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Preparation of *E*-(2-Substituted-1-Methylethylidene)indanones Derived from Monic Acid

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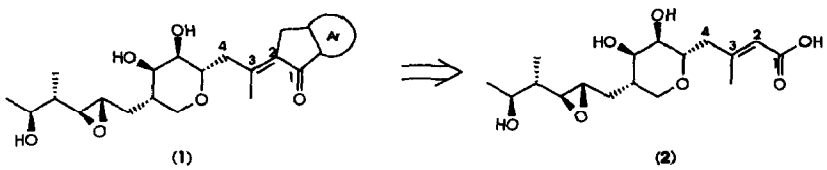
ABSTRACT: Alkylation of the lithium dienolate of the monic acid hydroxamate (**3**) with *o*-bromo(bromomethyl) benzene or heteroaromatic derivatives gave α-alkylated products (**5**). This alkylation procedure was surprisingly catalysed by 4-dimethylaminopyridine. Metal-halogen exchange with *t*-butyl lithium occurred with concomitant intramolecular cyclisation to give a mixture of the deconjugated ketones (**6**). Reconjugation with potassium *t*-butoxide stereoselectively produced the *E*-isomer (**7**). Deprotection gave the monic acid derived ketone (**1**).

As part of our ongoing studies on derivatives of pseudomonic acid[1], we required the synthesis of ketones of the general structure (**1**) containing either aromatic or heteroaromatic rings. Additionally, from earlier work on α,β-unsaturated derivatives of monic acid[1a], only the *E*-stereochemistry of the double bond was expected to result in compounds with antibacterial activity. The synthetic route chosen would need to be amenable to the synthesis of a wide range of derivatives, preferably using the readily available monic acid (**2**) as starting material[1a] (**Scheme 1**).

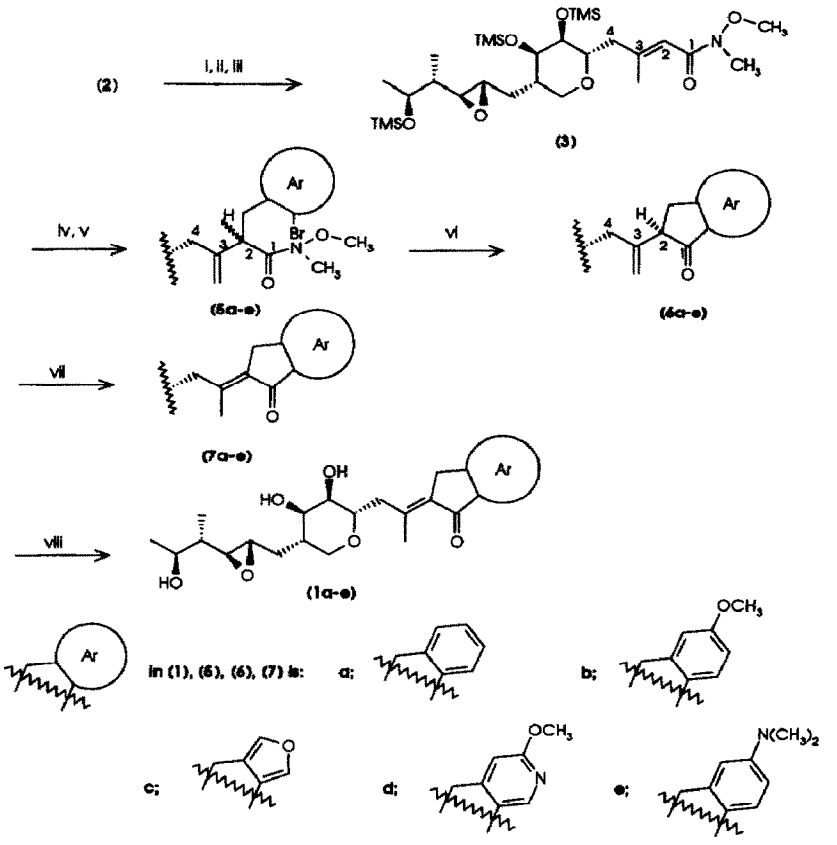
SCHEME 1



These factors have led us to develop a novel method for the construction of *E*-(2-substituted-1-methylethylidene)indanones (**1**) (**Scheme 2**).

