with dichloromethane. The resulting mixture was washed with water and brine. The organic layer was separated, dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash column chromatography (n-hexane/EtOAc, 7:3) to afford the products **17a–d** and **5**.

Ethyl 3-(11-Oxo-6,8,9,11-tetrahydro-7*H*-pyrido[2,1-*b*]quinazolin-6-yl)propanoate (17a)

Yield: 48 mg (68%); yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.23 (ddd, *J* = 8.0, 1.6, 0.7 Hz, 1 H), 7.72–7.66 (m, 1 H), 7.61 (ddd, *J* = 8.2, 1.3, 0.6 Hz, 1 H), 7.44–7.37 (m, 1 H), 4.31–4.22 (m, 1 H), 4.14–4.03 (m, 2 H), 3.97–3.86 (m, 1 H), 2.95–2.89 (m, 1 H), 2.60–2.53 (m, 2 H), 2.48–2.36 (m, 1 H), 2.05–1.93 (m, 4 H), 1.68–1.60 (m, 1 H), (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.55, 162.25, 156.96, 147.33, 134.10, 126.99, 126.66, 126.29, 120.34, 60.53, 41.60, 39.70, 32.16, 28.36, 25.13, 20.27, 14.31.

HRMS-DART: *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{21}N_2O_3$: 301.15522; found: 301.15512.

(1*R*,2*S*,5*R*)-2-Isopropyl-5-methylcyclohexyl 3-(11-Oxo-6,8,9,11-tetrahydro-7*H*-pyrido[2,1-*b*]quinazolin-6-yl)propanoate (17b)

Yield: 75 mg (65%); yellow oil; dr = 1:1.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.25 (d, *J* = 8.0 Hz, 1 H), 7.70 (t, *J* = 7.6 Hz, 1 H), 7.62 (d, *J* = 8.1 Hz, 1 H), 7.41 (t, *J* = 7.5 Hz, 1 H), 4.68 (qd, *J* = 10.8, 4.4 Hz, 1 H), 4.27 (dq, *J* = 17.1, 5.6 Hz, 1 H), 3.92 (td, *J* = 13.9, 6.0 Hz, 1 H), 2.99–2.85 (m, 1 H), 2.56 (t, *J* = 7.4 Hz, 2 H), 2.46 (dq, *J* = 13.9, 6.5 Hz, 1 H), 2.13 (dq, *J* = 13.0, 6.4 Hz, 1 H), 2.04–1.92 (m, 4 H), 1.86 (ddq, *J* = 13.5, 6.7, 3.4, 2.5 Hz, 1 H), 1.66 (ddt, *J* = 13.2, 10.3, 4.6 Hz, 3 H), 1.47 (dddt, *J* = 15.4, 9.9, 6.6, 3.4 Hz, 1 H), 1.36 (ddt, *J* = 14.7, 6.6, 3.2 Hz, 1 H), 1.04 (dddd, *J* = 18.5, 14.7, 9.9, 5.4 Hz, 1 H), 0.98–0.91 (m, 1 H), 0.91–0.86 (m, 7 H), 0.75 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 173.14, 162.29, 157.03, 147.44, 134.12, 127.08, 126.70, 126.31, 120.40, 74.37, 47.14, 41.62, 41.05, 39.77, 34.36, 32.52, 31.49, 28.44, 26.40, 25.11, 23.56, 22.14, 20.89, 20.33, 16.48.

HRMS-DART: *m*/*z* [M + H]$^+$ calcd for $C_{25}H_{35}N_2O_3$: 411.26477; found: 411.26551.

(8*R*,9*S*,10*R*,13*S*,14*S*,17*S*)-10,13-Dimethyl-3-oxo-2,3,6,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1*H*-cyclopenta[*a*]phenanthren-17-yl 3-(11-Oxo-6,8,9,11-tetrahydro-7*H*-pyrido[2,1-*b*]quinazolin-6-yl)propanoate (17c)

