Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

Preparation of Acrylophenones and 2-Alkyl Indanones Utilizing Hexamethylenetetramine as an Inexpensive Mannich Reagent.

Apurba Bhattacharya [a] , Brigitte Segmuller [a] & Arnold Ybarra [a]

[a] Hoechst Celanese Corporation, Corpus Christi Technical Center, P. O. Box 9077, Corpus Christi, Texas, 78469, U. S. A.

Published online: 21 Aug 2006.

To cite this article: Apurba Bhattacharya , Brigitte Segmuller & Arnold Ybarra (1996): Preparation of Acrylophenones and 2-Alkyl Indanones Utilizing Hexamethylenetetramine as an Inexpensive Mannich Reagent., Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 26:9, 1775-1784

To link to this article: http://dx.doi.org/10.1080/00397919608002617

SYNTHETIC COMMUNICATIONS, 26(9), 1775-1784 (1996)

Preparation of Acrylophenones and 2-Alkyl Indanones Utilizing Hexamethylenetetramine as an Inexpensive Mannich Reagent.

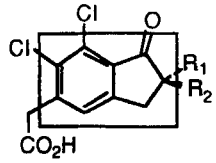
Apurba Bhattacharya*, Brigitte Segmuller and Arnold Ybarra

Hoechst Celanese Corporation, Corpus Christi Technical Center,
P. O. Box 9077, Corpus Christi, Texas 78469 U. S. A.

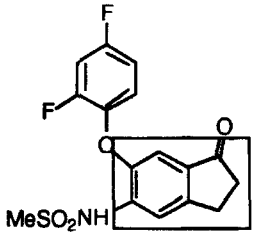
ABSTRACT: Hexamethylenetetramine/acetic anhydride-promoted α-methylenation of aryl alkyl ketones followed by acid-catalyzed cyclization of the resulting acrylophenones produce 2-alkyl indanones in excellent yields.

Alkyl indanones and their analogs have been demonstrated to be versatile and useful synthetic intermediates in the agrochemical as well as the pharmaceutical industry (Scheme 1). The synthetic utility of indanones are also enhanced by the fact that they undergo facile

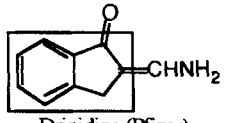
Scheme 1.



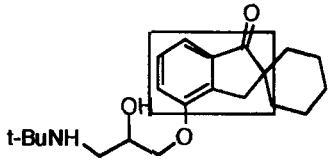
R_1=Ph R_2=Me [(+)-Indacrinone]
R1=Me R2= Cyclopentyl [MK 473]
Antihypertensive, diuretic (Merck)[1a]



ZK-38997
Cyclooxygenase inhibitor (Ciba-Geigy)[1b]



Drinidine (Pfizer)
Analgesic[1c]

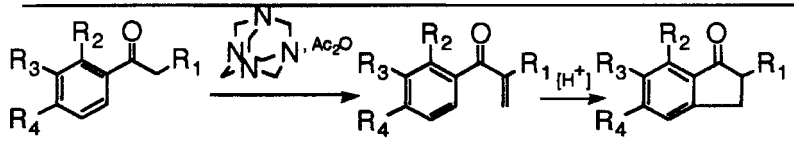


Spirendolol (Sandoz)
β-blocker[1d]

Robinson annulation, producing flurenone and its analogs, which exhibit important pharmacological activities.[1-3]

Although the synthesis of 2-alkyl indanones via Mannich condensation of aryl alkyl ketones with N,N,N'N'-tetramethyldiaminomethane followed by acid-catalyzed cyclization of the resulting acrylophenones is well-known, its utility is limited by the high cost of the Mannich reagent- N,N,N'N'-tetramethyldiaminomethane ($[CH_3)_2N]_2CH_2$) utilized in the methylenation step.[2] An alternate methylenation technology which involves treatment of the aryl alkyl ketones with paraformaldehyde, dimethylamine hydrochloride, and acetic acid are often complicated by poor yields and unwanted by-products.[3] Direct formation of acrylophenones via Friedel Crafts acylation, on the other hand, fails for electron-poor aromatics and is aluminum-waste

Table 1. Preparation of 2-alkylindanones.[a]



