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A simple and fast procedure for efficient synthesis of β- and γ-azidoarylketones

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Abstract—A simple and efficient method for preparing β- and γ-azido substituted arylketones has been achieved by short microwave irradiation of the corresponding halo arylketones and sodium azide in DMSO.

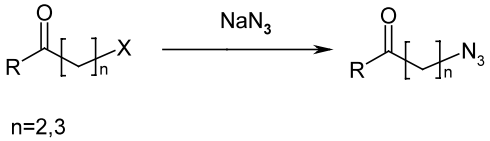
Recently, there has been a new focus on using azide functional groups in synthesis.[1–3] For example, Rozen et al. have demonstrated that alkyl azides can be safely oxidized to nitroalkyl.[1] Furthermore, alkyl azides undergo copper catalyzed cycloadditions in high yields and selectivity.[2] Azidoarylketones are also valuable in organic synthesis and can be transformed to yield a wide variety of organic molecules such as heterocyclic compounds.[3,5] There are several methods available for synthesizing azido carbonyl compounds, for example the oxidative addition of azide anion to silyl enol ether,[6] the reaction of halo ketone[3–5,7] or nosyloxy ketone[8] via nucleophilic substitution with sodium azide. These methods generally yield α-substituted azidocarbonyl compounds in good yields, however, the preparation of β- and γ-azidocarbonyl compounds have long reaction times and low yields.[9–13]

Microwave irradiation has become popular since it requires shorter reaction times, and generally gives high yields and enhanced selectivity compared to conventional heating.[14] We were curious whether microwave irradiation can be used to accelerate the formation of alkyl azides from the corresponding alkyl halogens and sodium azides (see Scheme 1), especially since alkyl azides are thermally labile and rearrange to form imines upon thermal activation (see Scheme 2).[15] We have shown that vinyl alkyl azides rearrange upon microwave irradiation to form 2H-azidirines (see Scheme 3)[16] and microwave irradiation has been used to catalyze cycloaddition of azides.[17,18] Thus, microwave irradiation of alkyl azides yields triazoles through 1,3 dipolar addition to alkenes in excellent yields.[17]

We set out to prepare β- and γ-azidoarylketones **2** from the corresponding halo compounds **1** and sodium azide with the aid of flash heating by microwave irradiation (see Scheme 4). Azides **2** are representative of different substituted analogs.

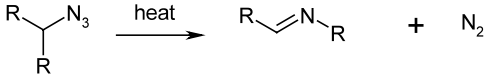
Azidoarylketones are thermally labile,[15] and we are using a conventional microwave oven that cannot be fitted with a condenser to prevent overheating. Therefore, we followed the procedure of Chan and co-workers,[19] and ran the reaction in a water bath inside the microwave. This ploy allowed us to safely make the azidoarylketones up to a 10 gram scale. The water was replaced whenever it boiled.

In a typical experiment, γ-chlorobutyrophenone (180 mg, 1.00 mmol) dissolved in DMSO (5 mL) and



n=2,3

Scheme 1.



Scheme 2.

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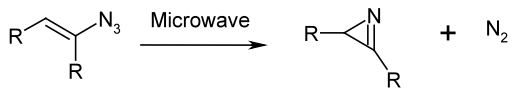
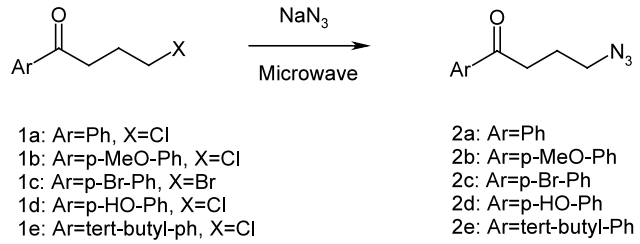
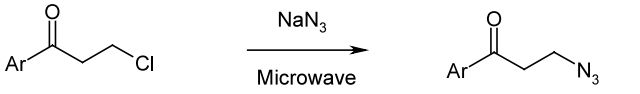


Scheme 3.



