Microwave-Assisted Dibromoolefination of Aromatic and Heteroaromatic Aldehydes and Ketones

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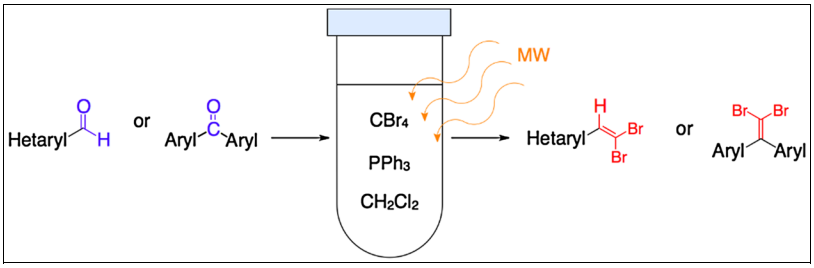

Microwave (MW) irradiation was successfully employed to convert aromatic and heteroaromatic aldehydes and ketones efficiently to the corresponding dibromoolefins. Exemplified by the successful dibromoolefination of traditionally inert pyridyl-flanked carbonyls, MW activation significantly broadens the scope of this valuable transformation, although some limitations especially with electron-rich aromatic ketone derivatives remain.

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INTRODUCTION

The conversion of aldehydes and ketones into the corresponding *gem*-dihaloolefins is a valuable functional group transformation [1] that delivers versatile intermediates for the synthesis of, *inter alia*, amides [2], ynamides [3], ketene *N*,*N*-acetals [4], 2-bromo-indoles [5], alkynyl methylidenes [6], 1-alkenyl-phosphonates [7] or allylsilanes [8]. *gem*-Dihaloolefins can also be used as starting materials in transition-metal-mediated CC cross-coupling reactions [9–11]. Perhaps the currently most prominent application lies in their suitability as a source for oligoalkynes by way of the Fritsch–Buttenberg–Wiechell rearrangement [12].

Dibromoolefins are routinely prepared from carbonyl compounds using CBr_4 and PPh_3 in a Wittig-type reaction first reported by Ramirez *et al.* [13,14] and subsequently with some variation by Corey and Fuchs [15]. More recently, a metal-induced modification with $CHBr_3/TiCl_4$/Mg was used for such a transformation [16]. It was also shown that a perchlorate phosphine salt [17] as well as triisopropyl phosphite can replace PPh_3 in generating *gem*-dihaloolefins [18]. These reactions, in general, run smoothly and in good yields with most aldehydes. However, the yields with less reactive ketones varies, and often, as in the case of benzophenone, no conversion is observed [19].

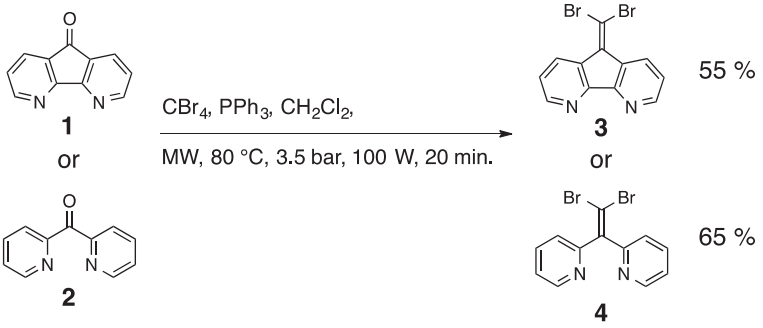
RESULTS AND DISCUSSION

Our ongoing research on molecular wires with appending metal fragments [20] prompted us to explore the dibromoolefination of pyridyl-based ketones. Conspicuously, dibromoolefins from pyridyl-flanked carbonyl derivatives have not been reported before. Indeed, attempts to convert diazafluoren-9-one **1** [21] to the corresponding dibromoolefin under standard Corey–Fuchs conditions even at elevated temperatures for extended periods of time (reflux in xylenes for 5 h) failed. Inspired by many reports on successful thermal activation of organic transformations by microwave irradiation [22], we submitted ketone **1** together with CBr_4 and PPh_3 in CH_2Cl_2 for 20 min at 80°C in a sealed reaction vessel to microwave irradiation of 100 W. Much to our satisfaction, the desired dibromoolefin **3** was obtained in 55% yield (Scheme 1). Remarkably, the product was purified by a simple flash filtration of the reaction mixture through a plug of silica followed by recrystallization of the crude product from acetone. Under identical conditions, the less rigid di-2-pyridylketone **2** was transformed to the corresponding dibromoolefin **4** in even higher yields (65%).