1 2 3

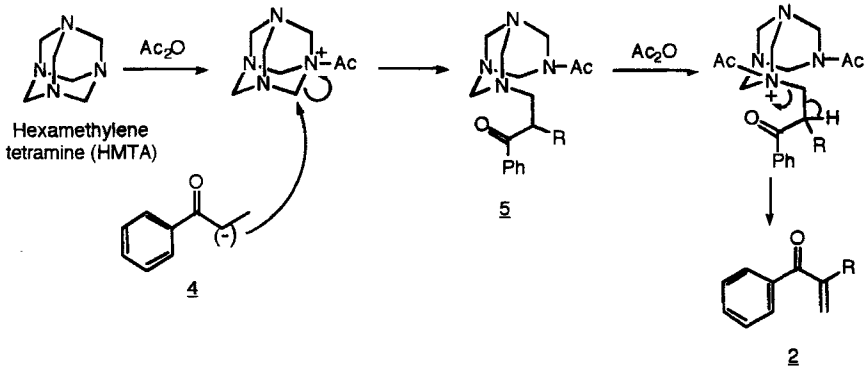
Entry	R_1	R_2	R_3	R_4	yield (1→3)	Ref.
1.	Me	H	H	H	82%	3d-g.
2.	Et	H	H	H	80%	3d-g.
3.	n-Bu	H	H	H	86%	3g.
4.	Me	H	Br	H	82%[5]	-
5.	n-Octyl	H	H	H	87%	3g.
6.	n-Propyl	Cl	Cl	OMe	84%	2a.
7.	Ph	Cl	Cl	OMe	76%	2a.
8.	Me	H	H	OMe	78%	3e.

[a] All products exhibited satisfactory spectral properties (^{1}H NMR and ^{13}C NMR) fully in accord with known or expected values.

producing. This report describes a facile and cost-effective route[4b] to acrylophenones utilizing hexamethylenetetramine in conjunction with acetic anhydride as the methylenation agent.[4] This simple but efficient methodology provides a unique entry into a diverse spectrum of acrylophenones and hence the corresponding indanones starting from alkyl aryl ketones.

The process for the transformation of aryl alkyl ketone to the indanone via the corresponding acrylophenone is outlined in Table 1. Thus treatment of the aryl alkyl ketones 1 with HMTA (1.4 eq) and acetic

Scheme 2.



anhydride (1.8 eq) at 80°C for 4 h followed by aqueous work-up produced the acrylophenones 2, which underwent acid-catalyzed cyclization (H_2SO_4, 50-60°C, 1h) to produce the corresponding indanones 3 in good to excellent yields from 1.

The formation of the acrylophenones can be explained by the pathway depicted in Scheme 2. Activation of HMTA with acetic anhydride followed by nucleophilic attack of the enolate anion 4 on N-acyl HMTA gives rise to the b-amino ketone intermediate 5, which after further activation by Ac_2O followed by Hofmann elimination, produces the acrylophenone 2.[6a,c] The mechanism is speculative at this point, although a similar mechanism involving protonation followed by acid-catalyzed fragmentation of HMTA, has been proposed for Sommelet reaction[6b]

We have demonstrated a simple, new methodology for the preparation of 2-alkyl indanones via olefination-cyclization of alkyl aryl ketones, which is superior to the existing technologies in terms of practicality[7] and does not involve the use of expensive reagents (e.g.,

tetramethyldiaminomethane). The methodology described herein demonstrates still another facet of the utility of hexamethylenetetramine, a readily available and inexpensive reagent, in organic synthesis.[4] Extension of this methodology to the preparation of synthetically useful chromone/chromane derivatives is in progress.[8]

EXPERIMENTAL

General. Melting points were determined on a Mel-Temp melting point apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on an IBM AF-200 and a Bruker ARX-400 spectrometer. The chemical shifts are reported in parts per million (δ) from internal tetramethylsilane, and the coupling constant (J) are given in Hz. All the solvents and reagents were of ACS-certified grade, were purchased from either Fisher Scientific or Aldrich and were used without purification.