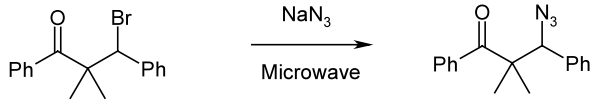
1a: Ar=Ph, X=Cl
1b: Ar=p-MeO-Ph, X=Cl
1c: Ar=p-Br-Ph, X=Br
1d: Ar=p-HO-Ph, X=Cl
1e: Ar=tert-butyl-ph, X=Cl

2a: Ar=Ph
2b: Ar=p-MeO-Ph
2c: Ar=p-Br-Ph
2d: Ar=p-HO-Ph
2e: Ar=tert-butyl-Ph



1f: Ar=Ph
1g: Ar=p-Br-Ph
1h: Ar=p-MeO-Ph
1i: Ar=p-F-Ph

2f: Ar=Ph
2g: Ar=p-Br-Ph
2h: Ar=p-MeO-Ph
2i: Ar=p-F-Ph



1j

2j

Scheme 4.

aqueous sodium azide (100 mg, 1.50 mmol) was placed in a test tube and the resulting solution stirred. The test tube was stored in a glass beaker containing water and irradiated with microwaves for 8 min. The reaction was monitored by TLC and after the completion, water was added to the reaction mixture and the resulting solution extracted with diethyl ether. The solvent was removed under vacuum and the resulting oil was purified on a silica column, eluting with 95:5 hexane:ethyl acetate to obtain γ-azidobutyrophenone in 95% yield.

This same reaction was also done in ethanol and without solvent. In both instances the reaction proceeded but the yields were lower. Thin layer chromatography of the reaction mixtures, which had undergone prolonged microwave irradiation, indicated the formation of additional products, presumably coming from the thermal reactivity of the azidoarylketone.

Azides **2a**, **2c**, and **2f** have been made previously and were characterized by obtaining their IR and ^{1}H NMR spectra,[20,21] which were identical to those in the literature.[10,11] Azides **2b**, **2d**, **2e**, **2f**, **2g**, **2h**, **2i** and **2j** were characterized by obtaining their IR, ^{1}H and ^{13}C NMR spectra.[20,21]

The isolated yields and the reaction times for preparing β- and γ-azidoarylketones **2** using sodium azide and microwave irradiation are summarized in Table 1. In all instances the azidoarylketones **2** are formed in high yield after a reaction time of 12 min or less. There is essentially no difference in the reaction rate for halo ketone bearing an electron withdrawing or donating substituent. The β- and γ-azidoarylketones are stable enough under this short microwave irradiation that they do not undergo thermal rearrangements to form imines. In all cases we noticed a remarkable acceleration in reaction rates compared to conventional heating.[9–12] The yields in the microwave assisted reaction are either as good or better than using conventional heating. Further, the method requires no catalyst such as sodium iodide as in the conventional method.[10] The high boiling point and the substantial dipole moment of DMSO were exploited in these reactions for the efficient absorption of the microwave irradiation.

In conclusion, the present work describes an efficient synthetic route to prepare β- and γ-azidoarylketones from easily available haloarylketones using sodium azide under microwave irradiation. This method generates β- and γ-azidoketones in a short reaction time, in high yield and by a simple procedure with excellent

Table 1. Isolated yields of azidoarylketones from microwave irradiations and conventional heating of haloarylketones and sodium azide

Halide	Azide	Reaction time (min)	Microwave yields (%)[a]	Reaction time (h)	Thermal yield (%)[b]
1a	**2a**	8	95	14	93–99[9]
1b	**2b**	10	88	14	93–99[9]
1c	**2c**	10	90		77[10]
1d	**2d**	8	90		
1e	**2e**	12	86		
1f	**2f**	6	87		54[12]
1g	**2g**	6	91		
1h	**2h**	7	90		
1i	**2i**	6	89		
1j	**2j**	12	85		

[a] Isolated yields of azidoarylketone from microwave irradiations of the corresponding haloarylketone and sodium azide.
[b] Literature values for isolated yields of azidoarylketone obtained from conventional heating of the corresponding haloarylketone and sodium azide.

purity. Experiments in progress show that this same method can be used to prepare alkyl azides without any ketones and azido formate esters and will be reported in due course. Whereas the more reactive acyl azides cannot be prepared in the same manner.

