Pergamon

Tetrahedron Letters, Vol. 38, No. 47, pp. 8121-8124, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)10181-2

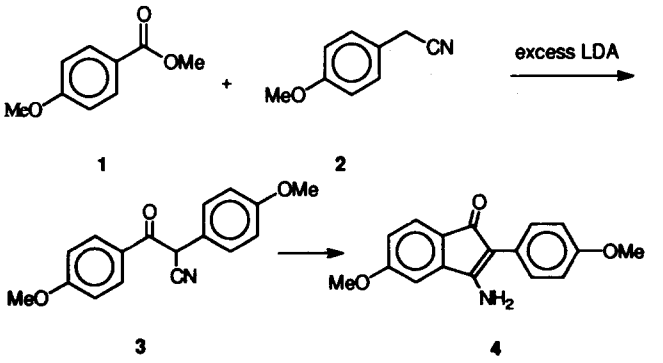
A New Anionic Cyclization Reaction: Condensation of Benzoate Esters with Nitriles to Give 3-Amino-2-Inden-1-Ones

Nadim E. Kayaleh, Ramesh C. Gupta, John F. Morrissey, and Francis Johnson*

Chemistry Department, State University of New York at Stony Brook, Stony Brook, NY 11790-3400

Abstract: A new type of anionic cyclization has been discovered in which the condensation of alkyl benzoates with simple nitriles, induced by an excess of LDA, leads directly to substituted-3-amino-2-inden-1-ones. The corresponding intermediate β-oxonitriles undergo cyclization to give, in most instances, superior yields of the same compounds. Acid hydrolysis of these indenones leads in high yield to the corresponding biologically active (anticoagulant) indandiones.

Esters of benzoic acid and simple nitriles are amongst the oldest types of compounds known[1] to organic chemistry and it would be difficult to believe that their condensation chemistry was not completely developed and thoroughly understood. Yet, we have found an entirely new type of reaction involving these substances.[2] When an equimolar mixture of an alkyl (preferably ethyl)[3] benzoate and a nitrile having an α-methylene is added to an excess of LDA in tetrahydrofuran at temperatures below -10° C, the solution develops an intense red color and after water quenching, a 2-substituted-3-amino-2-inden-1-one can be isolated in reasonable yield. This is exemplified in the equation shown below using methyl 4-methoxybenzoate (1) and 4-methoxyphenylacetonitrile (2) (the first case that we discovered) which leads to 4 in 57% yield. Further experimentation quickly revealed that 3 (prepared from 1 and 2 by using NaH/trace methanol as the condensing base) is a likely intermediate because it also gave rise to 4 (75% yield) when added to an excess of LDA.



We have examined the scope of this type of reaction and have found that it is quite general. However, in all cases, the yields of the 3-aminoindenones were superior overall (see Table: one-step reaction) when the keto-nitrile was prepared first, then cyclized separately (see Table: two-step reaction).

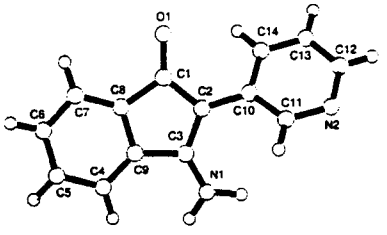
Table: Summary of the 3-aminoindenones obtained by using the one-step reaction and the two-step procedures. (Detailed experimental methods are noted in reference 4)

Entry	R_1	R_2	yield by one-step reaction	yield by two-step procedure	yield of 1,3-indan dione
1	4-OMe	*p*-methoxy phenyl	57%	59%	65%
2	H	*p*-methoxy phenyl	57%	55.5%	76%*
3	4-OMe	*o*-methoxy phenyl	15%	69%	81%
4	H	*o*-methoxy phenyl	10%	43%	-
5	3-OMe	*p*-methoxy phenyl	28%	-	-
6	3-Cl	*p*-methoxy phenyl	33%	55%	60%
7	4-OMe	phenyl	15%	56%	-
8	H	phenyl	13%	-	-
9	2-OMe	*p*-methoxy phenyl	8%	45%	-
10	4-OMe	3,4-dimethoxy phenyl	28%	-	-
11	H	CH_3	83%	-	-
12	4-OMe	CH_2CH_3	49%		-
13	H	3-pyridyl	-	65%	-
14	H	H	0%	0%	