Yield: 84 mg (55%); yellow oil; dr = 1:1.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.24 (d, *J* = 8.0 Hz, 1 H), 7.69 (t, *J* = 7.6 Hz, 1 H), 7.61 (d, *J* = 8.2 Hz, 1 H), 7.41 (t, *J* = 7.5 Hz, 1 H), 5.71 (s, 1 H), 4.60 (t, *J* = 8.4 Hz, 1 H), 4.31–4.21 (m, 1 H), 3.96–3.87 (m, 1 H), 2.92 (quin, *J* = 6.7 Hz, 1 H), 2.58 (t, *J* = 7.5 Hz, 2 H), 2.46–2.25 (m, 5 H), 2.19–2.09 (m, 2 H), 1.99 (dd, *J* = 14.5, 8.6 Hz, 4 H), 1.85–1.75 (m, 2 H), 1.68–1.48 (m, 6 H), 1.36 (ddd, *J* = 25.0, 12.6, 4.8 Hz, 2 H), 1.17 (m, 4 H), 1.04 (m, 2 H), 0.95–0.89 (m, 1 H), 0.83 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 199.58, 173.53, 171.07, 162.25, 156.96, 147.38, 134.11, 127.01, 126.69, 126.30, 124.04, 120.37, 82.60, 53.75, 50.29, 42.61, 41.64, 39.73, 38.68, 36.74, 35.77, 35.46, 34.01, 32.81, 32.29, 31.55, 28.44, 27.61, 25.11, 23.57, 20.60, 20.30, 17.47, 12.20.

HRMS-DART: *m*/*z* [M + H]$^+$ calcd for $C_{34}H_{43}N_2O_4$: 543.32228; found: 543.32199.

3-(11-Oxo-6,8,9,11-tetrahydro-7*H*-pyrido[2,1-*b*]quinazolin-6-yl)propanenitrile (17d)

Yield: 47 mg (66%); yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.27 (dt, *J* = 8.0, 1.6 Hz, 1 H), 7.73 (ddt, *J* = 8.4, 7.1, 1.5 Hz, 1 H), 7.68–7.59 (m, 1 H), 7.45 (ddt, *J* = 8.2, 7.0, 1.4 Hz, 1 H), 4.42 (dtd, *J* = 13.9, 6.0, 1.5 Hz, 1 H), 3.94–3.78 (m, 1 H), 3.05–2.90 (m, 1 H), 2.91–2.69 (m, 2 H), 2.56–2.45 (m, 1 H), 2.20 (dq, *J* = 12.9, 6.5 Hz, 1 H), 2.09–1.96 (m, 3 H), 1.69–1.59 (m, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 161.91, 155.96, 147.07, 134.25, 127.03, 126.77, 126.60, 120.45, 119.86, 41.02, 38.84, 28.70, 25.55, 20.61, 15.77.

HRMS-DART: *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{16}N_3O$: 254.12934; found: 254.13002.

(±)-Leucomidine C (5)

Yield: 44 mg (68%); yellow amorphous solid.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.23 (ddd, *J* = 8.1, 1.6, 0.7 Hz, 1 H), 7.69 (ddd, *J* = 8.4, 7.0, 1.6 Hz, 1 H), 7.60 (ddd, *J* = 8.2, 1.4, 0.7 Hz, 1 H), 7.48–7.37 (m, 1 H), 4.15–3.93 (m, 2 H), 3.53 (s, 3 H), 2.50–2.40 (m, 1 H), 2.36–2.21 (m, 2 H), 2.08–1.89 (m, 5 H), 1.76 (dd, *J* = 13.7, 7.1 Hz, 2 H), 0.86 (t, *J* = 7.4 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 174.18, 162.85, 158.80, 147.33, 134.02, 127.25, 126.53, 126.27, 119.95, 51.72, 43.81, 43.70, 34.94, 33.28, 29.55, 28.89, 19.10, 8.61.

HRMS-DART: *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{23}N_2O_3$: 315.17087; found: 315.17077.