A typical experimental procedure is as follows: A mixture of propiophenone (30 g, 223.6 mmol), hexamethylenetetramine (43.8 g, 313 mmol) and acetic anhydride (41 g, 402 mmol) was heated at 80°C for 4h. under nitrogen atmosphere. The reaction mixture was cooled to 30°C and quenched into a stirred mixture of methylene chloride (200 mL) and sodium hydroxide (200 mL of 2N solution). The organic layer was separated and washed with aqueous HCl (100 mL of 1N solution). The CH_2Cl_2-solution containing the product, 2-methyl-1-phenyl-prop-2-en-1-one was azeotropically dried by distilling CH_2Cl_2 to approximately 50 mL volume and was used without further purification in the next step. The CH_2Cl_2-solution was added to conc. H_2SO_4 (130 mL) at a rate such that the reaction temperature was maintained between 50°-60°C. The

CH_2Cl_2 was removed by distillation and nitrogen sweep, as soon as it was added. The reaction mixture was stirred at 50°C-60°C for one hour, cooled to 20°C and quenched into a stirred mixture of CH_2Cl_2 (200 mL) and water (200 mL). After separating the aqueous layer the organic layer was concentrated in the rotary evaporator to produce 121 g (82%) of 2-methyl-inden-1-one (entry 1, Table 1).

2-Methyl-indan-1-one (entry 1) [3d-g]: ^1H NMR (200 MHz, $CDCl_3$) 7.71-7.75 (d, 1H, J=8Hz), 7.26-7.60 (m, 3H), 3.30-3.44 (m, 1H), 2.60-2.77 (m, 2H), 1.26-1.30 (d, 3H, J=7Hz). ^{13}C NMR (50.3 MHZ, $CDCl_3$) 209.6 (s), 153.5 (s), 136.3 (s), 134.7 (d), 127.3 (d), 126.5 (d), 123.9 (d), 41.8 (d), 34.8 (t), 16.0 (q). MW ($C_{10}H_{10}O$)=146 amu as confirmed by CH_4-chemical ionization.

2-ethyl-indan-1-one (entry 2):[3d-g] ^1H NMR (200 MHz, $CDCl_3$) 7.74-7.78 (d, 1H, J=8Hz), 7.33-7.63 (m, 3H), 3.26-3.38 (dd, 1H, J=8Hz, J=17Hz), 2.76-2.87 (dd, J=17Hz, J=4Hz), 2.57-2.65 (m, 1H), 1.91-2.04 (m, 1H), 1.51-1.61 (m, 1H), 0.97-1.05 (t, 3H, J=7Hz). ^{13}C NMR (50.3 MHZ, $CDCl_3$) 209.1 (s), 153.9 (s), 137.0 (s), 134.7 (d), 127.3 (d), 126.6 (d), 123.8 (d), 48.6 (d), 32.1 (t), 24.2 (t), 11.3 (q). MW ($C_{11}H_{12}O$)=160 amu as confirmed by CH_4-chemical ionization.

2-Butyl-indan-1-one (entry 3):[3g] ^1H NMR (200 MHz, $CDCl_3$) 7.74-7.78 (d, 1H, J=8Hz), 7.29-7.63 (m, 3H), 3.26-3.39 (dd, 1H, J=8Hz, J=17Hz), 2.61-2.87 (m, 2H), 1.92-1.98 (m, 1H), 1.31-1.48 (m, 5H), 0.92-0.95 (t,

3H, J=3Hz). ^{13}C NMR (50.3 MHZ, $CDCl_3$) 209.3 (s), 153.7 (s), 136.9 (s), 134.6 (d), 127.3 (d), 126.6 (d), 123.6 (d), 47.3 (d), 32.7 (t), 31.0 (t), 29.4 (t), 22.5 (t), 13.7 (q). MW ($C_{13}H_{16}O$)=188 amu as confirmed by CH_4-chemical ionization.