The identity of the new dibromoolefins was confirmed by spectroscopic techniques and mass spectrometry (for details, refer to the Supporting Information). Unambiguous proof for the constitutions of both **3** and **4** was established by investigating their crystal structures under X-ray diffraction conditions [23].

As can be seen in Figure 1, the rigidity of **3** imposes an almost ideal planar conformation and gives rise to a herringbone arrangement of molecules of **3** in the solid state. That pattern is formed by a crystallographic gliding

Scheme 1. MW-assisted dibromoolefination of ketones **1** and **2**.



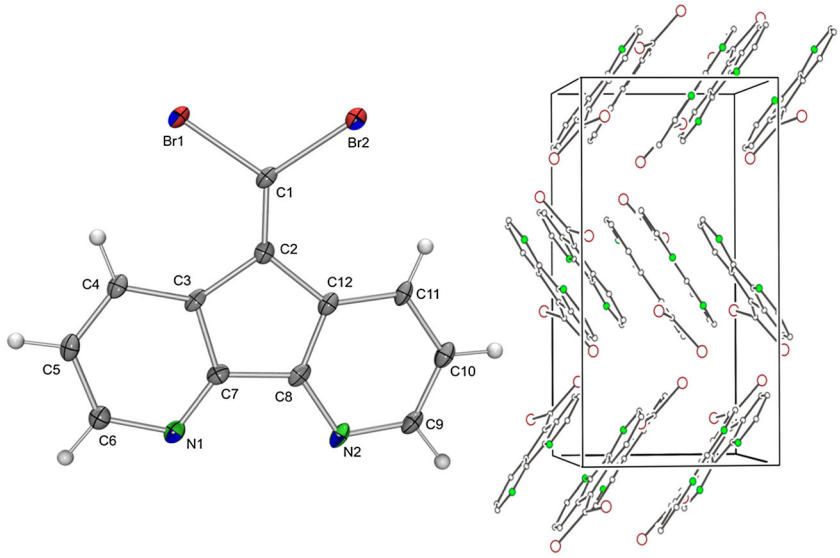


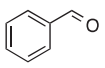
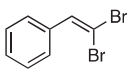
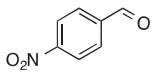
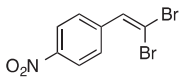
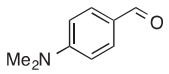
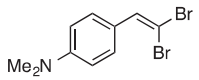
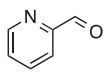
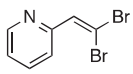
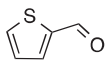
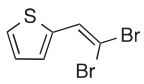
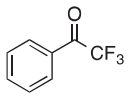
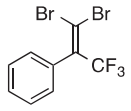
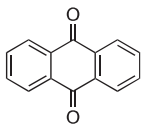
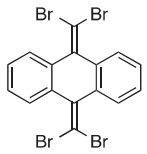
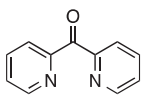
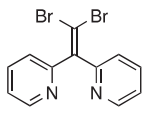
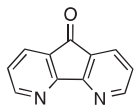
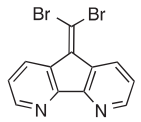
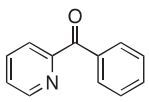
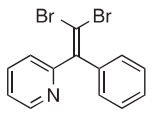
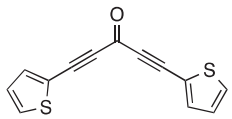
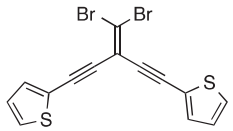
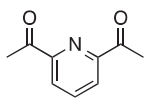
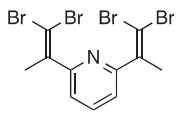
Figure 1. Crystal structure of **3** and its herringbone arrangement in the unit cell. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

plane along *c* that can be seen in a view of the unit cell along the *b*-axis. The packing reveals π-stacking interactions within the layers with a minimum distance of 3.222(7) Å between them. The structure of **4** in the solid state reveals similar features and is discussed in the Supporting Information.