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References

(1) (a) Michael, J. P. *Nat. Prod. Rep.* **2004**, *21*, 650. (b) Kshirsagar, U. A. *Org. Biomol. Chem.* **2015**, *13*, 9336.
(2) For reviews, see: (a) Han, Y. Y.; Jiang, H.; Wang, R. Z.; Yu, S. Y. *J. Org. Chem.* **2016**, *81*, 7276. (b) Tiwary, B. K.; Pradhan, K.; Nanda, A. K.; Chakraborty, R. *J. Chem. Biol. Ther.* **2016**, *1*, 104. (c) Selvam, T. P.; Kumar, P. V. *Res. Pharm.* **2011**, *1*, 1.
(3) (a) Amin, A. H.; Mehta, D. R. *Nature* **1959**, *184*, 1317. (b) Mehta, D. R.; Naravane, J. S.; Desai, R. M. *J. Org. Chem.* **1963**, *28*, 445. (c) Ghosal, S.; Chauhan, P. B. P. S.; Mehta, R. *Phytochemistry* **1975**, *14*, 830.
(4) (a) Liljegren, D. R. *Phytochemistry* **1968**, *7*, 1299. (b) Al-Shamma, A.; Drake, S.; Flynn, D. L.; Mitscher, L. A.; Park, Y. H.; Rao, G. S. R.; Wu, S. T.-S. *J. Nat. Prod.* **1981**, *44*, 745. (c) Johns, S. R.; Lamberton, J. A. *Chem. Commun.* **1965**, *12*, 267a.
(5) Motegi, M.; Nugroho, A. E.; Hirasawa, Y.; Arai, T.; Hadi, A. H. A.; Morita, H. *Tetrahedron Lett.* **2012**, *53*, 1227.
(6) For reviews, see: (a) Rohokale, R. S.; Kshirsagar, U. A. *Synthesis* **2016**, *48*, 1253. (b) Khan, I.; Zaib, S.; Batool, S.; Abbas, N.; Ashraf, Z.; Iqbal, J.; Saeed, A. *Bioorg. Med. Chem.* **2016**, *24*, 2361.
(7) For selected recent publications, see: (a) Larraufie, M. H.; Courillon, C.; Ollivier, C.; Lacôte, E.; Malacria, M.; Fensterbank, L. *J. Am. Chem. Soc.* **2010**, *132*, 4381. (b) Larraufie, M. H.; Malacria, M.; Courillon, C.; Ollivier, C.; Fensterbank, L.; Lacôte, E. *Tetrahedron* **2013**, *69*, 7699. (c) Xu, G.; Tong, C.; Cui, S.; Dai, L. *Org. Biomol. Chem.* **2018**, *16*, 5899. (d) Baguia, H.; Deldaele, C.; Romero, E.; Michelet, B.; Evano, G. *Synthesis* **2018**, *50*, 3022.
(8) For a review, see: Ghosh, P.; Ganguly, B.; Das, S. *Org. Biomol. Chem.* **2020**, *18*, 4497.
(9) Molander, G. A.; Colombel, V.; Braz, V. A. *Org. Lett.* **2011**, *13*, 1852.
(10) Bowman, W. R.; Elsegood, M. R. J.; Stein, T.; Weaver, G. W. *Org. Biomol. Chem.* **2007**, *5*, 103.
(11) Mahajan, P. S.; Mhaske, S. B. *Org. Lett.* **2018**, *20*, 2092.
(12) Huang, H. M.; Adams, R. W.; Procter, D. J. *Chem. Commun.* **2018**, *54*, 10160.
(13) Menes, M.; Martínez, R.; Cruz, R.; Muchowski, J. M.; Osornio, Y. M.; Miranda, L. D. *J. Org. Chem.* **2004**, *69*, 4001.
(14) For selected examples, see: (a) Zard, S. Z. *Acc. Chem. Res.* **2018**, *51*, 1722. (b) Blechy, A.; Zard, S. Z. *Org. Lett.* **2009**, *11*, 2800. (c) Huang, Q.; Zard, S. Z. *Org. Lett.* **2018**, *20*, 5304. (d) Paleo, E.; Osornio, Y. M.; Miranda, L. D. *Org. Biomol. Chem.* **2011**, *9*, 361. (e) Osornio, Y. M.; Miranda, L. D. *Rev. Soc. Quím. Méx.* **2004**, *48*, 288.
(15) Quiclet-Sire, B.; Zard, S. Z. *Synlett* **2016**, *27*, 680.
(16) López, P.; Díaz, J. E.; Loaiza, A. E.; Miranda, L. D. *Tetrahedron* **2018**, *74*, 5494.
(17) Banwell, M. G.; Edwards, A. J.; Jolliffe, K. A.; Smith, J. A.; Hamel, E.; Verdier, P. *Org. Biomol. Chem.* **2003**, *1*, 296.
(18) Quiclet-Sire, B.; Zard, S. Z. *Sci. China Chem.* **2019**, *62*, 1450.