4-Bromo / 6-bromo-2-methyl isomers (entry 4): ^1H NMR (400 MHz, $CDCl_3$) 4-bromo: 7.74 (d, J=0.8Hz, 1H), 7.63-7.7 (m, 1H), 7.25-7.28 (m, 1H), 3.31-3.37 (m, 1H), 2.63-2.76 (m, 2H), 1.29-1.34 (m, 3H); 6-bromo: 7.84 (d, J=1.7 Hz, 1H), 7.63-7.7 (m, 1H), 7.31-7.35 (m, 1H, major), 3.31-3.37 (m, 1H), 2.63-2.76 (m, 2H), 1.29-1.34 (m, 3H). ^{13}C NMR (50.3 MHZ, $CDCl_3$) 4-bromo: (d) 16.07 (CH_3), 35.88 (CH_2), 41.91 (CH), 122.09 (C), 122.72 (CH), 130.07 (CH), 133.31 (CH), 138.30 (C), 153.03 (C), 208.32 (C). 6-bromo: (d) 16.07 (CH_3), 34.50(CH_2), 42.35 (CH), 121.44 (C), 126.80 (CH), 128.03 (CH), 137.27 (CH), 138.13 (C), 151.81 (C), 207.64 (C). MW ($C_{10}H_9OBr$)=224 amu as confirmed by CH_4-chemical ionization.

2-octyl-indan-1-one (entry 5):[3g] ^1H NMR spectrum (200 MHz, $CDCl_3$) 7.75-7.78 (d, 1H, J=7Hz), 7.28-7.63 (m, 3H), 3.26-3.39 (dd, 1H, J=17Hz, J=8Hz), 2.76-2.86 (dd, 1H, J=17Hz, J=4Hz), 2.61-2.70 (m, 1H), 1.91-1.97 (m, 1H), 1.27-1.51 (m, 13H), 0.85-0.91 (t, 3H, J=7Hz). ^{13}C NMR spectrum (50.3 MHZ, $CDCl_3$) 209.3 (s), 153.9 (s), 137.0 (s), 134.7 (d), 127.3 (d), 126.6 (d), 123.9 (d), 47.4 (d), 32.7 (t), 31.7 (t), 31.3 (t), 29.5 (t), 29.3 (t), 29.1 (t), 27.3 (t), 22.5 (t), 13.7 (q). MW ($C_{17}H_{24}O$)=244 amu as confirmed by CH_4-chemical ionization.

6,7-dichloro-5-methoxy-2-propyl-indan-1-one (entry 6):[2a] m.p. 116-117°C, ^{1}H NMR spectrum (400 MHz, $CDCl_3$) 6.86 (s, 1H), 3.19-3.26 (dd, 1H, J=17Hz, J=8Hz), 2.67-2.75 (m, 2H), 1.91-1.92 (m, 1H), 1.40-1.46 (m, 3H), 0.94-0.98 (t, 3H, J=7Hz). ^{13}C NMR spectrum (100.6 MHz, $CDCl_3$) 203.7 (s), 160.6 (s), 155.3 (s), 131.6 (s), 126.6 (s), 122.6 (s), 106.7 (d), 56.8 (q), 48.1 (d), 33.7 (t), 32.3 (t), 20.5 (t), 14.0 (q). MW ($C_{13}H_{14}O_2Cl_2$)=272 amu as confirmed by CH_4-chemical ionization.

6,7-dichloro-5-methoxy-2-phenyl-indan-1-one (entry 7):[2a] m. p. 192-193°C (lit[2a] 193-195°C), ^{1}H NMR (400 MHz, $CDCl_3$) 7.24-7.33 (m, 3H), 7.15-7.17 (m, 2H), 6.93 (s, 1H), 4.00 (s, 3H), 3.86-3.91 (m, 1H), 3.54-3.61 (m, 1H), 3.19-3.20 (m, 1H). ^{13}C NMR (100.6 MHz, $CDCl_3$) 200.5 (s), 160.9 (s), 155.3 (s), 139.2 (s), 132.2 (s), 128.8 (d, 2C), 127.7 (d, 2C), 127.1 (d), 126.0 (s), 123.1 (s), 106.6 (s), 56.9 (d), 54.0 (q), 34.9 (t).

5-Methoxy-2-methyl-indan-1-one (entry 8):[3e] ^{1}H NMR (200 MHz, $CDCl_3$, δ): 7.69 (d, 1H, J=8Hz), 6.88-6.93 (m, 2H), 3.88 (s, 3H), 3.28-3.41 (m, 1H), 2.61-2.74 (m, 2H), 1.30 (t, 3H, J=8Hz). ^{13}C NMR (50.3 MHZ, $CDCl_3$, δ): 207.8 (s), 165.4 (s), 156.5 (s), 138.3 (s), 129.6 (s), 125.6 (d), 115.3 (d), 109.6 (d), 55.5 (q), 42.0 (d), 34.9 (t), 16.4 (q). MW ($C_{11}H_{12}O_2$)=176 amu as confirmed by CH_4-chemical ionization.

