A Simple and Versatile Heterocyclic Synthesis from Aminonitriles and Ketones (1)

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Sir:

The utility of *o*-aminonitriles in heterocyclic syntheses has been dramatically shown by Taylor and co-workers (3) in a series of papers which spans fifteen years. We wish to describe a simple and efficient method of preparing a variety of heterocyclic systems by reaction of α- and β-aminonitriles with carbonyl compounds. The scope of this process is herein briefly described utilizing cyclohexanone as a typical ketone and the aminonitriles **1-4**.

The procedure for the preparation of heterocyclic systems **5-8** (X = tosylate) is merely to reflux a toluene solution containing the aminonitrile (1.0 equiv.), ketone (2.0 equiv.) and toluenesulfonic acid (1.0 equiv.) for 18-30 hours (4). Upon cooling, the toluenesulfonate salts crystallize in excellent yields (90-99%). Analytically pure samples (5) are obtained after recrystallization in 75-90% yields (Table I).

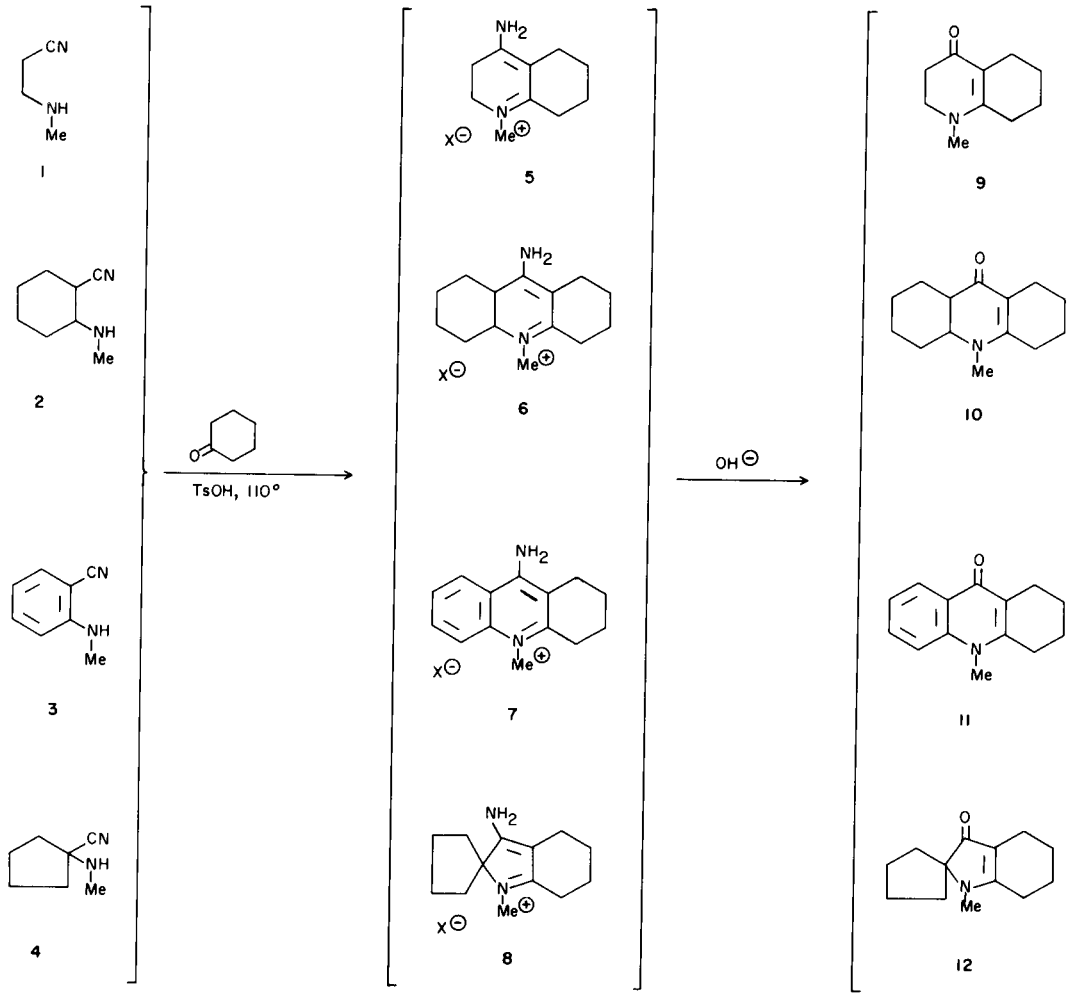


TABLE I

Physical Data for Amino Tosylates

Cpd.	M.P. (a)	Yield (%) (b)	ν nujol cm^{-1} (N^{+}=C–C=C–N)	(NH_2)	λ max ethanol mμ (ε)
5	204-205	75	1635, 1670	3100, 3300	350 (15,270)
6	179-180	80	1675, 1575	3085, 3180	356 (16,110)
7	245-247	91	1675, 1618	3195, 3350	349 (14,136)
					336 (14,513)
					248 (36,226)
8	169-170	80	1655, 1605	3310, 3120	339 (13,686)

(a) From ethanol-ether. (b) Nmr spectra were completely consistent with structural assignment exhibiting low field broad singlet (NH_2) which exchanged upon addition of deuterium oxide.