Treatment of the readily available α,β-unsaturated hydroxamate (**3**) with lithium diisopropylamide (generated *in situ*), followed by treatment of the resulting lithium dienolate with 2-bromobenzyl bromide (**4a**) (see Table 1), gave a mixture of the alkylated hydroxamates (**5a**). Metal-halogen exchange with *t*-butyl lithium occurred with concomitant intramolecular cyclisation to afford a mixture of the deconjugated ketones (**6a**)[2]. It had previously been found[1c] that reconjugation of 2-alkylsubstituted deconjugated monic acid esters to a 4 to 1 mixture of *E*- and *Z*- 2-alkylsubstituted monic acid esters could be achieved using potassium *t*-butoxide in *t*-butanol/THF mixtures at 0°C. However, by lowering the reaction temperature to -78°C, treatment of the deconjugated ketones (**6a**) with potassium *t*-butoxide resulted in a highly stereoselective conversion to the required *E*-ketone (**7a**)[3]. Subsequent deprotection gave the required ketone (**1a**).

SCHEME 2

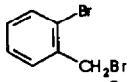
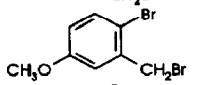
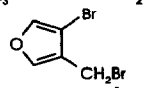
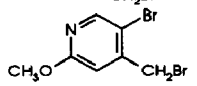
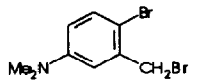


Scheme 2. Reagents and conditions: i, ^{i}BuOCOCl, NEt_3, tetrahydrofuran (THF), 0°C, 30 min; ii, *N,O*-dimethylhydroxylamine, CH_2Cl_2 , room temperature (RT)., 1 h; iii, chlorotrimethylsilanc (TMSCl), NEt_3, THF, catalytic 4-dimethylaminopyridine (DMAP), RT, 2 h (75%); iv, 10 mol% $^{i}Pr_2NH$, ^{t}BuLi, THF, -78°C, 1 h; v, alkylating agent (**4a-e**), (see **Table 1**), THF, RT to reflux, 2 h to 3 days; vi, ^{t}BuLi, THF, -78°C, 1 h; vii, KO^{t}Bu, THF, 1 to 3 h, then acetic acid, -78° to -90°C, 15 min; viii, catalytic DMAP.2HCl, methanol, RT, 1 to 2 h/or 0.4 *N* HCl, THF, water, 2 min.

Using this methodology a wide range of compounds was prepared (**Table 1**).

In order to prepare the furan analogue (**1c**), the deconjugated ketone (**6c**) was prepared from 3-bromo-4-bromomethylfuran (**4c**)[4]. However, the use of potassium *t*-butoxide in THF at -78°C to reconjugate the double bond, resulted in a 3 to 1 mixture of the inseparable *E*- and *Z*- isomers. However, it was found that merely

Table 1: Preparation of Ketones (**1a-e**) from Hydroxamate (**3**)

Example	Alkylating agent (4)	(5)	Yield [i] (%) (6)	(7)	1
a		45 (66[ii])	86	84[iv]	80
b[4]		58[iii]	54	80[iv]	92
c[5]		73	82	75[v]	56
d[6]		76[ii]	78	63[v]	80
e		42[ii]	52	58[v]	89

i. Isolated yields of compounds after flash chromatography on silica gel. All new compounds gave satisfactory spectral data.

ii. 10 mol% DMAP added.

iii. 50 mol% LiI added.

iv. Reaction at -78°C.

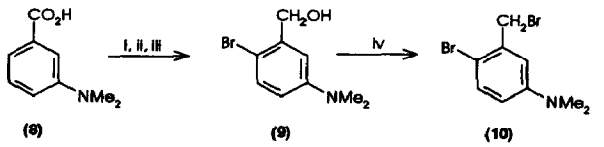
v. Reaction at -90°C.

lowering the reaction temperature to -90°C and careful quenching with acetic acid at that temperature, resulted in a clean conversion to the required *E*-isomer (**7c**) in 75% yield. (These conditions were used for all subsequent derivatives).

In the course of preparing ketone (**1d**) it was surprisingly found that the presence of catalytic DMAP in the alkylation step had a dramatic effect on the reaction rate. Hence, the presence of 10 mol% of DMAP resulted in a 66% yield of the amides (**5a**), using only a 2 hour reaction time at RT (compared with a 45% yield after heating to reflux for 3 days). Although the use of DMAP as an acylation catalyst is well known, its use as a C-alkylation catalyst is not. This catalysis may be due to quaternisation of the pyridyl nitrogen of DMAP by the benzylic bromide, thus generating catalytic amounts of a very reactive benzylating agent. The general applicability of DMAP in this context remains to be investigated.