* commercially known as anisindione

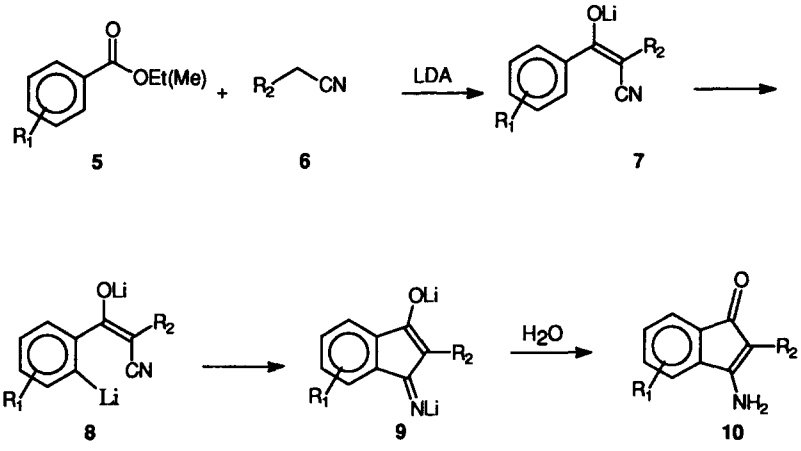
Although the NMR (^1H and ^{13}C) and MS data[5] are completely consistent with the assigned structures, an X-ray analysis[6] was obtained for entry 13 (see Table) and the results, shown in Figure 1, confirm the general structural assignment.

Figure 1: ORTEP structure of X-ray data for 3-amino-2-(3-pyridyl)-2-inden-1-one

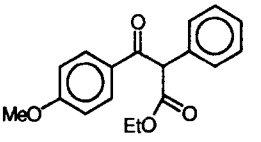


We believe that the process can be represented as shown in the scheme below. It seems likely that the enolate ion 7 coordinates a second mole of LDA and this then effects deprotonation at the ortho position to give 8. The ortho-deprotonation of the enolate ions of simple acetophenones has been studied at length by Klein and Medlik-Balan[7] who used principally BuLi/TMEDA in hexane as the reagent of choice. However, in the interim, virtually no further significant synthetic chemistry has been evolved in which an enolate ion mediates the deprotonation at the ortho position of an aromatic ring. Our results represent the first report of a truly useful synthetic method involving such anionic species.

Scheme



The stereochemical preferences for enolate ions of this type (8) have never been examined. However steric effects must play a significant role and it seems highly likely that in cases of 8 where R_2 is alkyl or aryl the preferred geometry, because of 1,3-allylic strain[8], will be that in which the aryl ring and R_2 are anti in orientation. In the case of the dianion derived from benzoyl acetonitrile (8, R_2=H) no cyclization product could be obtained. However the above steric argument would place the nitrile group anti to the phenyl ring, and thus inaccessible to the second lithium anion. Surprisingly even the addition of HMPA, known to induce enolate ion equilibration, did not lead to any cyclization product. Nevertheless the addition of $(CH_3)_3SiCl$ did lead to a species having a silyl group on the aromatic ring. The further chemistry of the dianions derived from 7 (R=H) will be reported later. As might be anticipated compound 11 (where enolate anion distribution could be expected to be delocalized over both carbonyl groups), did not give any indane-1,3-dione under the same reaction conditions.



11

Finally, acid hydrolysis by 20% H_2SO_4 in boiling water led to the corresponding indan-1,3 diones (seeTable) in good yield in all cases.

Previously reported methods for the preparation of 3-aminoindenones have required at least six synthetic steps,[9] whereas indan-1,3-diones, which have significant anticoagulant and antibacterial activities[10], can be prepared by a number of methods,[11-17] None however is more versatile than the procedure described here. The methods reported currently represent a simple entry in both classes of compound. Further studies aimed at expanding the scope of this new directed-ortho-metallation (DoM) reaction are being pursued.

Acknowledgment. We thank Ganes Chemicals Inc. (Carlstadt, NJ) for a generous sample of 4-methoxyphenylacetonitrile.