TABLE II

Physical Data for Enaminoketones

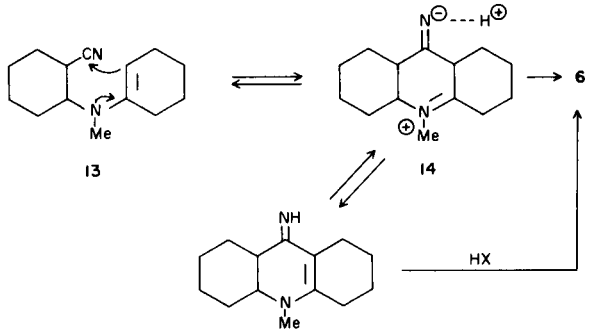
Cpd.	M.P.	Yield (%)	ν $CHCl_3$ cm^{-1} (N=C=C–C=O)	λ max ethanol mμ (ε)
9 (a)				
10	71-72	55 (b)	1620, 1555	342 (15,666)
11	171-172	96	1620, 1595, 1550	346 (15,700)
	(lit. (7) 170-172)			333 (14,515)
				246 (33,769)
12	109-111	80	1635, 1550	337 (11,553)

(a) Previously described, ref. 6. (b) An 80% yield consisting of a mixture of two isomers, *trans-cis*, (77:23) was obtained. The pure *trans* isomer was obtained in 55% yield.

This method represents a distinct improvement over one previously described which involved formation of heterocycles (*i.e.*, **5**, X = ClO_4) from the enamine of **1** and magnesium perchlorate (6). That the enamines were intermediates in this cyclization was readily confirmed by treating them with one equivalent of *p*-toluenesulfonic acid and observing the high yields of **5-8** produced. It is of interest to note that without an electrophile (H^+, Mg^{++}), every effort to cyclize the enamines (*i.e.*, **13**) failed. This is presumably due to the instability of systems such as **15**, which can be considered simply as tautomers of **13** and **14**. However, if the latter can be trapped by a suitable electrophile it would give rise to **6**. The heterocycles, **5-8**, are merely the protonated form of the tautomeric system **13-14-15** and the corresponding enamines of **1**, **3**, and **4**. However, treatment with alkali does not return the amino tosylate salts to the enamines or nitriles, but instead converts them to enaminoketones (**9-12**). Thus, nucleophilic attack on **15** precedes proton removal (to **14**) and the synthetically useful (7) enaminoketones are formed in

good yield. The benzonitrile derivative, **3**, which produced the tetrahydroacridinium salt (**7**) (X = TsO) in 91% yield is noteworthy since it allows the formation of the tetrahydroacridones, **11**, under much milder conditions (8).

Many aminonitriles (9) and carbonyl compounds have been or are being investigated in an effort to evaluate the utility of this technique.



REFERENCES

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(2) On leave from Banaras Hindu University, Varanasi, India.

(3) E. C. Taylor, A. McKillop, and S. Vromen, *Tetrahedron*, 23, 885 (1967); E. C. Taylor, A. McKillop, and R. N. Warrener, *ibid.*, 23, 891 (1967) and earlier references cited therein.

(4) Added in two equal portions, 10-15 hours apart.

(5) All new compounds gave satisfactory elemental analyses.

(6) A. I. Meyers, A. H. Reine, J. C. Sircar, K. B. Rao, S. Singh, H. Weidmann, and M. Fitzpatrick, *J. Heterocyclic Chem.*, 5, 151 (1968); the explosive tendency of this technique leaves something to be desired.

(7) A. I. Meyers and S. Singh, *Tetrahedron Letters*, 5319 (1967).

(8) R. A. Reed, *J. Chem. Soc.*, 425 (1944); J. A. Moore and L. D. Kornreich, *Tetrahedron Letters*, 1272 (1963).

(9) The aminonitrile, **4**, was prepared according to the procedure described by E. Schipper and E. Chinery, *J. Org. Chem.*, 26, 4480 (1961). The aminonitriles, **1** and **2**, were obtained by Michael addition of methyl amine to the appropriate α,β-unsaturated nitrile.

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