Encouraged by this success, we explored the scope of the microwave-assisted dibromoolefination with aromatic and heteroaromatic aldehydes and ketones (Table 1). In general, the results suggest that the conversion of carbonyl compounds flanked by relatively electron-poor aromatic substituents benefits from microwave irradiation. Electron-rich substituents seem to decrease the yields of the corresponding dibromoolefins. In the aldehyde series (entries 1–5 in Table 1), yields under microwave activation are either comparable or better than the conventional Corey–Fuchs conditions. While the yields are satisfactory with benzaldehyde, *p*-nitrobenzaldehyde, and 2-pyridylcarbaldehyde, the aldehydes flanked by the electron-rich substituents 4-dimethylaminophenyl, 2-thienyl, and 2-pyrryl give moderate yields or, in the latter case, no conversion. A similar trend was observed in the ketone series (entries 6–12, Table 1) as it can be seen in the poor to moderate conversion yields of 2-benzoylpyridine and the bis(2-thienylethynyl) ketone, respectively. However, the microwave-assisted dibromoolefination shows its superiority in the successful conversion of diazafluoren-9-one and di-2-pyridylketone as well as 2-benzoylpyridine, which could not be obtained otherwise. There are reports in the literature [24] about a high yielding dibromoolefination of thioxanthene-9-one in refluxing benzene at 150°C for 44 h. In our hands, the transformation was only successful under microwave assistance. Furthermore, compounds with two carbonyl centers (anthraquinone and 2,5-diacetylpyridine) could easily be transformed into the corresponding dibromoolefins with simply doubling the amount of the reagents. The cleanliness of the conversion and the less harmful solvent CH_2Cl_2 used under the given conditions render this procedure a valuable alternative. In line with our observed trend, attempts to convert benzophenone or fluorenone failed under conventional conditions as well as under microwave irradiation.

Table 1

Conversion of aldehydes and ketones into dibromoolefins using microwave irradiation.[a]

Entry	Aldehyde or ketone	Dibromoolefin	Yield (%)
1			75
2			95
3			20
4			73
5			75
6			91
7			80
8			65
9			55
10			23
11			41
12			85

[a]Microwave conditions are CBr_4, PPh_3, CH_2Cl_2, 80°C, 3.5 bar, 100 W, and 20 min.

In conclusion, we could show that the microwave-assisted dibromoolefination is a convenient method for the conversion of aromatic and heteroaromatic aldehydes and ketones into the corresponding dibromoolefins. As typically observed in microwave reactions, the method is characterized by short reaction times and clean transformations with a facile purification of products. Particularly noteworthy is the successful conversion of pyridyl-substituted aldehydes and ketones into their corresponding dibromoolefins, which will prove helpful in the design of new cross-conjugated ligand systems to transition metal fragments.

EXPERIMENTAL

All chemicals were purchased from commercial suppliers and used without further purification. CH_2Cl_2 for synthesis was dried over CaH_2. ^{1}H-NMR and ^{13}C-NMR spectra were recorded on a 500 or 400-MHz Varian spectrometer (^{1}H 500/400 MHz, ^{13}C 125/100 MHz) using $CDCl_3$ or tetrahydrofuran (THF)-d_8 as the solvent with tetramethylsilane (TMS) as the internal standard at room temperature. Chemical shifts are given relative to TMS; the coupling constants J are given in Hz. Mass spectra were recorded on a Finnigan LCQ DECA (ThermoQuest) using an atmospheric pressure chemical ionization technique. The high-resolution mass spectrometry (HRMS) was recorded on a time of light spectrometer (micrOTOF—Bruker Daltonics) using an Apollo "Ion Funnel" electrospray ionization (ESI) as the ion source. Melting points were determined with a Büchi M-565 apparatus and are uncorrected. Microwave reactions were run on a CEM Discover SP or Biotage Initiator Classic, each monomode apparatus. All known compounds (Table 1, entries 1 [25], 2 [26], 3 [27], 5 [28], 6 [29], 7 [24], and 11 [30]) afforded analytical data identical to those reported in literature (refer to Supporting Information for further details).

