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ONE POT SYNTHESIS OF FURYL α-BROMOKETONES FROM FURYL KETONES USING THE A-162 Br_3^- RESIN/CH_3NO_2 SYSTEM

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ABSTRACT
Furyl ketones are brominated in a single - step reaction using the A-162 Br_3^- /CH_3NO_2 system .Furyl α-bromoketones are obtained with good yield and high selectivity .

The transformation of 2-furyl ketones into the α-bromo derivatives is a crucial step in the preparation of synthetic intermediates or products of potential industrial interest in this series of heteroaromatic compounds (1). We have previously reported the marked antifungal activity of 2-furyl α-bromo ketones against *Candida albicans* and *Aspergillus* (2,3).
The numerous reagents and methods for direct (4-8) or indirect synthesis of α-halo ketones are not readily applicable to the direct synthesis of furyl α-bromo ketones from furyl ketones bearing a methylene group α to the carbonyl group. This is due to the particular sensitivity of the furan ring to reaction conditions of α-halogenation, which are often harsh, lengthy, non-selective and give poor yields. Arcoria et al. (8) prepared 2-bromoacetyl furan in 50% yield by the direct action of molecular bromine in CCl_4 on 2-acetyl furan. The yield was improved to 85% by Maraval et al. (14) in a two step synthesis involving transformation of a furyl enoxysilane intermediate by molecular bromine at low temperature (-20°C).Improved selectivity and yield were anticipated using the perbromide ion Br_3^-, as the pyridinium (15), ammonium (16), pyrolidinium (17), phosphonium (18) or imidazo-pyridazine complex (19) perbromides have been successfully employed in the bromination of numerous aromatic and aliphatic substrates . Unfortunately these reagents are unstable .

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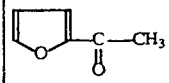
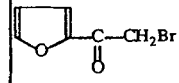
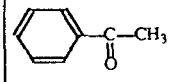
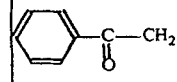
TABLE 1: Bromination of acetylfuran and acetophenone using A-26 Br_3^- / CH_3NO_2, A-162 Br_3^- / CH_3NO_2 or $TBABr_3$ / $CHCl_3$ at 35°C

Substrates	Reagents	Time (hours)	Products	Yield (%)[a]
	$TBABr_3$ (22)	1		80
	$A_{162}Br_3^-$	3		85
	$A_{26}Br_3^-$	3		85
	$TBABr_3$ (22)	1		77
	$A_{162}Br_3^-$	3		97
	$A_{26}Br_3^-$	3		98

[a] Yield determined by ^1H NMR

Bound to an ion exchange resin or in the form of tetrabutylammonium tribromide ($TBABr_3$), Cacchi (20) and Bongini (21) and more recently Berthelot et al. (22) carried out the α-bromination of aliphatic and aromatic ketones, or the selective bromination of benzene and phenol rings.

We employed the A-162 resin Br_3^-/CH_3NO_2 system which appeared suited for bromination of furyl ketones. We initially compared the reactivity of the A-26 Br_3^-/CH_3NO_2, A-162 Br_3^-/CH_3NO_2 and $TBABr_3/CHCl_3$ (22) systems in the bromination of acetylfuran and acetophenone (Table 1).

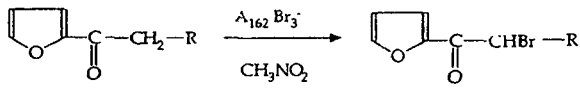
The anionic resin A-162 Br_3^-, prepared in the laboratory according to the method described by Cacchi (20), led to regioselective bromination at the α position to the carbonyl group. The furyl and phenyl methyl ketones were transformed exclusively into the α-monobromoketones in almost quantitative yield.

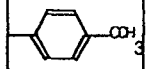
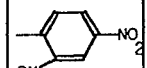
The end of the reaction was indicated by bleaching of the resin and an orange coloration of the reaction mixture.

Neither the methyl groups, nor the furan or benzene rings were brominated. The resin A-162 Br_3^- like A-26 Br_3^- and $TBABr_3$ thus appeared to be suited for bromination of methylene groups activated by the ketofuran system.

Although $TBABr_3$ was more reactive in homogeneous media, the product was more

TABLE 2 : Bromination of furylketones by the A-162 Br_3^- / CH_3NO_2



R	Time (hours)	Yield %[a]	1 H NMR δ (-CHBr-) ppm	IR (cm-1) ν C=O	B.p. °C	UV max
CH_3—	3	95	5.18	-	94-96[b]	-
$CH_3(CH_2)_{23}$—	3	90	5.08	-	137[b]	-
	4	95	6.11	1780	52[c]	276-204
	4	90	6.17	1872	57[c]	276-208
	4	95	6.16	1780	72[c]	276-206
	4	80	6.37	1825	54[c]	272-206
	4	60	6.60	1808	65[c]	248-202

[a] Yield in product isolated ; [b] Boiling point at 14 mm Hg ; [c] Boiling point at 10 mm Hg

readily isolated using the A-162 Br_3^- resin system. Almost pure 2-acyl bromofuran or 2-acyl 2-bromobenzene were obtained after filtration of the resin and evaporation of the solvent.

In further experiments, the methylene groups of series of 2-acyl furans were brominated exclusively at the α position in excellent yield at room temperature using the A-162 Br_3^-/CH_3NO_2 system (Table 2).

The reaction was regioselective with the all substituents (R) tested, although there was a drop in yield with the 2-nitro and 2-4 dinitro derivatives. This was accounted for by steric hindrance by these substituents to attack by the bulky bromine.

The stability of these compounds was tested under various conditions prior to investigation of their antifungal activity. They were resistant to acid and neutral pH, but decomposed in basic media. Unlike the ketones, they could be kept for several months at room temperature or in the cold (4°C). However, polymerization of the furan structure took place at high temperature (100°C).

EXPERIMENTAL SECTION

The ^1H NMR spectra were recorded on a Bruker instrument at 300 MHz in $CDCl_3$, and the IR spectra were recorded on a Hewlett Packard 8452A spectrophotometer. $TBABr_3$ and the other reagents were obtained from Janssen Chimica. A-26 Br_3^- was obtained from Fluka, and A-162 Br_3^- was prepared in the laboratory according to Cacchi (20). The α-furyl ketones were obtained by acylation of furan with carboxylic acids using a previously described method (23).

20 mmoles of ketone in 80 ml of CH_3NO_2 were placed in a 250 ml three-neck flask equiped with a stirrer and cooling system. 25 g of A-162 Br_3^- or A-26 Br_3^- were added slowly, and the reaction mixture was agitated for 3 h at room temperature. At the end of the reaction, the resin was filtered off and washed with ether. The reaction mixture was neutralized with 15% aqueous $KHCO_3$. After extraction with ether and evaporation of the solvent, the crude product was purified by flash-chromatography on a chromagel column (60 Å, 70-230 mesh) using dichloromethane as eluent.

The brominated α-furyl ketones listed in table 2 were obtained by acylation of furan with carboxylic acids according to Fayed (23) followed by bromation with A-162 Br_3^-/CH_3NO_2.

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