REFERENCES AND NOTES

1. (a) U. S. Pat. 4,587,357; U. S. Pat. 4,605,706 assigned to Merck & Co. (b) EP 9554 assigned to Schering AG. (c) U.S. Pat.

4,022,386; U.S. Pat. 4,064,272; U.S. Pat. 4,117,012; U.S. Pat. 4,164,514 assigned to Pfizer Inc. (d) U.S. Pat. 4,322,437; BE 854567 assigned to Sandoz. (e) Zacchei, A. G.; Dobrinska, M. R.; Wilshouky, T. I.; Kwan, K. C.; White, S. D.; Drug Met. and Disp. 1982, 10, 20

2. (a) Jane deSolms, S. *J. Org. Chem.* **1976,** 41, 2650. (b) Cragoe, E. J. Jr.; Schultz, E. M.; Schneeberg, G. E.; Stocker, O. W.; Woltersdorf, Jr., Fenetti, G. M.; Watson, L. S. *J. Med. Chem.*, **1975**, 18, 225. (c) U. S. Pat. 3,483,227 (1969). (d) U. S. Pat. 4,316,043 (1982). (e) Cost of ($[CH_3)_2N]_2CH_2$) is $264/Kg for 100 Kg lots available from TCI America.

3. (a) Schultz, E. M.; Cragoe, E. J.Jr.; Blocking, J. B.; Bolhofer, W. A.; Sprague, J. M. *J. Med. Pharm. Chem.*, **1962,** 5, 660. (b) Tramontini, M. *Synthesis*, **1973**, 703. (c) Tramontini, M.; Angionlini, L. Tetrahedron, **1990**, 46, 1791. (d) Burckhalter, J. H.; Reynold, C. F.; *J. Am. Chem. Soc.*, **1948**, 70, 4184. (e) Grebenyuk, A. D.; Shaipova, N. Zh. *J. Org. Chem. U.S.S.R. (Engl. Transl.),* **1976,** 12, 1502. (f) Pinnick, H. W.; Brown, S. P.; Mclean, E. A.; Zoller, L. W. *J. Org. Chem.*, **1981**, 46, 3758. (g) Morriconi, E. J.; Creegan, F. J. *J. Org. Chem.*, **1966**, 31, 2090.

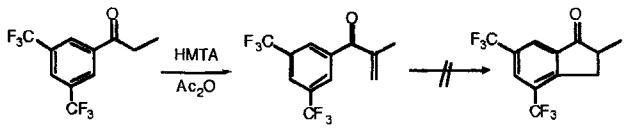
4. (a) Hexamethylenetetramine, readily obtainable from ammonia and formaldehyde, is a stable reagent with an adamantane-like structure. Hexamethylenetetramine has been widely used for the introduction of the formyl group and amino group (Sommelet reaction and Duff reaction) in aromatic compounds. (For review,

see *Synthesis.*, **1979,** 161).

(b) Cost 40¢ / lb for commercial quantities (Chemical Marketing Reporter, May 1, **1995**).

(c) The HMTA/Ac_2O-mediated methylenation is limited to the preparation of 2-alkyl indanones. Thus simple acetophenone fails to undergo methylenation under the reaction conditions presumably due to lack of enolization of the substrate.

(d) Electron poor aryl alkyl ketones, although undergoes facile methylenation, fails to cyclize under acidic conditions to the indanones due to deactivation of the aromatic ring e.g.



5. (a) A mixture (60:40) of the two regioisomeric cyclized products (6-bromo and the 4-bromo) was obtained; the ratio was verified by C-H correlation and quantitative 13C NMR experiments.

6. (a) Hofmann, A. W. *Ber.,* **1881,** 14, 2725. (For review, see Cope; Trumbull.*Org. React,* **1960,** 11,317). (b) Angyl, S. J. *Org. React. 1954,* 8, pp 197. (c) A finite concentration of the enolate anion would be present by the action of HMTA on the aryl alkyl ketone.

7. The olefination which was performed neat without any solvent is also environmentally attractive.

8. Ellis, G. P.; Barker, G. *Prog. Med. Chem.*, **1972,** 9, 65.

(Received in the USA 24 October 1995)