Typical procedure. Diazafluoren-9-one **1** [21] (300 mg, 1.65 mmol), CBr_4 (2 equiv, 1.09 g, 3.29 mmol), and PPh_3 (4 equiv, 1.73 g, 6.59 mmol) were placed into a microwave vial, which was purged with argon (in case of bis-dibromoolefination, twice the amount of the reagents was used). Dry CH_2Cl_2 was added to the mixture, and the vial was capped tightly and put into the microwave reactor (CEM Discover SP or Biotage Initiator Classic). After 20-min irradiation (80°C, 3.5-bar internal pressure, 100 W), the reaction mixture was cooled and poured onto a plug of silica gel. The silica gel was washed with an additional amount of CH_2Cl_2 (100 mL) before the eluate was evaporated on the rotary evaporator to dryness. The pure product was obtained by recrystallization from acetone to furnish **3** (310 mg, 55%) as colorless needles.

9H-Dibromomethylene-4,5-diazafluorene (3).
Yield 310 mg (55%), colorless needles.
mp 164°C (recrystallization from acetone).
^{1}H-NMR ($CDCl_3$) $\delta = 8.79$ (dd, $J = 5.0$ and 1.5 Hz, 2 H), 7.99 (dd, $J = 7.5$ and 1.5 Hz, 2 H), 7.35 (dd, $J = 7.1$ and 4.8 Hz, 2H).
^{1}H-NMR (THF-d_8) $\delta = 8.96$ (dd, $J = 8.2$ and 1.0 Hz, 2 H), 8.69 (dd, $J = 4.7$ and 1.3 Hz, 2H), 7.37 (dd, $J = 8.2$ and 4.7 Hz, 2H).
^{13}C-NMR ($CDCl_3$) $\delta = 157.15$, 155.14, 150.76, 132.56, 131.41, 123.00, 95.14.
^{13}C-NMR (THF-d_8) $\delta = 158.77$, 151.81, 135.67, 134.02, 133.17, 123.74, 95.74.
HRMS/ESI (+) $m/z = 336.8977$, calculated ($C_{12}H_7Br_2N_2$) = 336.8971.

1,1-Dibromo-2,2-di(2-pyridyl)ethene (4).
Yield 360 mg (65%), colorless needles.
mp 120°C (recrystallization from acetone).
^{1}H-NMR $\delta = 8.60$ (ddd, $J = 4.2$, 2.7, and 0.7 Hz, 2 H), 7.75 (dd, $J = 6.1$ and 1.4 Hz, 2 H), 7.65 (dd, $J = 7.8$ and 1.7 Hz, 2H), 7.24 (ddd, $J = 5.1$, 4.2, and 1.5 Hz, 2H).
^{13}C-NMR $\delta = 157.85$, 149.54, 146.18, 136.93, 125.06, 123.11, 96.08.
HRMS/ESI (+) $m/z = 338.9125$, calculated ($C_{12}H_9Br_2N_2$) = 338.9127.

1,1-Dibromo-2-(2-pyridyl)-2-phenylethene (Table 1, entry 10).
Yield 128 mg (23%), yellow oil.
^{1}H-NMR $\delta = 8.64$ [s (br), 1H], 7.71 (dd, $J = 1.46$ and 7.76 Hz, 1H), 7.41–7.30 (m, 7H).
^{13}C-NMR $\delta = 158.65$, 149.23, 146.53, 139.84, 137.26, 131.12, 129.05, 127.32, 124.43, 122.97, 93.78.
MS/ESI (+)$m/z = 340$.

2,6-Bis(1,1-dibromoprop-1-en-2-yl)pyridine (Table 1, entry 12).
Yield 740 mg (85%), yellow oil.
^{1}H-NMR $\delta = 7.71$ (t, $J = 7.74$ Hz, 1H), 7.27 (d, $J = 7.79$ Hz, 2H), 2.26 (s, 6H).
^{13}C-NMR $\delta = 159.02$, 142.29, 137.00, 122.43, 90.54, 29.78.
MS/ESI (+) $m/z = 475$.

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