Acknowledgements

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20. The NMR and IR spectra of the γ-azidoarylketones are as follow. **2a**: Yellowish dense liquid. ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.03 (quin, 7 Hz, 2H), 3.07 (t, 7 Hz, 2H), 3.41 (t, 7 Hz, 2H), 7.45 (t, 7 Hz, 2H), 7.5 (t, 7 Hz, 1H), 7.95 (d, 7 Hz, 2 H) ppm. IR (neat): 1687, 2098 cm^{-1}. **2b**: White crystalline solid. Mp 41°C. ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.03 (quin. 7 Hz, 2H), 3.03 (t, 7 Hz, 2H), 3.41 (t, 7 Hz, 2H), 3.41 (s, 3H), 6.92 (d, 8.5 Hz, 2H), 7.93 (d, 8.5 Hz, 2H) ppm. ^{13}C NMR (60 MHz, $CDCl_3$) δ 23.2, 34.4, 50.6, 55.1, 113.5, 129.6, 163.3, 197.1 ppm. IR (KBr): 1677; 2099 cm^{-1}. **2c**: Yellowish dense liquid ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.03 (quin, 7 Hz, 2H), 3.05 (t, 7 Hz, 2H), 3.42 (t, 7 Hz, 2H), 7.60 (d, 8 Hz, 2H), 7.81 (d, 8 Hz, 2H) ppm. IR (neat): 1686, 2098 cm^{-1}. **2d**: Crystalline solid. Mp 66–67°C. ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.03 (quin, 7 Hz, 2H), 3.04 (t, 7 Hz, 2H), 3.41 (t, 7 Hz, 2H), 7.03 (broad s, 1H), 6.91 (d, 8.4 Hz, 2H), 7.90 (d, 8.4 Hz, 2H) ppm. ^{13}C NMR (60 MHz, $CDCl_3$) δ 20.6, 23.9, 52.1, 71.6, 126.8, 128.1, 128.2, 128.3, 128.8, 130.4, 135.9, 139.7, 209.4, 23.8, 33.2, 35.1, 50.9, 114.4, 117.1, 132.3, 132.4, 161.4, 199.6 ppm. IR (KBr): 1660, 2100 cm^{-1}. **2e**: Colorless dense liquid. ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.34 (s, 9H), 2.03 (quin, 7 Hz, 2H); 3.06 (t, 7 Hz, 2H), 3.41 (t, 7 Hz, 2H); 7.46 (d, 8 Hz, 2H), 7.89 (d, 8 Hz, 2H) ppm. ^{13}C NMR (60 MHz, $CDCl_3$) δ 23.2, 30.1, 31.9, 32.0, 32.1, 32.9, 35.0, 50.8, 126.2, 126.7, 129.2, 134.0, 156.9, 198.5 ppm. IR (neat): 1682, 2098 cm^{-1}.
21. The NMR and IR spectra of the β-azidoarylketones are as follows **2f**: Yellowish dense liquid. ^{1}H NMR (250 MHz, $CDCl_3$) δ 3.15 (t, 7.5 Hz, 2H), 3.63 (t, 7.5 Hz, 2H), 7.37 (t, 7.4 Hz, 2H), 7.47 (t, 7.0 Hz, 1H), 7.86 (d, 7.6 Hz, 2H) ppm. IR (neat): 1684, 2105 cm^{-1}. **2g**: Yellowish dense liquid ^{1}H NMR (250 MHz, $CDCl_3$) δ 3.21 (t, 6.3 Hz, 2H); 3.74 (t, 6.2 Hz, 2H), 7.63 (d, 8.4 Hz, 2H), 7.83 (d, 8.4 Hz, 2 H) ppm. ^{13}C NMR (60 MHz, $CDCl_3$) δ 37.3, 45.7, 128.5, 129.2, 131.8, 134.8, 195.8 ppm. IR (Neat): 1686, 2105 cm^{-1}. **2h** Brownish dense liquid. ^{1}H NMR (250 MHz, $CDCl_3$) δ 3.42 (t, 7.5 Hz, 2H), 3.88 (s, 3H), 3.92 (t, 7.5 Hz, 2H), 6.95 (d, 8 z, 2H), 7.95 (d, 8 Hz, 2H) ppm. ^{13}C NMR (60 MHz, $CDCl_3$) δ 36.9, 46.1, 55.2, 113.6, 129.3, 130.0, 163.5, 195.3 ppm. IR (neat): 1693, 2099 cm^{-1}. **2i**: Yellowish dense liquid. ^{1}H NMR (250 MHz, $CDCl_3$) δ 3.20 (t, 7.5 Hz, 2H), 3.74 (t, 7.5 Hz, 2H), 7.63 (d, 8 Hz, 2H), 7.83 (d, 8 Hz, 2H) ppm. ^{13}C NMR (60 MHz, $CDCl_3$) δ 38.8, 41.4, 116.1 (d) 130.1, 165 (d), 195.1 ppm. IR (neat): 1686, 2105 cm^{-1}. **2j**: White crystalline solid: 54–57°C. ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.13 (s, 3H), 1.25 (s, 3H), 5.24 (s, 1H), 7.34–7.46 (m, 10H) ppm. ^{13}C NMR (60 MHz, $CDCl_3$) δ 20.6, 23.9, 52.1, 71.6, 126.8, 128.1, 128.2, 128.3, 128.8, 130.4, 135.9, 139.7, 209.4 ppm. IR (neat): 1677, 2103 cm^{-1}.