References and Notes

1. The synthesis of methyl benzoate, for example, was first reported in 1828 (Dumas, J; Boullay, R. *Ann. Chim.* **1828,** [273], 20: *ibid Ann Physik,* **1828,** *12*, 435) and of propionitrile in 1869 (Gautier, M., *Ann. Chim.* **1869,** [4], *17*, 181).
2. A preliminary account of this work was presented at the 211th ACS National Meeting at New Orleans, LA, **1996**, *Abstr. Pt II.*, ORGN 239.
3. A by-product of the reaction is the formation of the *N,N*-diisopropylamide derived from the benzoate. This was significant in quantity when a methyl ester was employed but diminished greatly when the ethyl ester was used.
4. The following are representative examples of both the one-step and the two-step procedures for entry 1. a) One-step method: Methyl 4-methoxybenzoate (1) (1.23 g; 7.40 mmol) and 4-methoxy phenylacetonitrile (2) (1.08 g, 7.37 mmol) were dissolved in dry THF and the mixture was added slowly to 22.0 mL of 2.0 M LDA at -10°C (44.0 mmol). The reaction was left to stir overnight and allowed to warm to room temperature. It was then quenched with water and most of the THF was evaporated under reduced pressure. The crude 3-aminoindenone (4) was then filtered, dried, and recrystallized from isopropanol to give the pure material (1.18 g). b) Two-step method : 4-methoxy phenylacetonitrile (2) (5.42 g, 36.8 mmol) was dissolved in dry THF, and NaH (60% in oil; 2.98 g) was added to the mixture. Neat methyl 4-methoxybenzoate (1) (6.14 g, 36.9 mmol) was added to the solution, which was boiled. After 5 hours, the solution was cooled and quenched with water. Most of the THF was evaporated under reduced pressure. Acidification gave a precipitate which was extracted with dichloromethane. The extract was washed with bicarbonate followed by brine. The solution was then dried with magnesium sulfate, filtered, and concentrated under reduced pressure to afford the keto-nitrile (3; 7.60 g). It was then dissolved in dry THF and the mixture was added to 61.0 mL of 2.0 M LDA at -10° C. The procedure then followed exactly that described in a) above. The weight of 4 was 6.10 g.
5. Accurate mass determinations (HRMS) or elemental analyses were obtained for all compounds.
6. Crystal data for 3-amino-2-(3-pyridyl)-2-inden-1-one, $C_{14}H_{10}N_2O$: M.W.=222.25, primitive, orthorhombic, space group Pbcn (#60), a=8.206(3), b=14.588(3), c=17.90(5) Å, V=2143(3) Å^3, Z=8, d_{calc}=1.377g.cm^{-3}, μ (MoKα)=0.89 cm^{-1}. A crystal of the red-colored 3-amino-2-(3-pyridyl)-2-inden-1-one, $C_{14}H_{10}N_2O$, having approximate dimensions of 0.30 x 0.30 x 0.40 mm was mounted on a glass fiber. All measurements were made on an Enraf-Nonius diffractometer with graphite monochromated Mo-Kα radiation.
7. Klein, J.; Medlik-Balan, A. *J. Org. Chem.* **1976**, *41*, 3307.
8. a) Johnson, F. *Chem. Rev.* **1968**, 375; b) Hoffmann, R.W. *Chem. Rev.* **1989**, 1841
9. Bond, C. C.; Hooper, M. *J. Chem. Soc. (C)*, **1969**, 2453.
10. a) Horeau, A; Jacques, J. *Bull. Soc. Chim. Fr.* **1948**, 53; b) Jaques, L. B.; Gordon, E.; Lepp. E. *Can. Med. Assoc. J.* **1950**, *62*, 465. b) Blaustein, A. *Ibid.* **1950**, *62*, 470.
11. Dieckmann, W. *Ber.* **1914**, *47*, 1439.
12. Koelsch, C. F. *J. Am. Chem. Soc.* **1936**, 1328.
13. Schoenberg, A.; Mustafa, A.; Asker, W. *J. Am. Chem. Soc.* **1953**, *75*, 4645.
14. Horton, R. L.; Murdock, K.C. *J. Org. Chem.* **1960**, *25*, 938.
15. Shapiro, S. L. ; Geiger, K.; Freedman, L. *J. Org. Chem.* **1960**, *25*, 1860.
16. Beringer, F. M.; Galton, S.A.; Huang, S.J. *J. Am. Chem. Soc.* **1962**, *84*, 2819.
17. Mosher, W. A; Soeder, R.W. *J. Org. Chem.* **1971**, *36*, 1561.

(*Received in USA* 23 *June* 1997; *revised* 15 *August* 1997; *accepted* 10 *September* 1997)