In order to prepare the dimethylamino substituted ketone (**1e**) the preparation of 1-bromo-2-(bromomethyl)-4-(dimethylamino)benzene (**10**) was required. We were concerned that polymerisation of this compound would prevent its isolation if formed. We were pleasantly surprised to find however, that conversion of 3-(dimethylamino)benzoic acid (**8**) to the hydroxymethyl compound (**9**) followed by treatment with triphenylphosphine and bromine gave the required bromomethyl compound (**10**) as an isolable crystalline product (**Scheme 3**). Subsequent conversion to the ketone (**1e**) was uneventful.

SCHEME 3



Scheme 3. Reagents and conditions: i. methanol, concentrated H_2SO_4, reflux, 16 h, (80%); ii. 2,4,4,6-tetrabromocyclohexadienone, CH_2Cl_2, -20°C 1 h then warmed to RT over 2 h (91%); iii. diisobutylaluminium hydride, THF, -70°C, 2 h, (78%); iv. PPh_3 then bromine, CH_2Cl_2, -20°C, 1 h then 10% aqueous sodium carbonate solution (75%).

In conclusion, a stereoselective method for the construction of *E*-(2-substituted-1-methylethylidene)-indanones (1) has been developed, which is applicable to a wide range of structural types.

The compounds described show good antibacterial activity against gram positive and some gram negative bacteria. The preparation of further compounds of general structure (1) and their biological activity will be published elsewhere.

ACKNOWLEDGEMENTS

We thank Professor P.J. Kocienski for helpful discussions and J.W. Tyler for performing n.O.e. experiments.

NOTES AND REFERENCES

1. See for example: (a) Coulton, S.; O'Hanlon, P.J.; Rogers, N.H. *J. Chem. Soc., Perkin Trans. 1*, 1982, 729. (b) Crimmin, M.J.; O'Hanlon, P.J.; Rogers, N.H., *J. Chem. Soc., Perkin Trans. 1*, 1985, 541. (c) Crimmin, M.J.; O'Hanlon, P.J.; Rogers, N.H., *J. Chem. Soc., Perkin Trans. 1*, 1985, 549.

2. During this work related cyclisations were published; (a) Selnick, H.G.; Radzilowski, E.M.; Ponticello, G.S., *Tetrahedron Lett.*, 1991, **32**, 721; (b) Souchet, M., Clark, R.D., *Synlett*, 1990, **151**; (c) Aidhen, I.S., Ahuja, J.R., *Tetrahedron Lett.*, 1992, **33**, 5431.

3. By ^1H n.m.r. the unwanted *Z*-isomer was present as a minor contaminant (approximately 5%) and was readily removed by flash chromatography (or recrystallisation of the deprotected ketone (1)). The stereochemistry was determined by n.O.e. experiments.

4. Kanapure, S.L. Das, K.G.; Bhaval, B.M., *Synth. Commun.*, 1984, **14**, 1205..

5. For the preparation of 3,4-dibromofuran see Gorzynski, M.; Rewicki, D. *Liebigs Ann. Chem.*, 1986, 625. 3,4-Dibromofuran was treated with *t*-butyl lithium (THF, -78°C, 1 h) followed by the addition of *N,N*-dimethylformamide (-70°C, 1 h). Reduction of the resulting aldehyde with sodium borohydride (aqueous ethanol, 5°C, 2 h) gave 3-bromo-4-hydroxymethylfuran (58%). Treatment with phosphorus tribromide (diethyl ether, 5°C, 1 h) gave the crude 3-bromo-4-bromomethylfuran which was used without further purification.

6. For the preparation of 2-amino-5-bromo-4-methylpyridine see Dunn, A.D.; Currie, A.; Hayes, L.E., *J. Prakt. Chem.*, 1989, 331, 369. Diazotisation of 2-amino-5-bromo-4-methylpyridine (sodium nitrite, 20% sulphuric acid, 0°C, 1 h) then heating to reflux for 1 h gave the hydroxypyridine (31%) which on alkylation (methyl iodide, silver carbonate, benzene, 60°C, 3 days) gave 3-bromo-6-methoxy-4-methylpyridine (74%). Radical bromination (N-bromosuccinimide, carbon tetrachloride, hv, reflux, 3 h) gave the required 3-bromo-4-bromomethyl-6-methoxypyridine (27%).

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